Antitrombóticos en los Síndromes Coronarios Agudos: Tratamiento Inicial y a Largo Plazo

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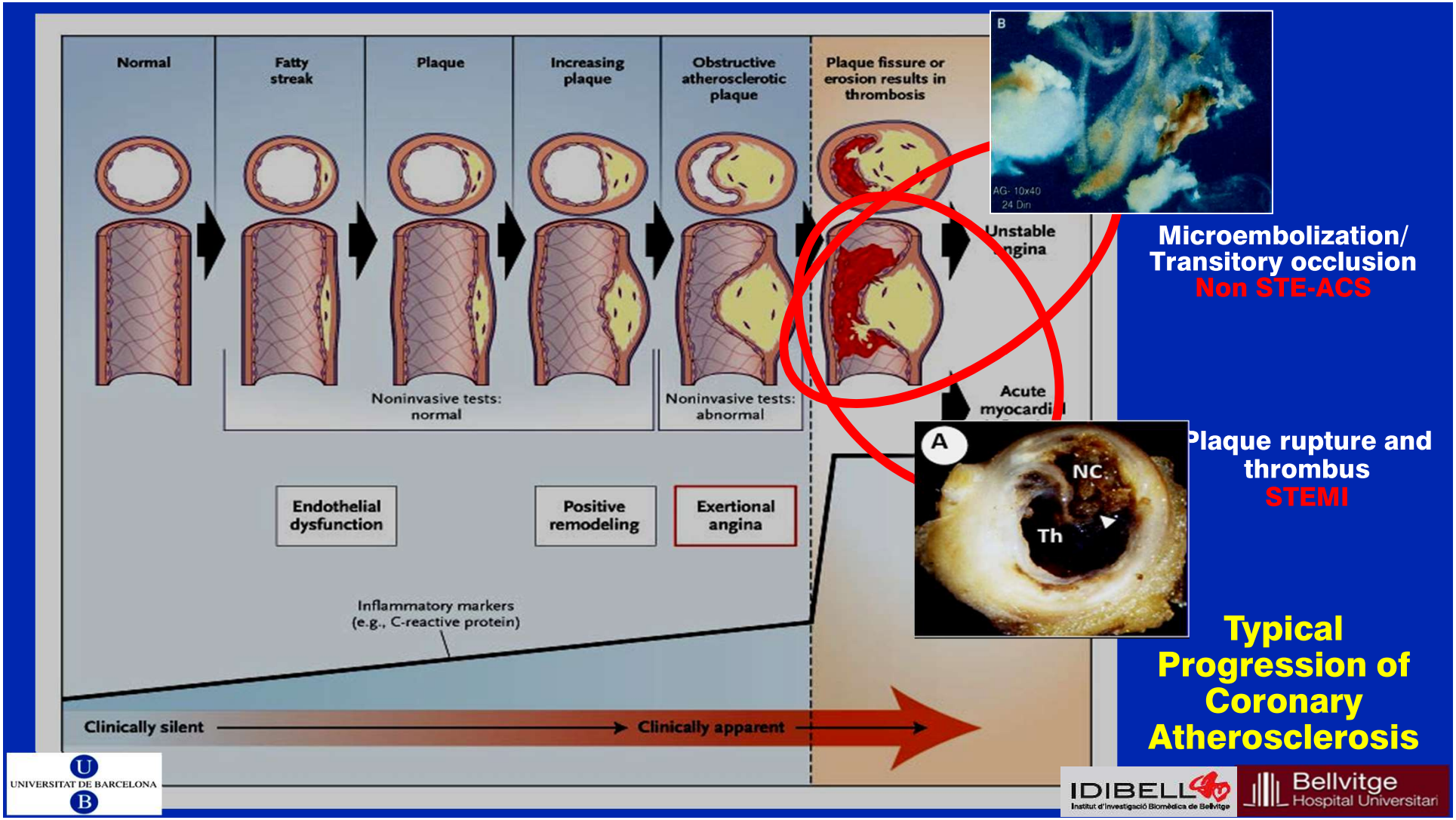
Plasencia
21 Abril, 2017

Generalitat de Catalunya
Departament de Salut

Bellvitge Hospital
Institut Català de la Salut


Normal
Fatty streak
Plaque
Increasing plaque
Obstructive atherosclerotic plaque
Plaque fissure or erosion results in thrombosis
Unstable angina
Acute myocardial
Noninvasive tests: normal
Noninvasive tests: abnormal
Endothelial dysfunction
Positive remodeling
Exertional angina
Inflammatory markers (e.g., C-reactive protein)
Clinically silent
Clinically apparent
B
AG- 10x40
24 Din
Microembolization/
Transitory occlusion
Non STE-ACS
A
NC
Th
Plaque rupture and thrombus
STEMI
Typical Progression of Coronary Atherosclerosis
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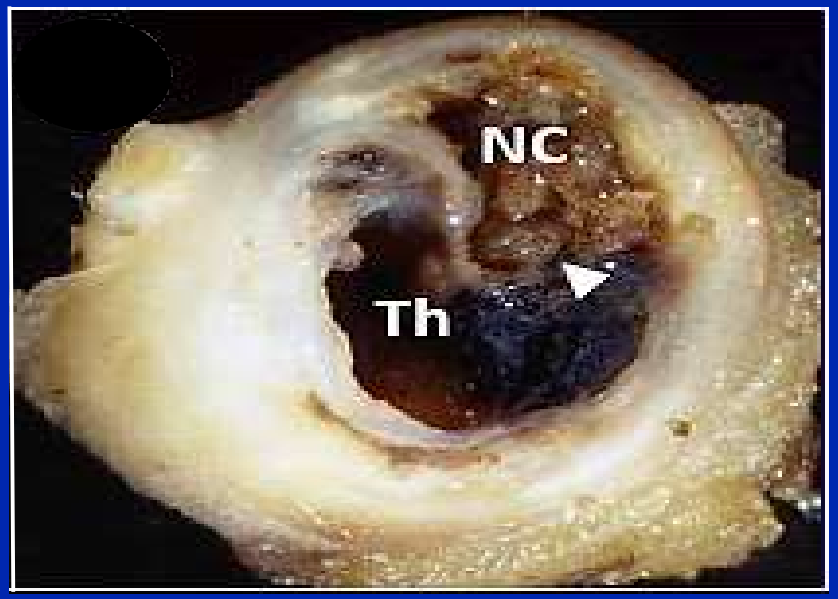
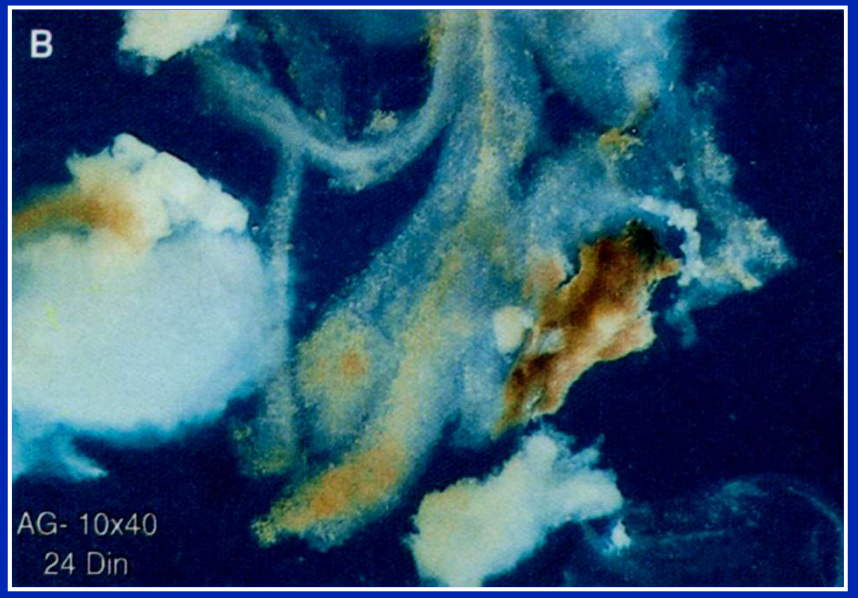
ST-Elevation Acute Myocardial Infarction



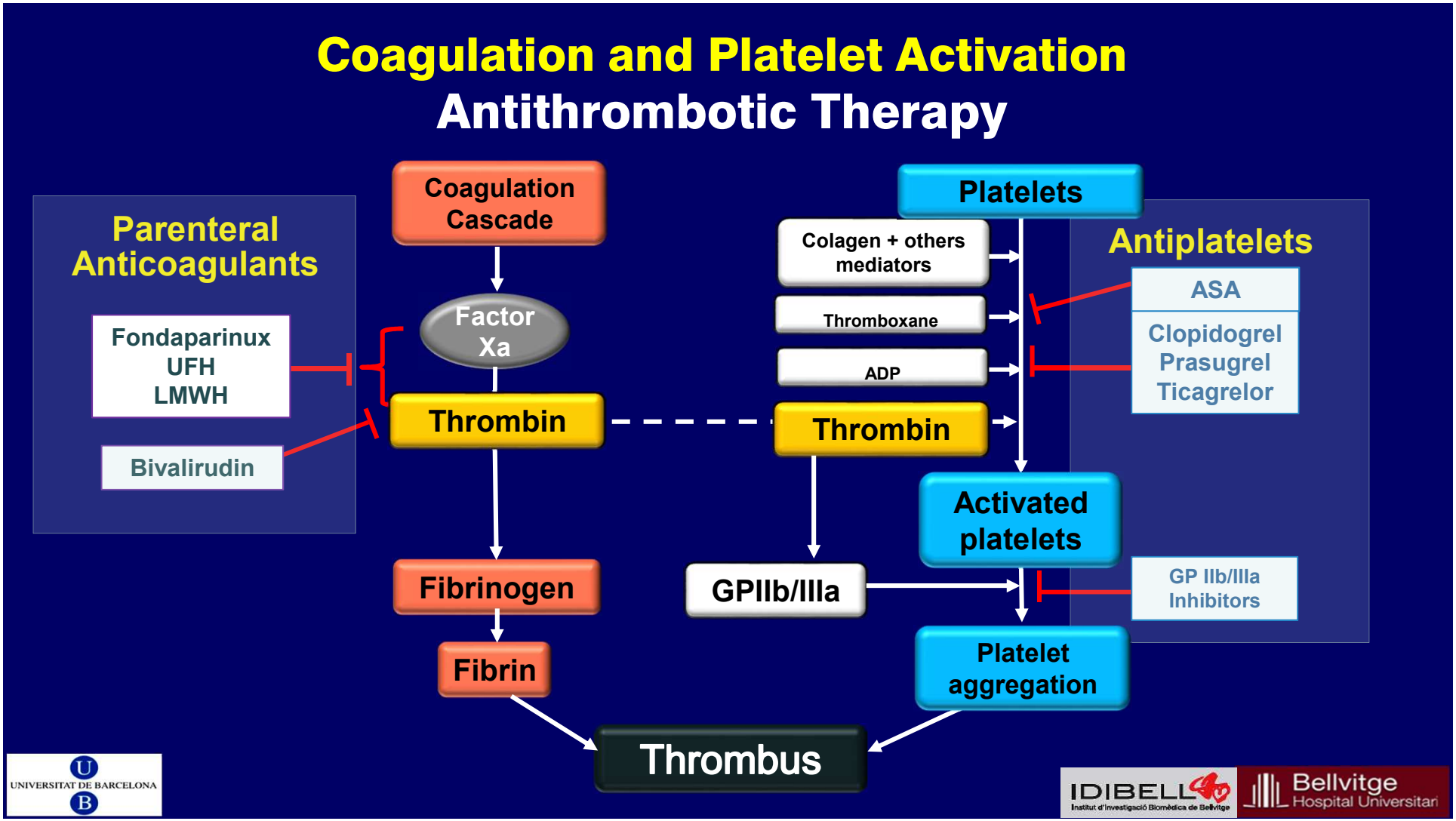
Plaque rupture and thrombus in STEMI

Non ST-Elevation Acute Coronary Syndrome



Embolization and microvascular occlusion in non-ST ACS

Coagulation and Platelet Activation
Antithrombotic Therapy



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Tratamiento Antitrombótico en los Síndromes Coronarios Agudos

1.- Escenario fisiopatológico común

2.- Tratamiento inicial

- SCA Con Elevación del ST
- SCA Sin Elevación del ST

3.- Tratamiento antitrombótico a largo plazo

- En Prevención Secundaria
- Post-implantación de stents
- ¿Tratamientos mas prolongados (>1 año)?

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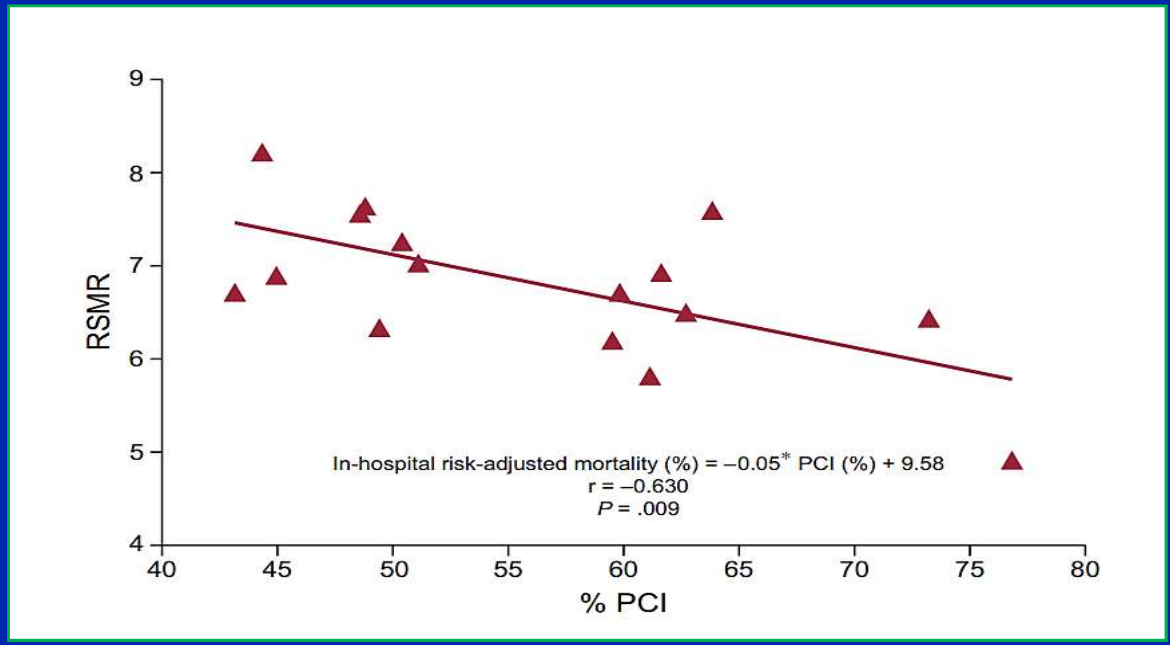
Impact on Mortality of Different Network Systems in the Treatment of STEMI in Spain



Association between PCI rate in the treatment of STEMI and adjusted in-hospital mortality

Cequier A, et al. REC 2017; 70: 155

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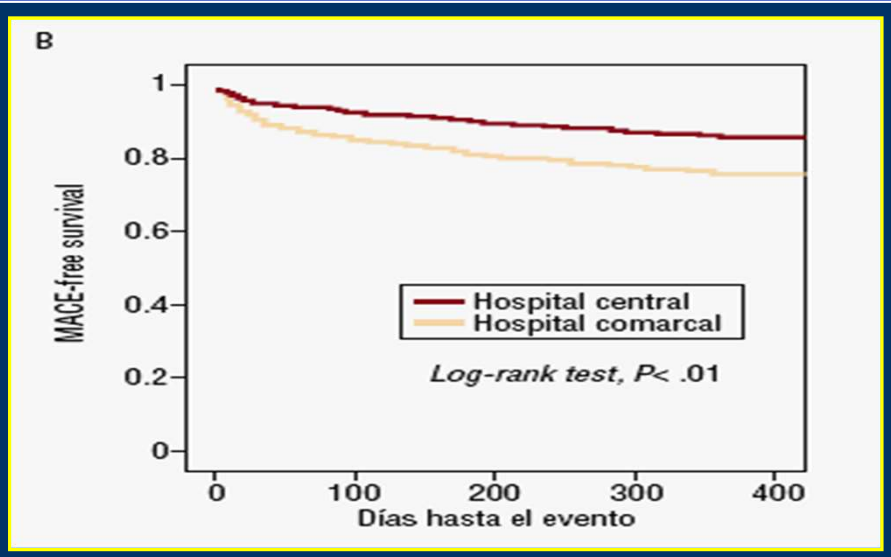
Influence of Hospital Type on Treatment and Prognosis in Patients With NSTE-ACS

GYSCA Trial

		Hospital Central	Comarcal	
Catheterization				
Performed	687 (60.6)	424 (70.8)	263 (49.2)	<.01
Revascularizations	417 (36.8)	258 (43.1)	159 (29.7)	<.01



Kaplan-Meier curves of MACE-free survival (death, non-ST ACS or revascularization)

Ptes admitted for NSTE-ACS in hospitals without a catheterization laboratory were managed less invasively and with less compliance with guidelines recommendations. Hospital type have influence on prognosis.

Ruiz-Nodar JM, Cequier A, et al. REC 2010; 63: 390

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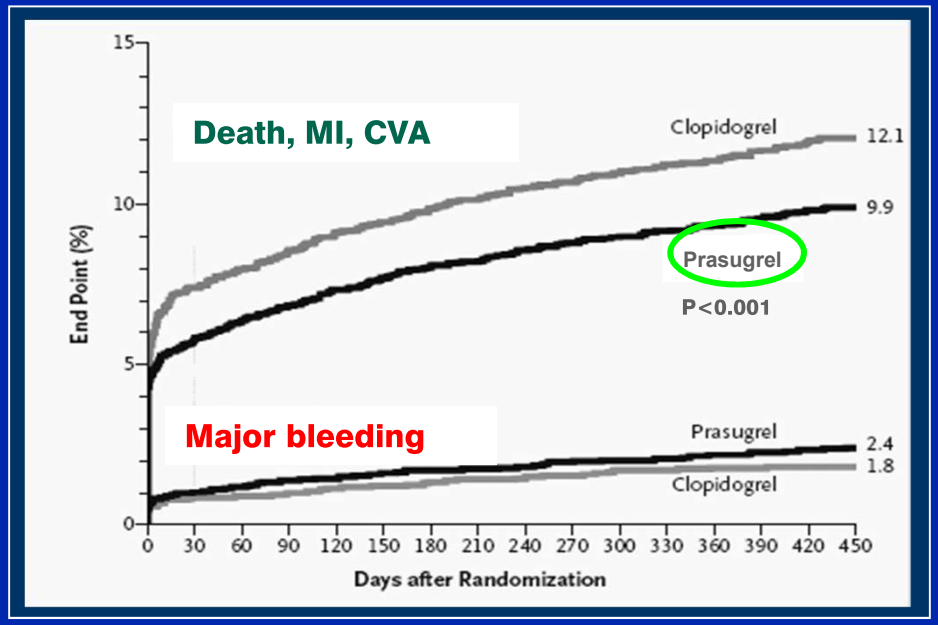
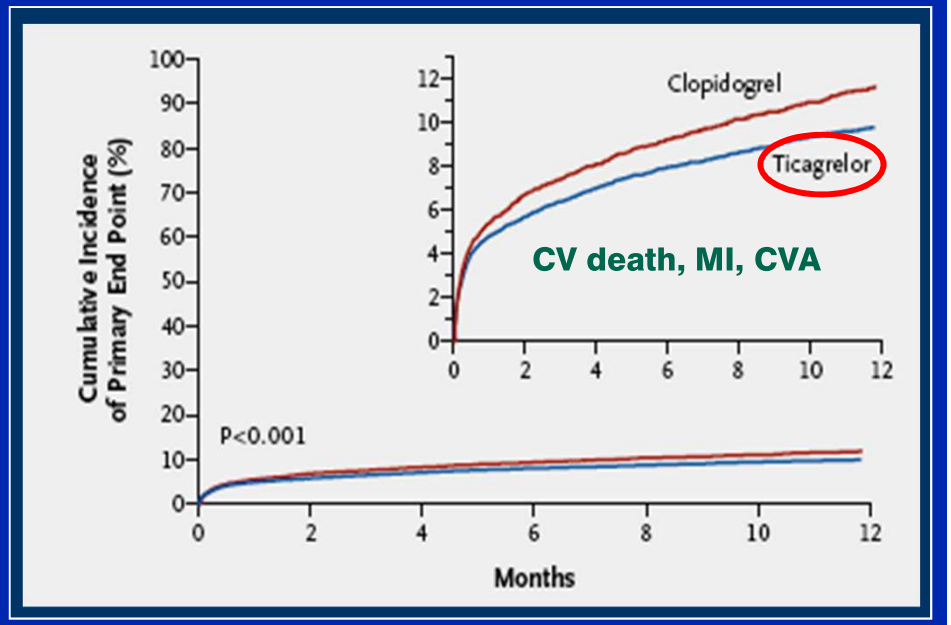
Oral Antiplatelets in Patients with Acute Coronary Syndromes

TRITON-TIMI 38
(Prasugrel vs Clopidogrel)



TRITON-TIMI 38. NEJM 2007; 357: 2001

PLATO
(Ticagrelor vs Clopidogrel)



Wallentin et al. NEJM 2009; August 30; on line

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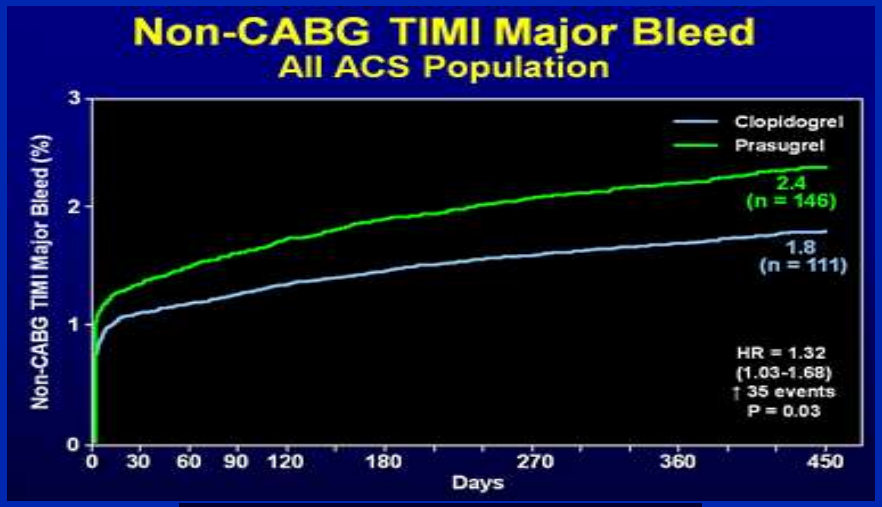
Non-CABG TIMI Major Bleeding

TRITON

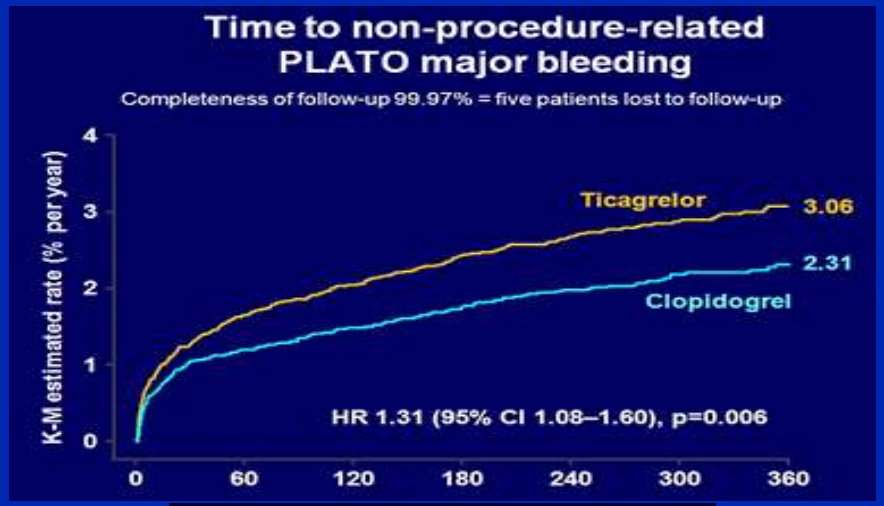


Prasugrel vs Clopidogrel

2.4% vs 1.8%

ARD 0.6%
HR 1.32
P=0.03
NNH=167

PLATO



Ticagrelor vs Clopidogrel

2.8% vs 2.2%

ARD 0.6%
HR 1.25
P=0.03
NNH=167

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- ¿Tratamientos mas prolongados (>1 año)?

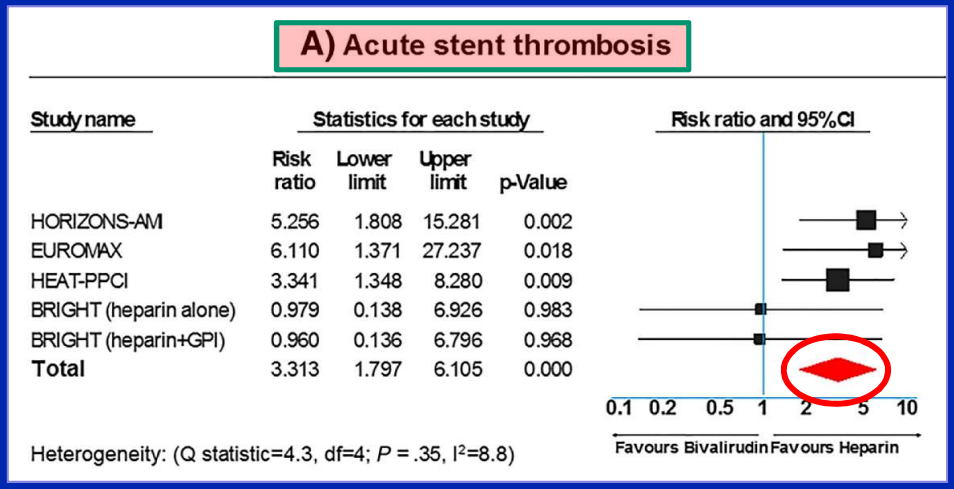
Recommendations for Anticoagulation in STEMI

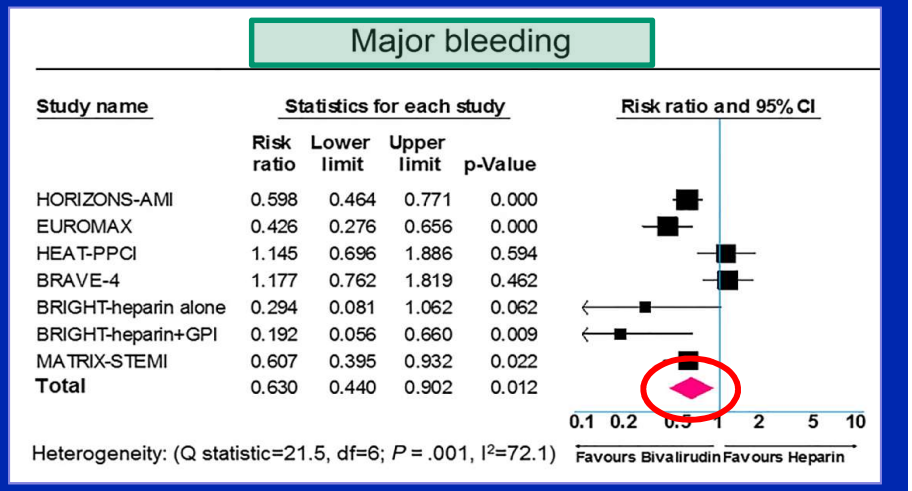
ACC/AHA and ESC Guidelines

	UFH	Enoxaparin	Fondaparinux	Bivalirudin
STEMI				
ESC 2014	I	IIa	III	IIa
ACC/AHA 2013	I	Not mentioned	III	I

Zeymer U, et al. EHJ 2016; 37: 3376

Meta-Analysis of Bivalirudin vs Heparin in PPCI





Compared with heparin, bivalirudin increases the risk of stent thrombosis, but decrease the risk of bleeding.

The benefit in bleeding is modulated by the administration of P2Y12 inhibitors, using radial access, and avoiding routine GPI.

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Shah R, et al. AHJ 2016; 171: 14

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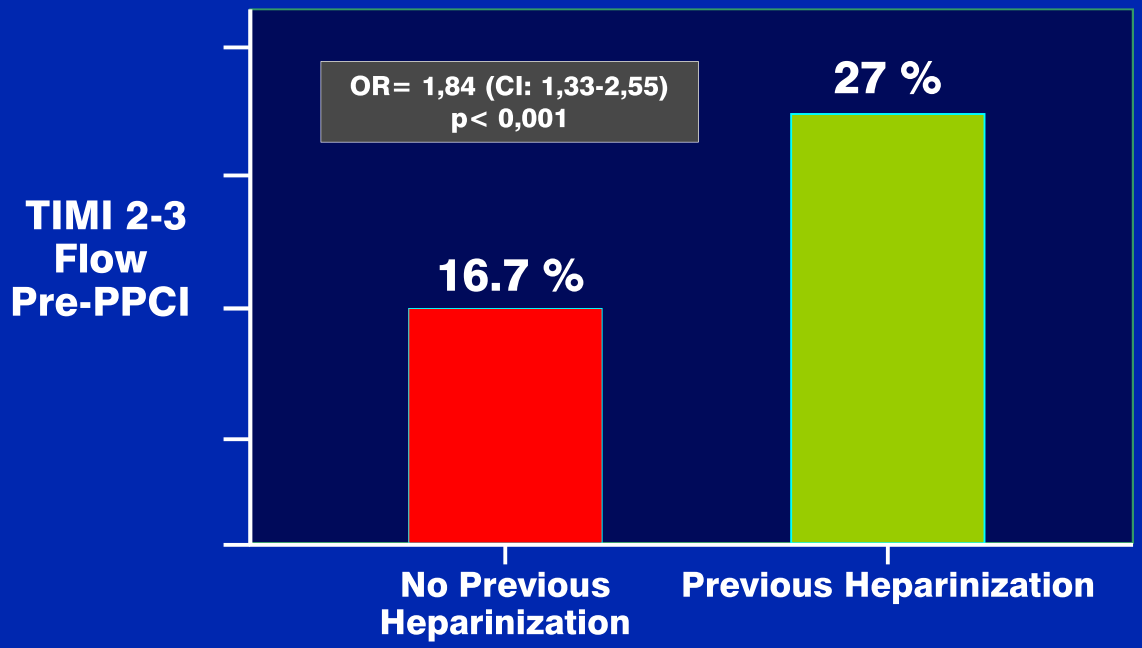
Early Anticoagulation Improve Preprocedural Patency of the IRA in PPCI

- 1075 ptes with STEMI and Primary Angioplasty indication
- 623 ptes received UFH at the time of the diagnosis (0,75-1 mg/kg iv)
- 452 ptes no previous heparinization before the procedure

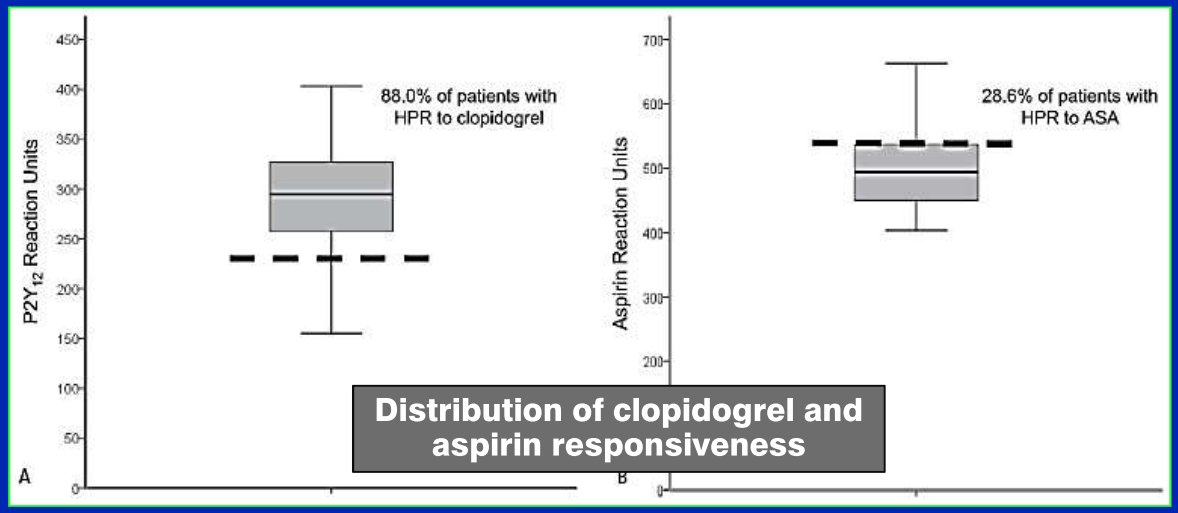


Conclusions: In ptes with STEMI, early administration of UFH at the time of the diagnosis, is associated with improvement in the permeability in the IRA immediately pre-PPCI.

Ariza A, Cequier A, et al. REC 2013; 66: 145

Clopidogrel Pre-Treatment in PPCI

High on-treatment platelet reactivity (HPR)
Mean time of clopidogrel pre-treatment: 85 m.



Distribution of clopidogrel and aspirin responsiveness

Conclusions: **A high percentage of STEMI patients have inadequate levels of clopidogrel-induced platelet inhibition.**

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Ferreiro JL, Cequier A, et al. Thromb and Haemost 2013; 110: 110.

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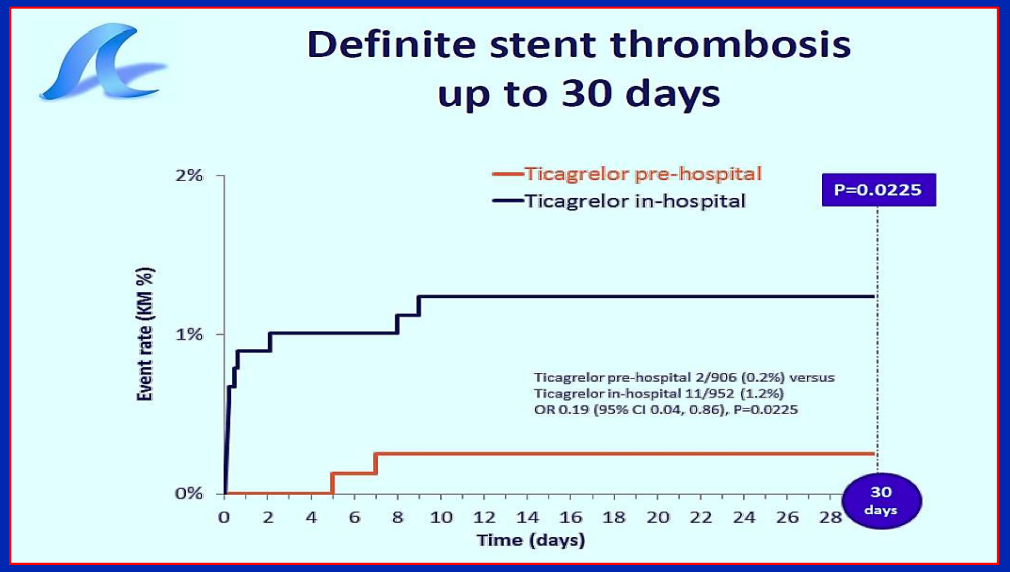
Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction

ATLANTIC Trial

1862 ptes with STEMI < 6 hrs with PPCI indication.

Randomized to prehospital (ambulance) vs in-hospital (cath lab) ticagrelor



Conclusions: **Prehospital ticagrelor in STEMI is safe, did not improve pre-PCI coronary perfusion but reduce the incidence of acute stent thrombosis.**

Montalescot G, Cequier A, et al. NEJM 2014; September 1, 2014, on line.

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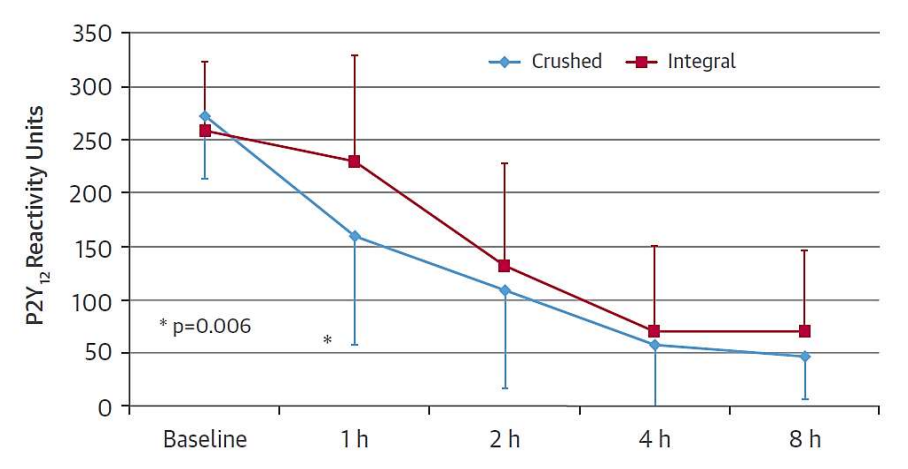
Crushed Tablet Administration in STEMI

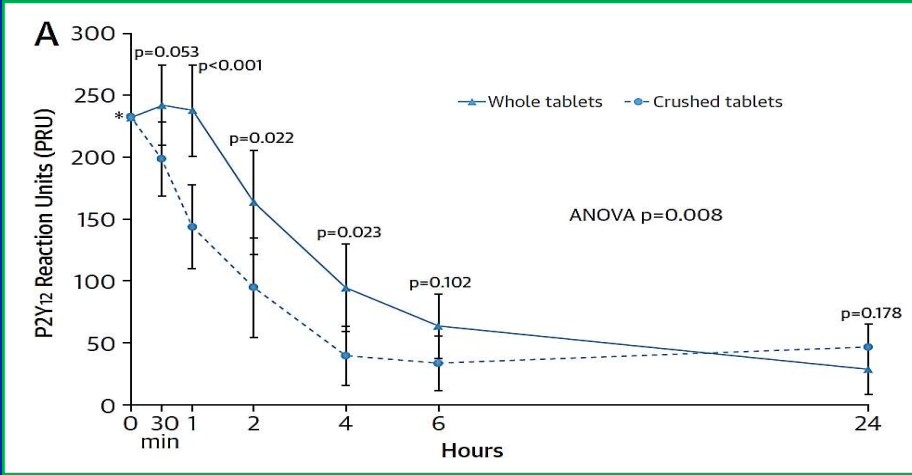
The MOJITO Study (Ticagrelor)



Platelet inhibition with Ticagrelor

Parodi G, et al. JACC 2015; 65: 511

The CRUSH Study (Prasugrel)



Platelet inhibition with Prasugrel

Rollini F, et al. JACC 2016; 67: 1994

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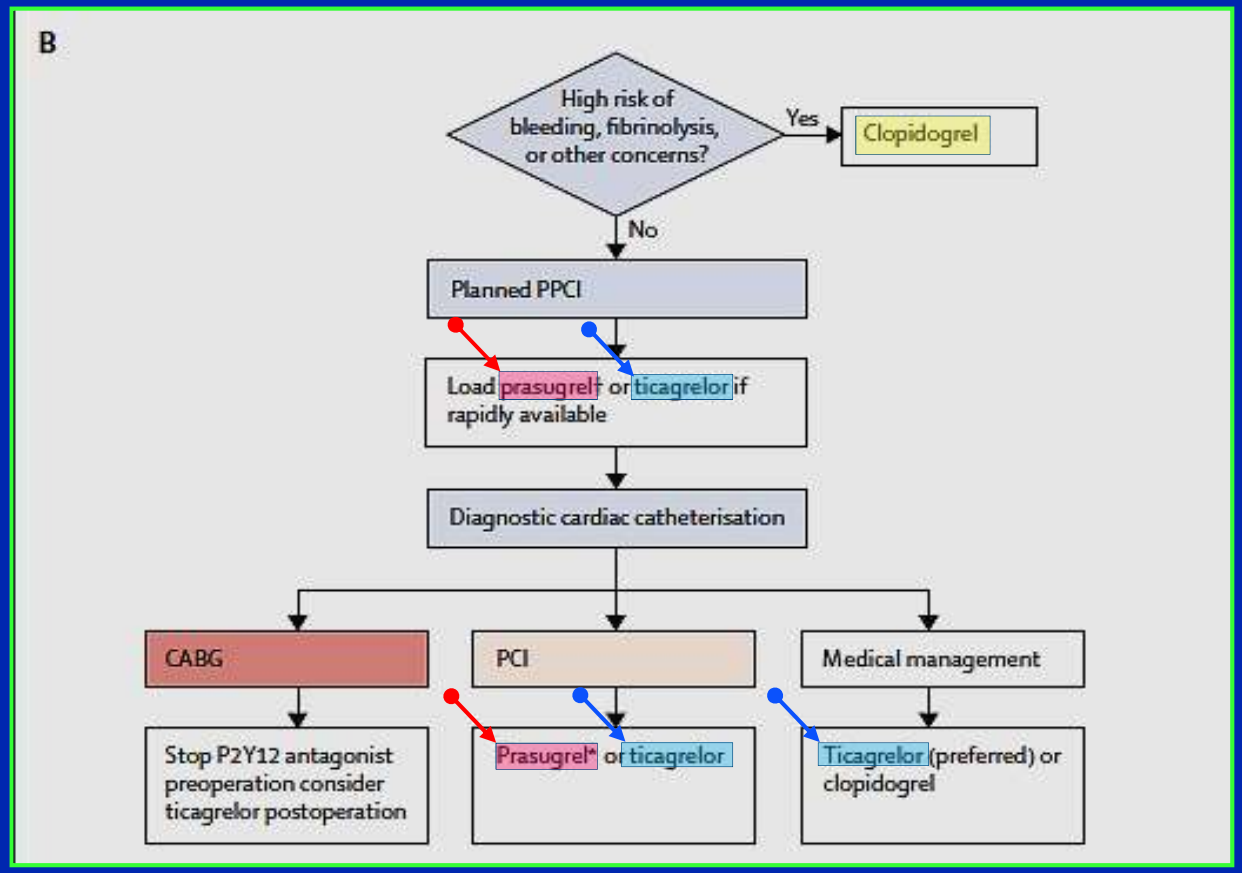
Choice of P2Y12 Antagonist in ACS based on European and US Guidelines

STEMI



Wiviott SD, Steg PG. Lancet 2015, March 14

Integrating Treatment in ACS

Primary PCI in STEMI

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Pre-PPCI:

ASA + Clopidogrel / Prasugrel / Ticagrelor
+
UFH / LMWH

Per-PPCI:

High-Risk Patient

- High Bleeding Risk → Bivalirudin
- Acute stent thrombosis / Large thrombus burden / No reflow → IIb/IIIa Inhibitors

Low-Risk Patient

¿Catheter aspiration? (+++thrombus burden)
Preferably DES (especially in LAD)

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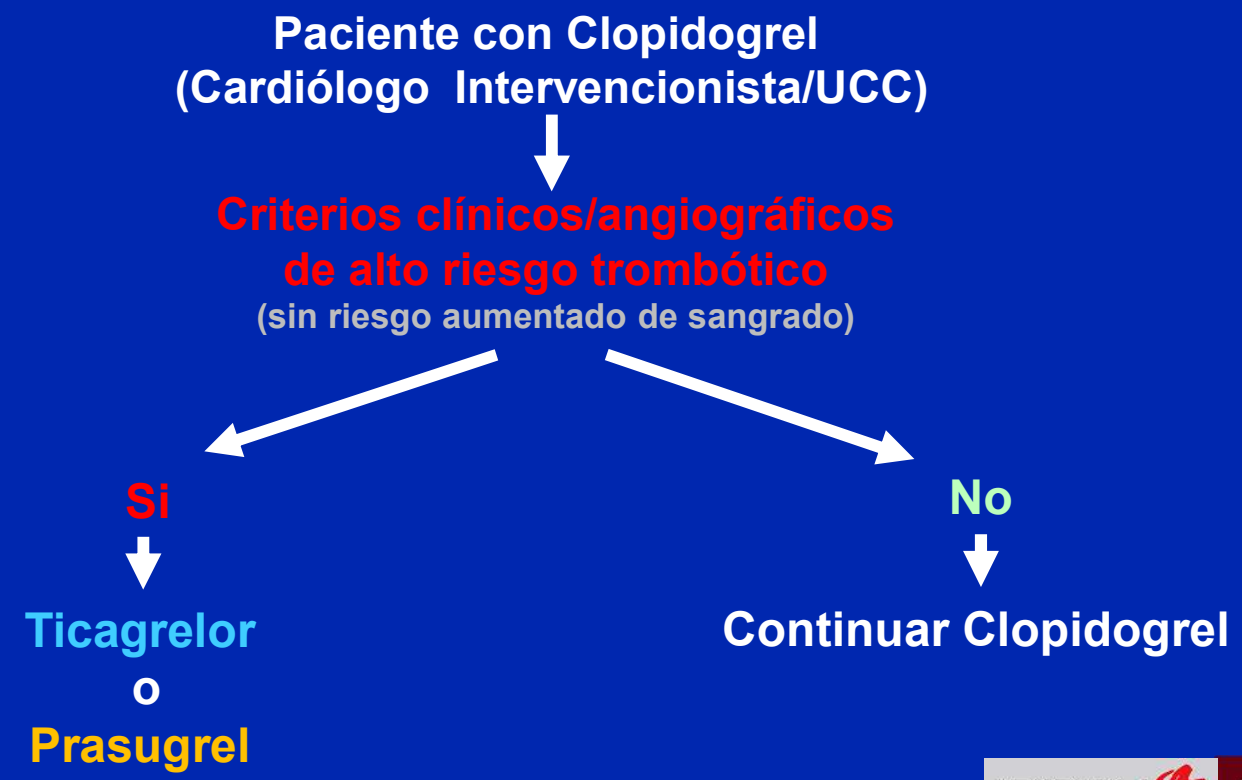
Conversión de Clopidogrel a un Tratamiento Antiplaquetario mas Potente



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Conversión de Clopidogrel a un Tratamiento Antiplaquetario mas Potente

Criterios de Alto Riesgo Trombótico

Escenario ICP Primario

Primeras horas

Criterios Clínicos

- IAM por trombosis stent
- Territorio de la ARI +++
- IAM extenso por ECG
- No resolución ST al abrir la ARI
- IAM de alto riesgo (Killip ≥2)

Criterios Angiográficos

- Trombo residual importante
- TIMI flow final < 3
- Disección residual no cubierta
- Stent en el TC
- Longitud stent +++, Ø<2.5 mm

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- ¿Tratamientos mas prolongados (>1 año)?

Recommendations for Anticoagulation in NSTE-ACS

ACC/AHA and ESC Guidelines

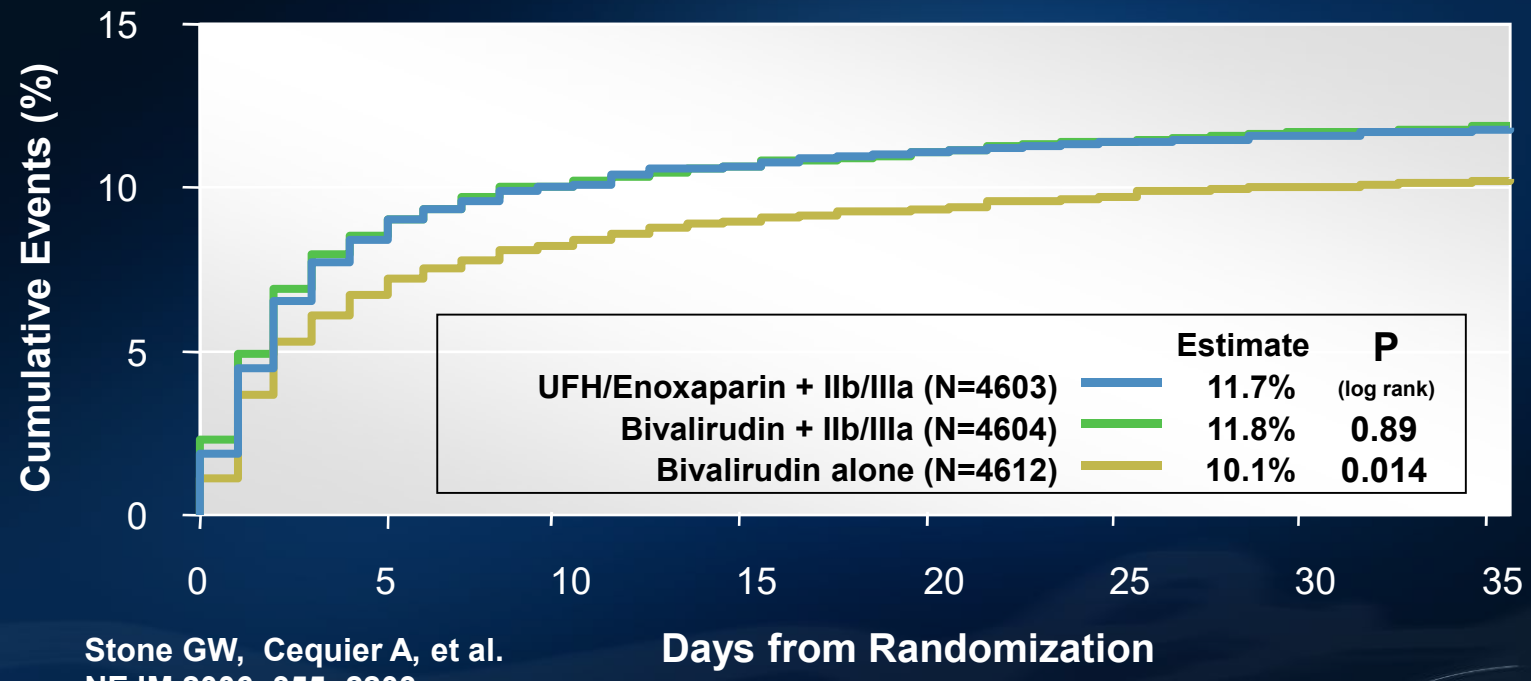
	UFH	Enoxaparin	Fondaparinux	Bivalirudin
NSTE-ACS				
ESC 2015	I (in patients who cannot receive bivalirudin)	IIa (in patients pre-treated with enoxaparin)	I (if used additional UFH during PCI)	I
ACC/AHA 2014	I	IIb (in patients pre-treated with enoxaparin)	III as sole anticoagulant during PCI	I

Zeymer U, et al. EHJ 2016; 37: 3376

Bivalirudin for Patients With Acute Coronary Syndrome

Net Clinical Outcome

(Ischemia or Major Bleeding)



Stone GW, Cequier A, et al.
NEJM 2006; 355; 2203

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ACUITY

ACCOAST Trial

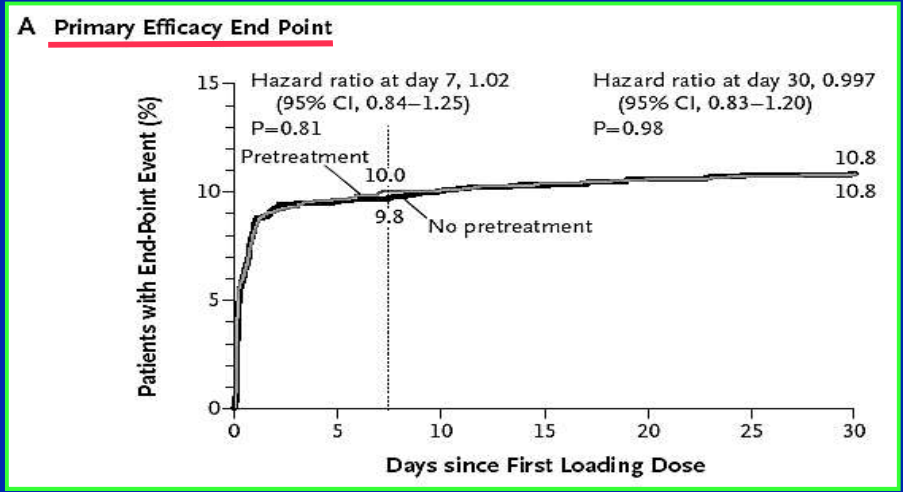
Pretreatment with Prasugrel in Non-ST-Segment Elevation ACS

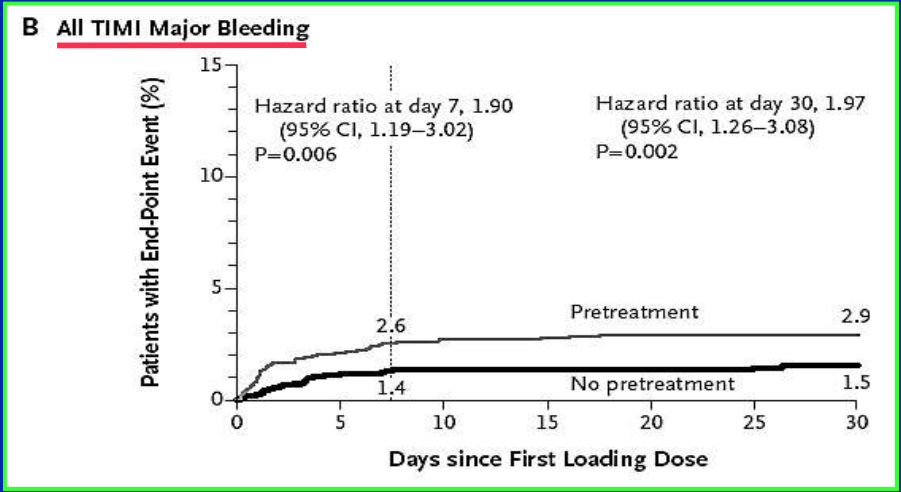
n= 4033 pts, ACS and + troponin and angiography 2-48 hrs after randomization.

Primary endpoint: Composite of death, MI, stroke, urgent revasc and rescue IIb/IIIa inhibitors.

Pretreatment: prasugrel 30 mg pre-angiography + prasugrel 30 mg with PCI

Control group: placebo pre-angiography + prasugrel 60 mg with PCI





Conclusion: In ptes with NSTE ACS, pretreatment with prasugrel did not reduce the rate of major ischemic events but increased the rate of major bleeding complications.

Montalescot G et al. NEJM 2013; 369: 999

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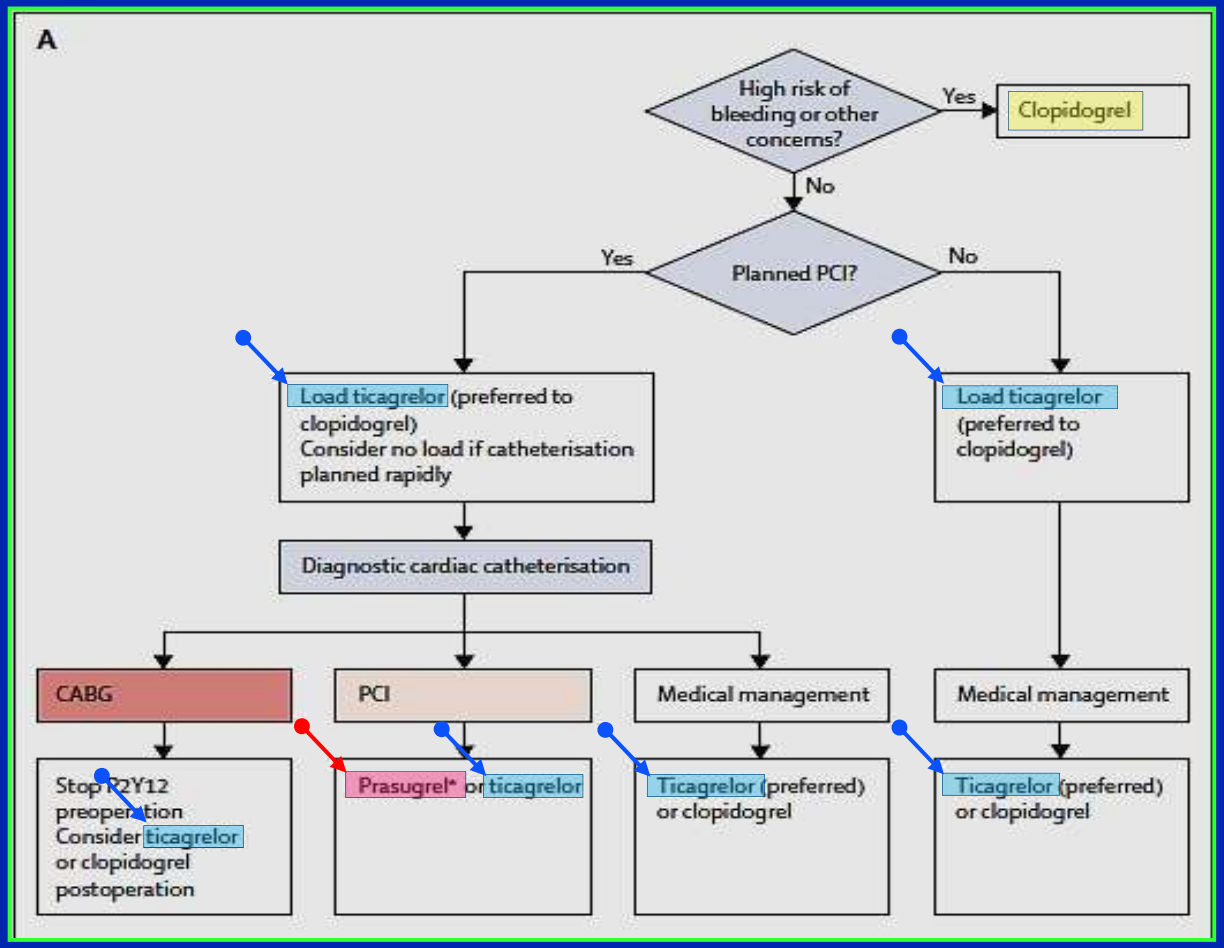
Ticagrelor vs Clopidogrel in ACS Patients

PLATO Trial

Benefits of Ticagrelor were consistent in patients:

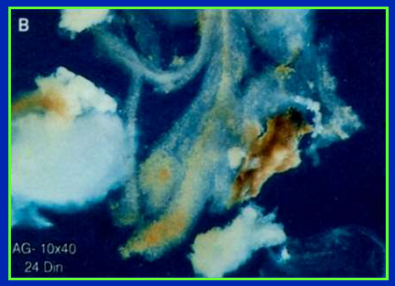
- With non-invasive management[1]
- With or without revascularization[2]
- In elderly[3]
- In women[4]
- With renal dysfunction[5]
- With history of stroke or TIA[6]

1- James SK, et al. BMJ 2011; 342: d3527
2- Lindholm D, et al. Eur Heart J 2014; April 11, on line
3- Husted S, et al. Circ CV Qual Out 2012; 5: 680
4- Husted S, et al. Eur Heart J 2014; March 28, on line
5- Montalescot G, Silvain J. Circulation 2010; 122: 1049
6- James SK, et al. Circulation 2012; 125: 2914



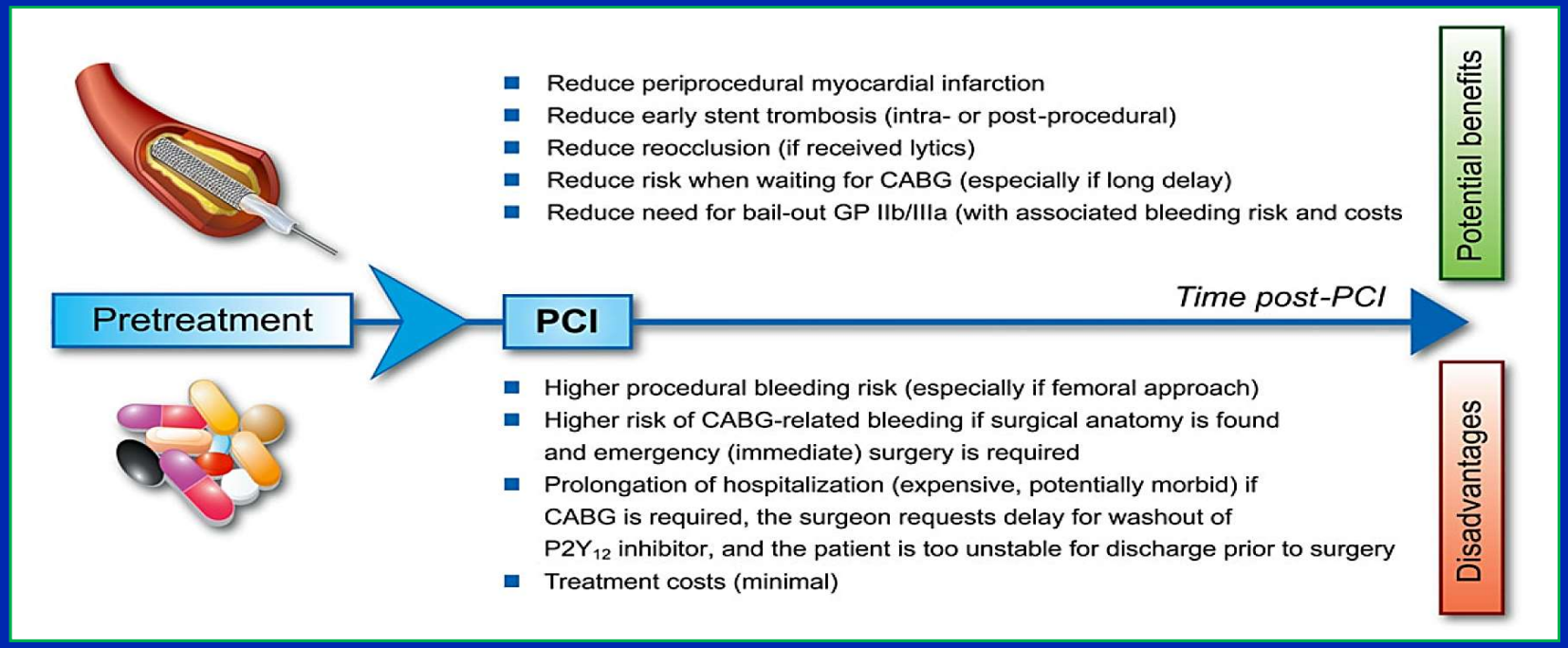
Choice of P2Y12 Antagonist in ACS based on European and US Guidelines

Unstable Angina /Non-STEMI



Wiviott SD, Steg PG. Lancet 2015, March 14

Pre-Treatment with $P2Y_{12}$ Inhibitors in ACS



Potential benefits and disadvantages of $P2Y_{12}$ pre-treatment

Sibbing D, et al. EHJ 2016; 37: 1284

Integrating Treatment in ACS

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Non ST-Elevation ACS
Invasive Strategy

Pre-PCI:

ASA + Clopidogrel / Ticagrelor
+
Enoxa / UFH

Intermediate risk

Angiography 24 – 48 hrs

High – risk

Early upstream IIb/IIIa* + UFH/Enoxa
+
Angiography < 24 hrs

*not preloaded with $P2Y_{12}$ inhibitors

Per-PCI:

Increased anatomic risk: Abciximab
DES vs BMS

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Conversión de Clopidogrel a un Tratamiento Antiplaquetario mas Potente (Ticagrelor)

Criterios de Alto Riesgo Trombótico

Escenario SCASEST

Primeras 24-48 hrs

Criterios Clínicos

- Diabetes Mellitus
- Antecedentes IAM otro territorio
- Troponinas +++
- Cambios dinámicos ST/T
- GRACE > 140
- Angina post- IAM
- ICP reciente /CABG previa

Criterios Angiográficos

- Trombo residual
- Disección residual no cubierta
- Stent en el TC/territ. hipocinetico
- Dudas expansión/aposición stents
- Longitud stent +++, Ø<2.5 mm
- Enfermedad coronaria extensa
- Carga aterosclerotica +++

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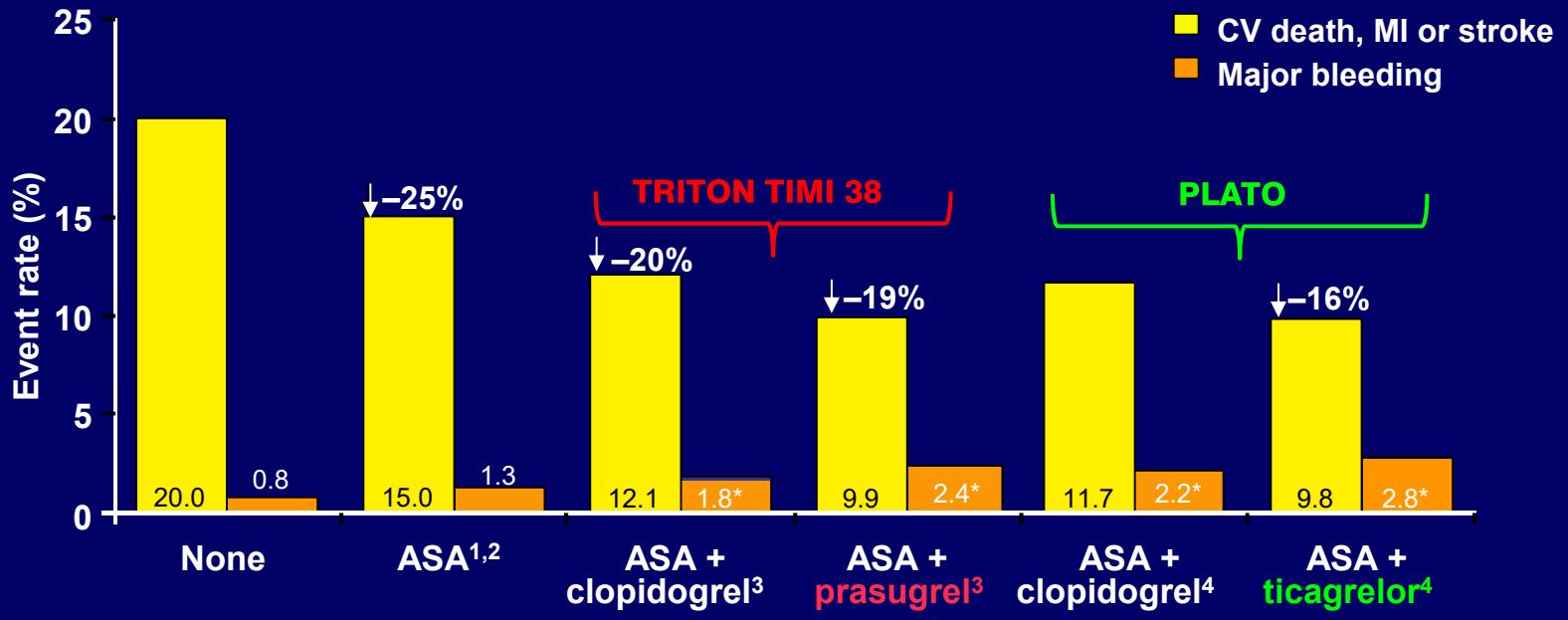
Secondary Prevention in ACS

1 year after an initial ischemic event, the incidence of a new CV event (death, MI or CVA) is ~10%



*Major bleeding: non-CABG-related TIMI major bleeding

1. Antiplatelet Trialists' Collaboration, 1994; 2. Antithrombotic Trialists' Collaboration, 2002; 3. Wiviott *et al*, 2007; 4. Wallentin *et al*, 2009

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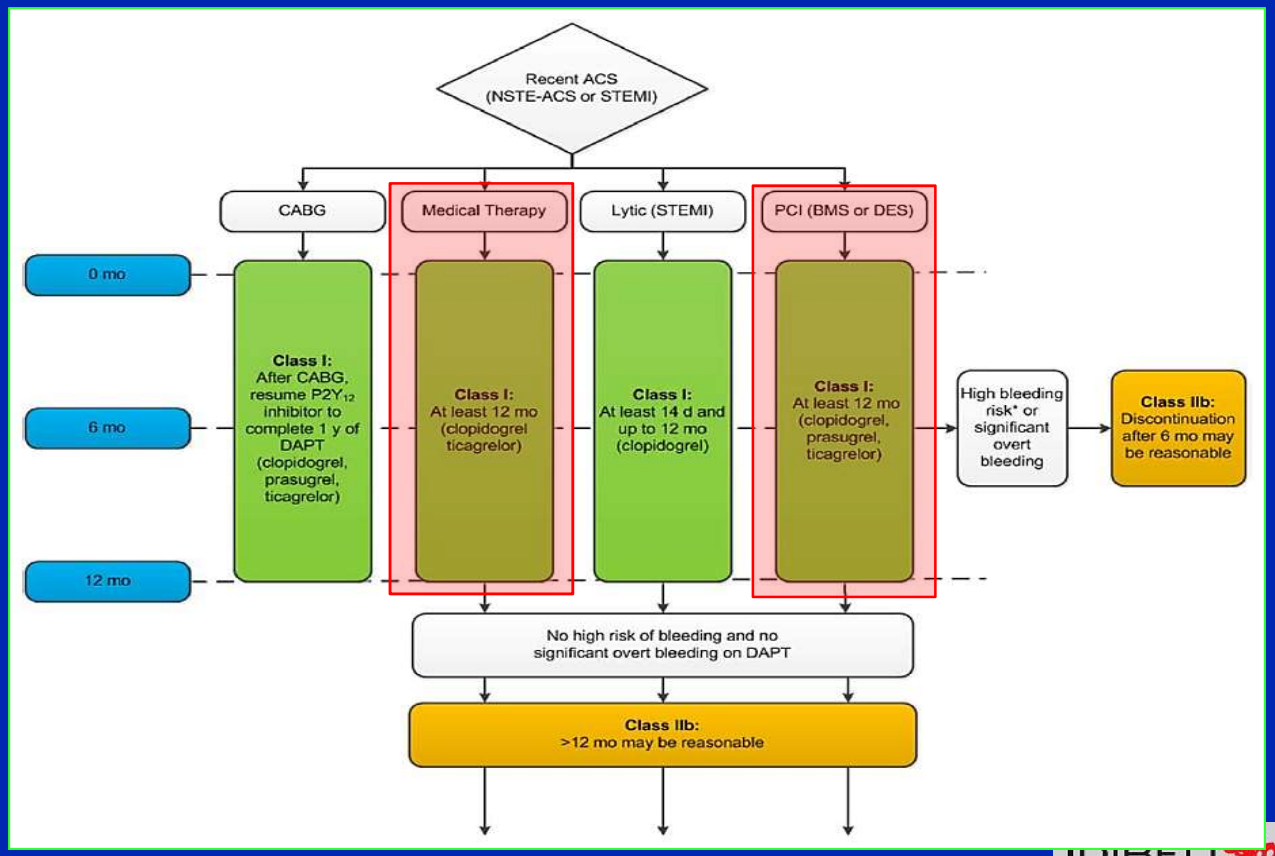
2016 ACC/AHA Guideline Focused Update on Duration of DAPT

Treatment Algorithm for Duration of P2Y12 Inhibitor Therapy in Patients With Recent ACS (NSTE-ACS or STEMI)



Levine GN, et al.
JACC & Circulation
2016

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WHAT DO THE ESC GUIDELINES SAY?

2014 ESC- Revascularization Guidelines STEMI/NSTEACS

A $P2Y_{12}$ inhibitor is recommended in addition to ASA and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A

2016 ESC- NSTE-ACS Guidelines

A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A
$P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk.	IIb	A
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient.	IIb	A

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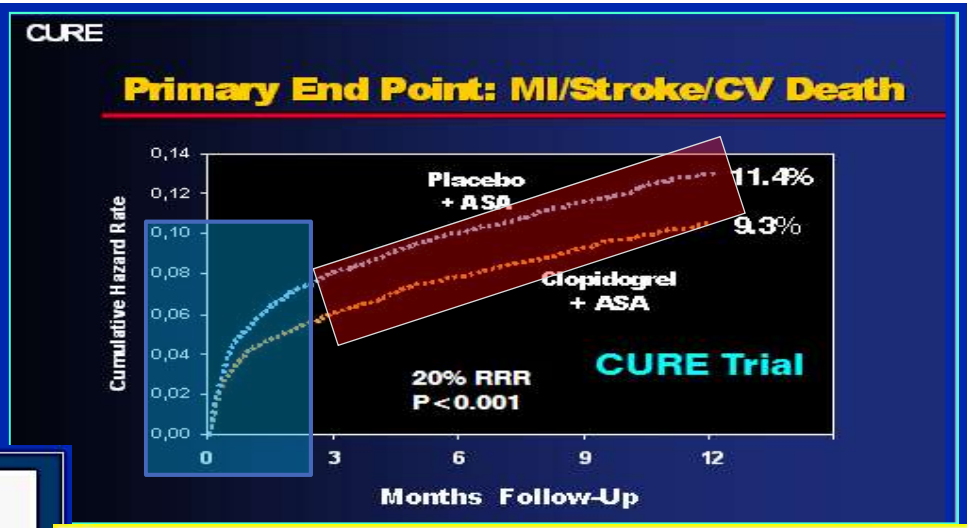
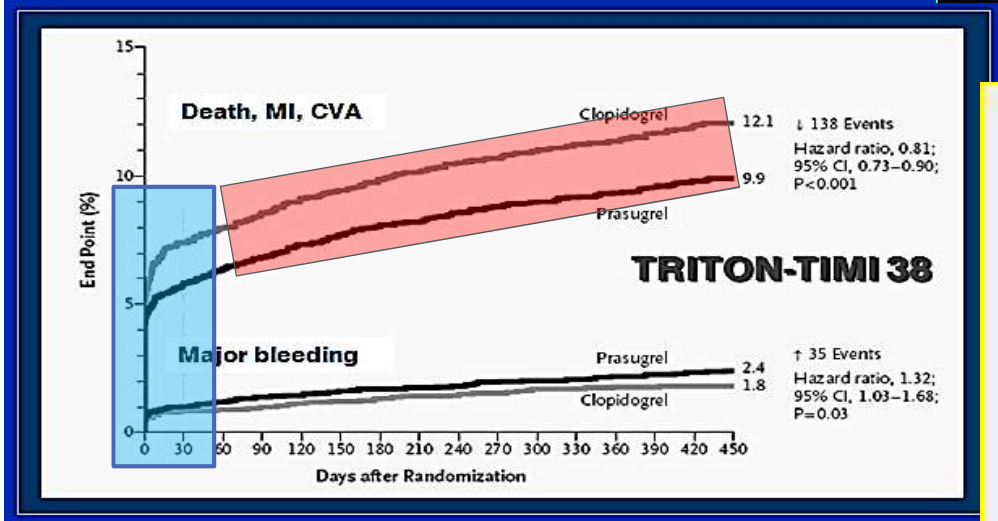
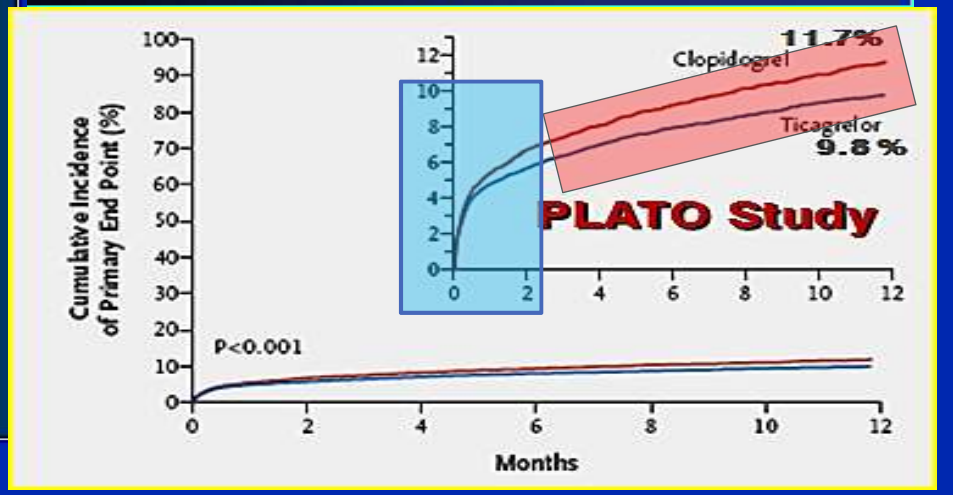
Oral Antiplatelets Inhibitors Post-ACS

Long-Term Treatment







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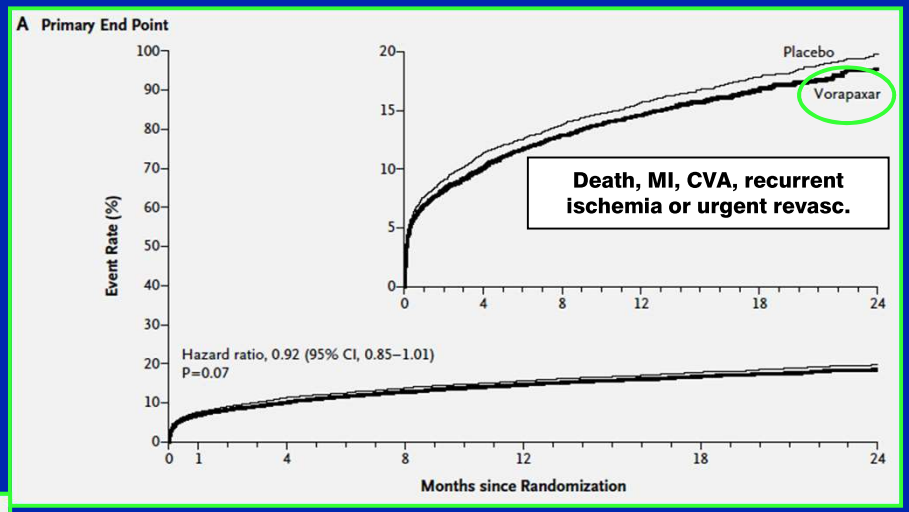
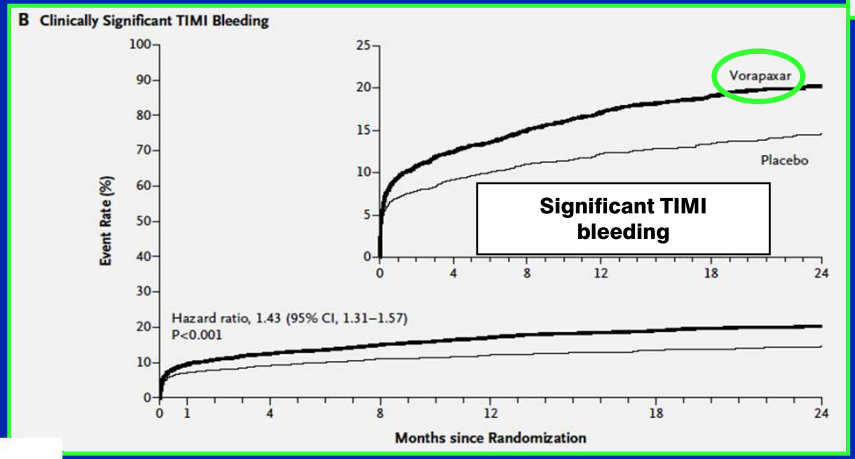
Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes

TRA-CER Trial

- 12.944 pts with moderate-to-high-risk NSTEACS. Standard of care based on practical guidelines.
- Randomized Vorapaxar vs Placebo.
- ASA + Clopidogrel: 92 %; PCI: 58 %.
- Trial terminated after a safety review.





Conclusions

The addition of vorapaxar to standard therapy did not reduce the primary end-point and increased the risk of major bleeding.

Tricoci P, Cequier A, et al. NEJM 2012; 366:20

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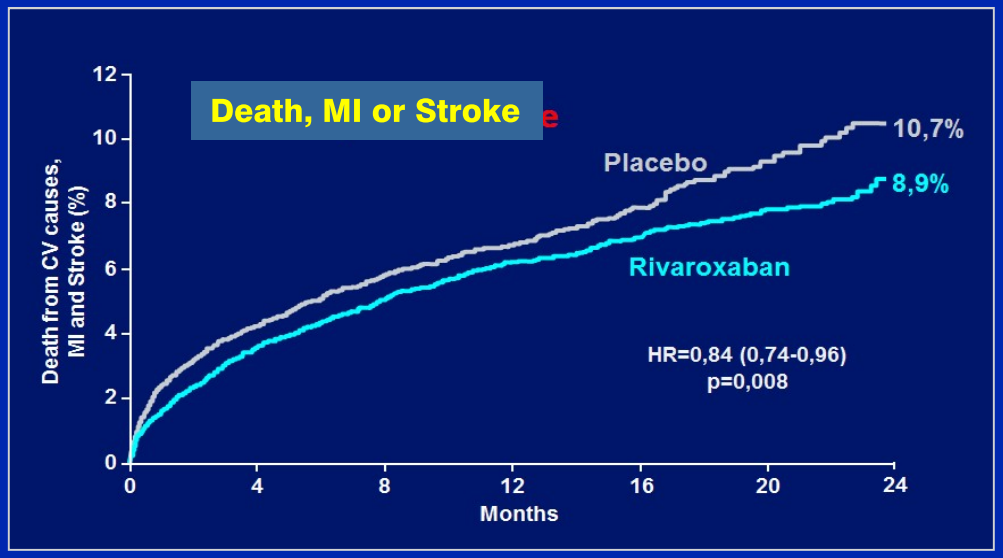
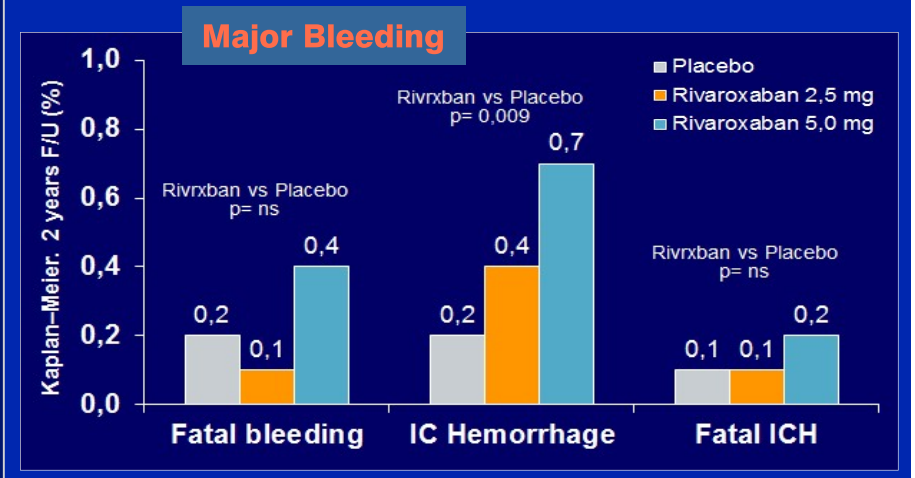
Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

ATLAS ACS 2-TIMI 51 Trial

Mega JL et al. NEJM 2012; 366: 9

- 15.526 pts with a recent ACS < 7 d. Standard of care based on practical guidelines.
93% with AAS + thienopyridine. / Randomized Rivaroxaban (2.5 mg or 5 mg, bid) vs Placebo. /
Mean F/U: 13 months. / Primary end-point: CV death , MI or stroke.





Rivaroxaban reduce the risk of ischemic events. Rivaroxaban increased the risk of intracranial hemorrhage but not the risk of fatal bleeding. The 2,5 mg dose resulted in fewer fatal bleeding events than the 5 mg dose.

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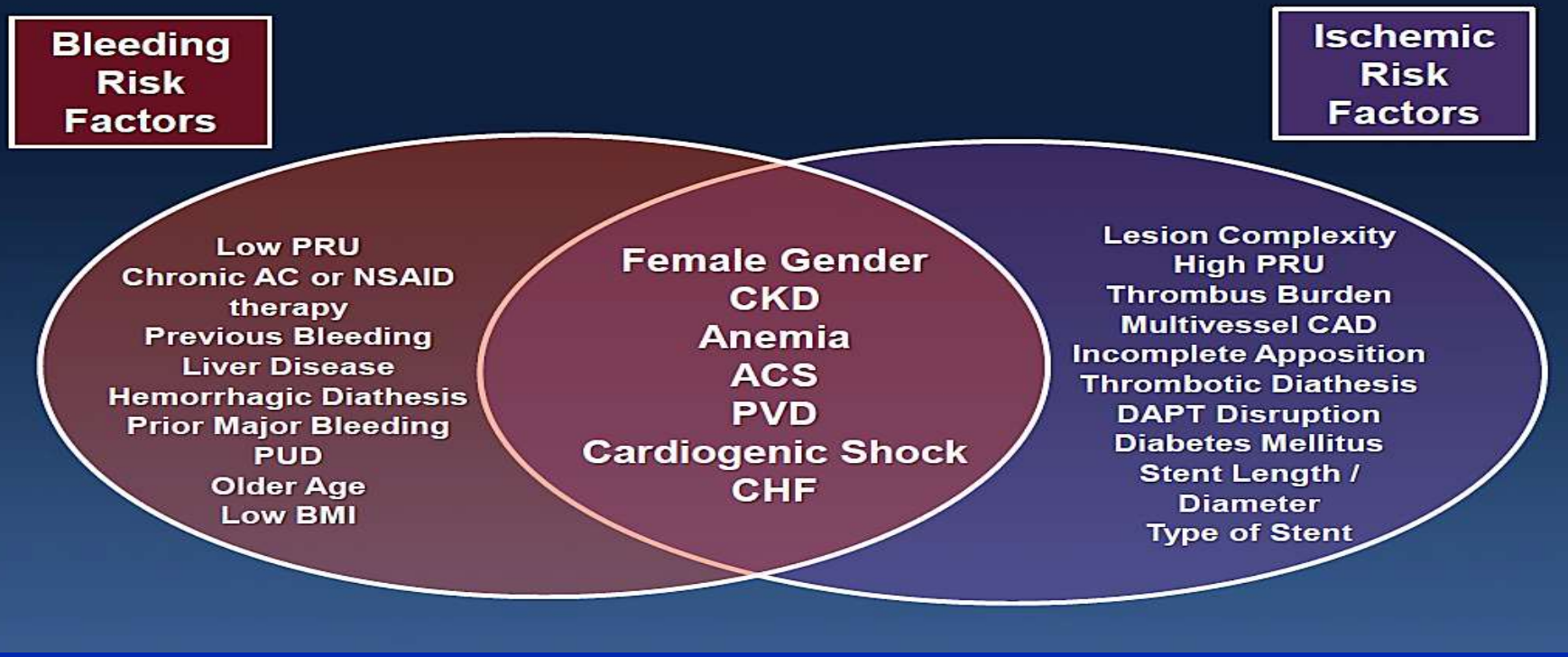
Overlap Between Bleeding and Ischemic Risk Clinical Factors

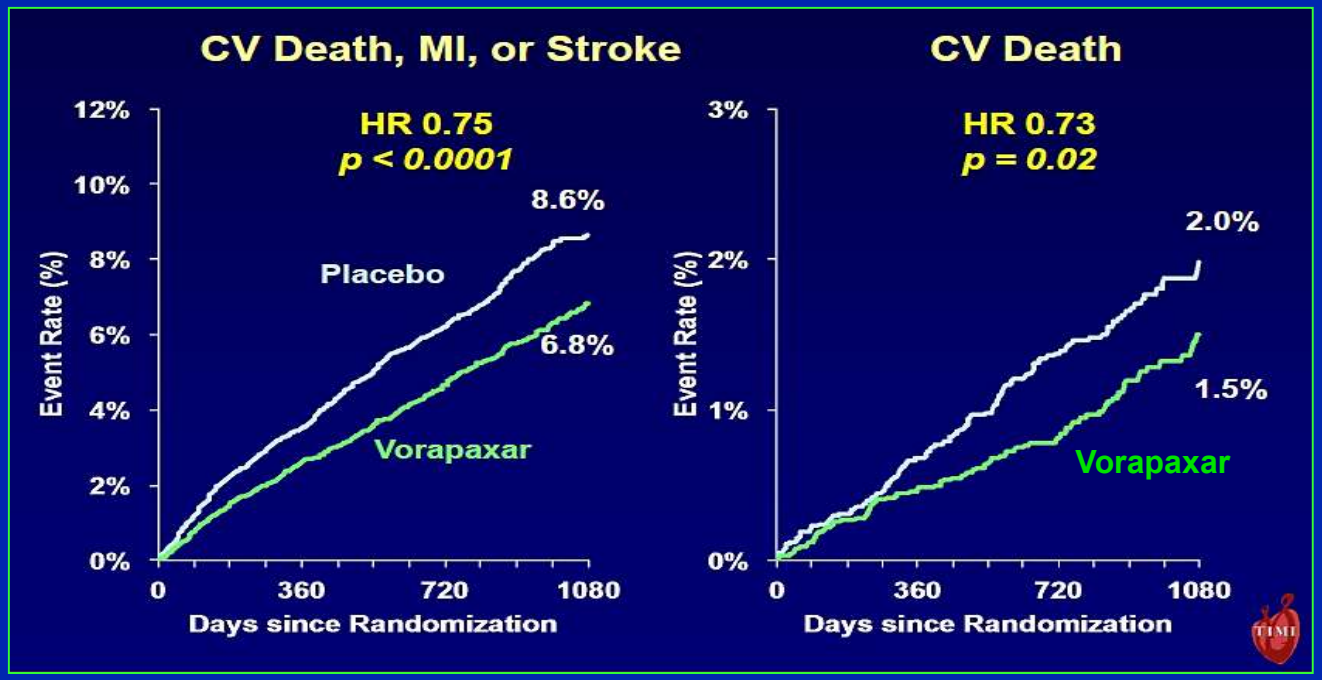


Vorapaxar for Secondary Prevention of Thrombotic Events for Patients with Previous MI

TRA 2ºP-TIMI 50 Trial

Subgroup with previous MI (78% with DAPT)

Low Bleeding Risk Cohort



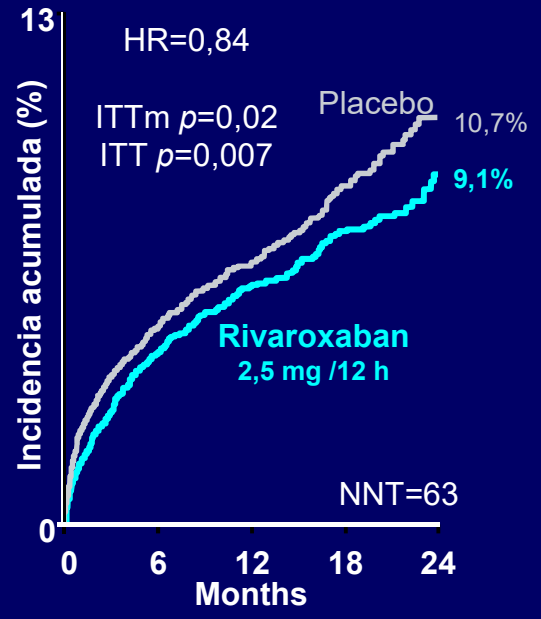
Scirica BM, et al. Lancet 2012; 380: 1317

Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

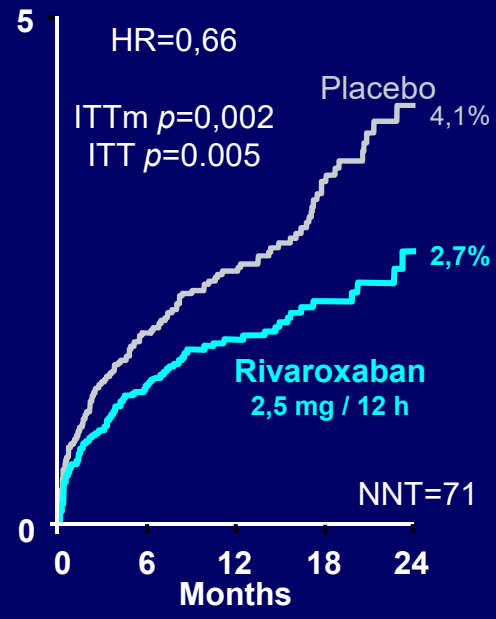
ATLAS ACS 2-TIMI 51 Trial

Rivaroxaban, 2,5 mg BID (93% con AAS + Thienopyridine)

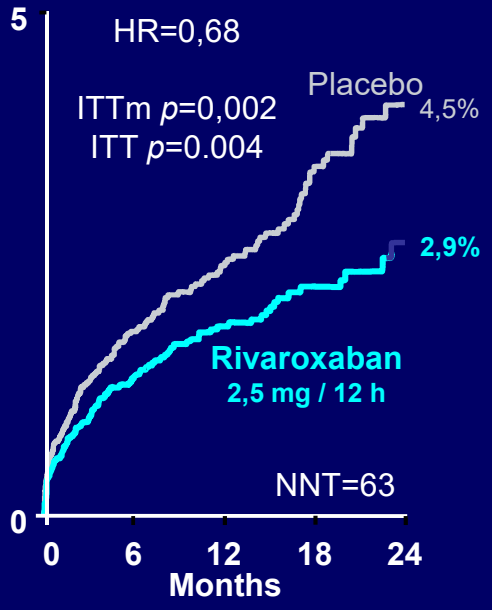
CV Death / MI / Stroke



CV Death



Death from any cause



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Mega JL *et al*, NEJM 2012; 366: 9

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Tratamiento Antitrombótico en los Síndromes Coronarios Agudos

1.- Escenario fisiopatológico común

2.- Tratamiento inicial

- SCA Con Elevación del ST
- SCA Sin Elevación del ST

3.- Tratamiento antitrombótico a largo plazo

- En Prevención Secundaria
- Post-implantación de stents
- ¿Tratamientos mas prolongados (>1 año)?

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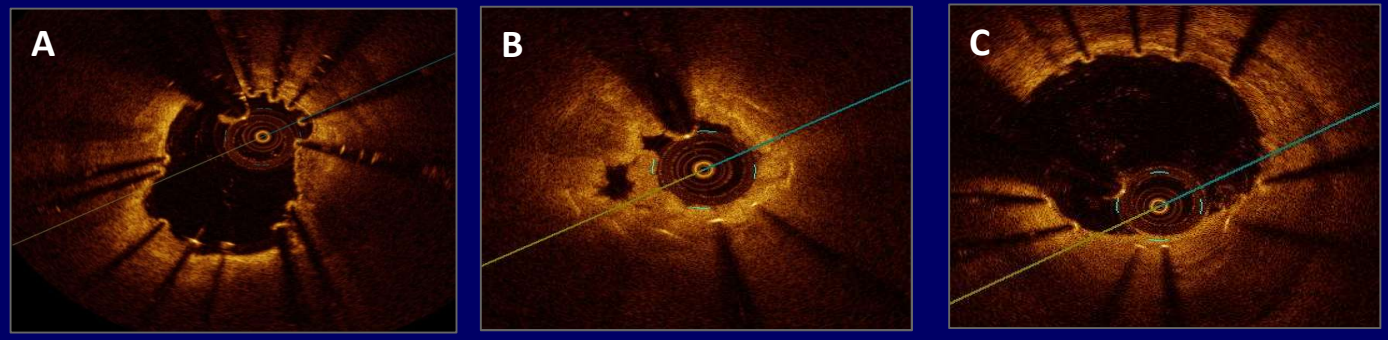
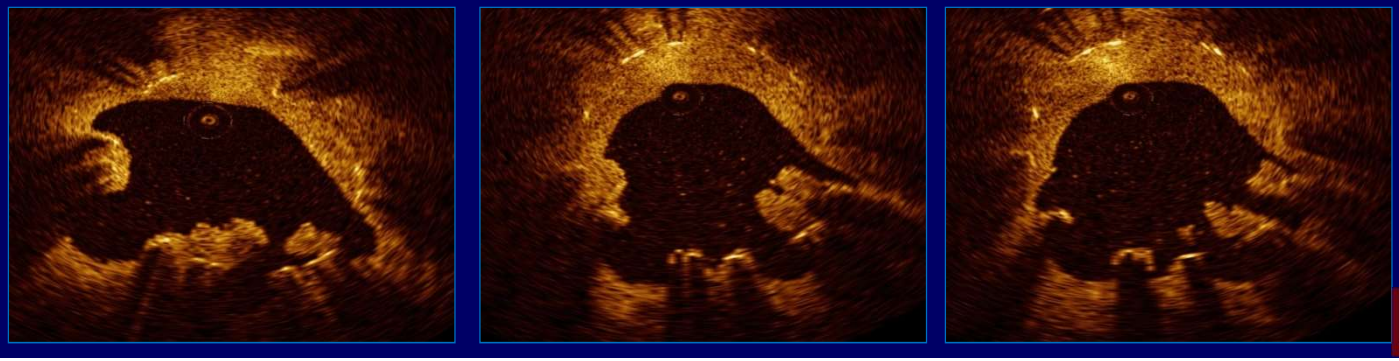
Stent Thrombosis

Patient 1.- Late Stent Thrombosis.
9 months after implantation



Patient 2.- Very Late Stent Thrombosis.
29 months after implantation



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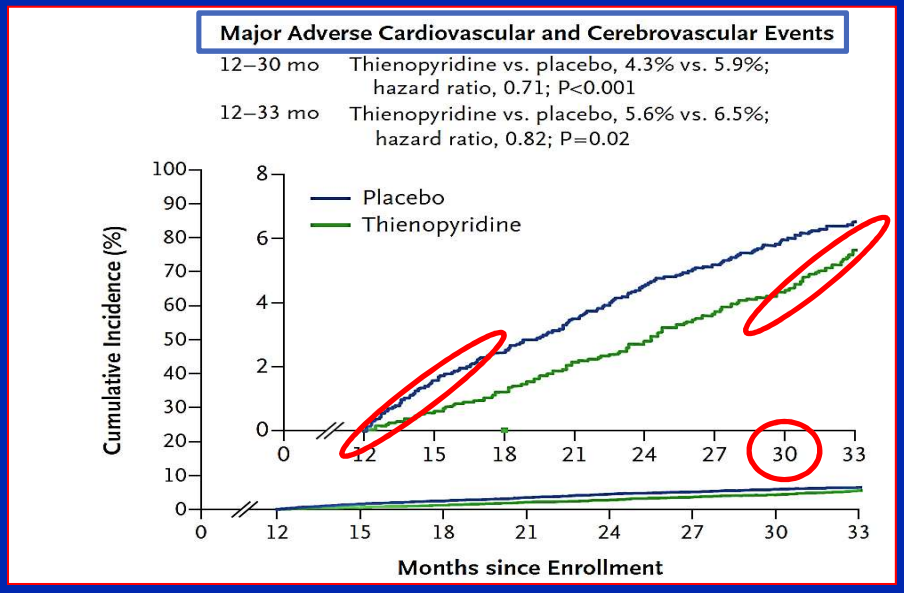
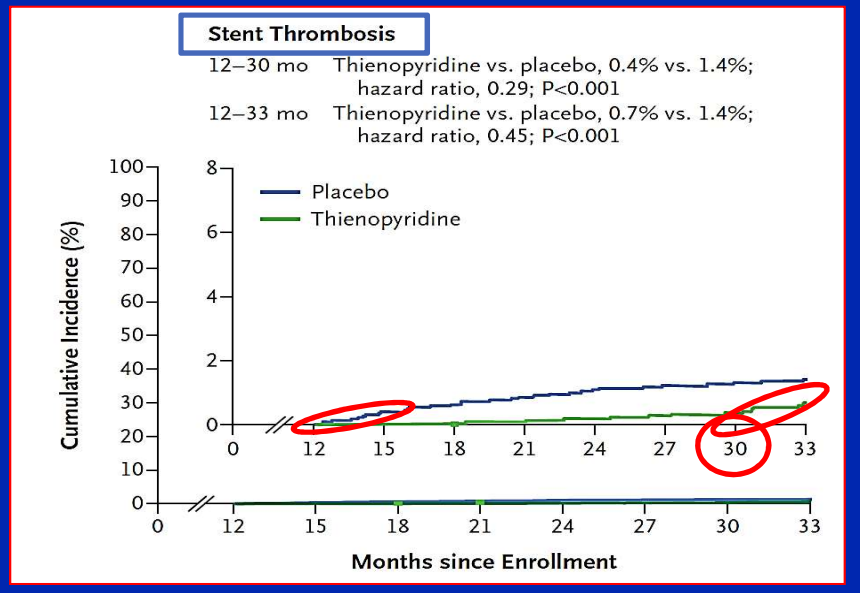
12 or 30 Months of Dual Antiplatelet Therapy after DES

DAPT STUDY

- 9961 ptes 12 months after DES treated with AAS+Clopi/Prasu.
- Randomized to continued DAPT or receive placebo.





Conclusions: DAPT beyond 1 yr after DES, as compared with AAS alone, significantly reduced the risk of stent thrombosis and MACE but with an increase of risk of bleeding.

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Mauri L, et al. NEJM 2014; November 16, on line

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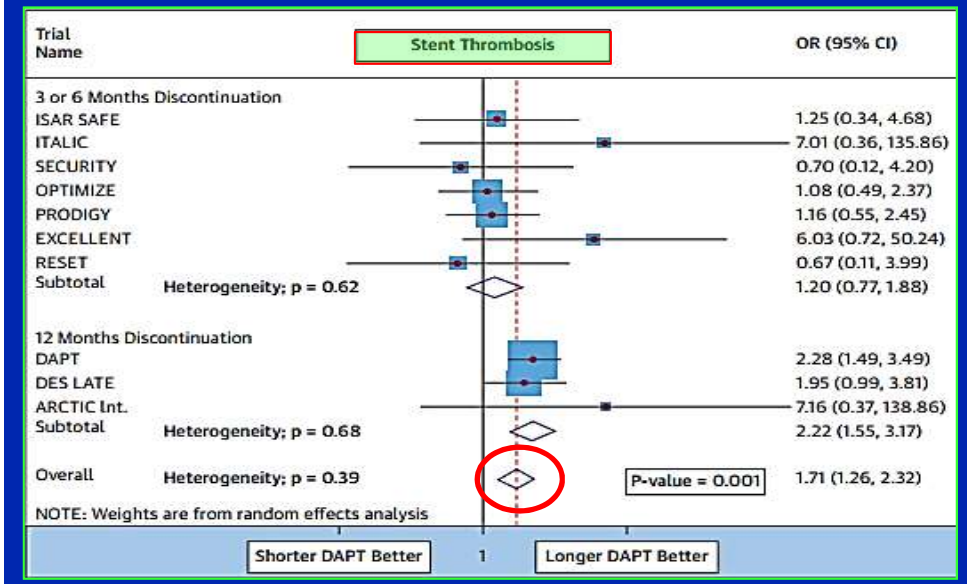
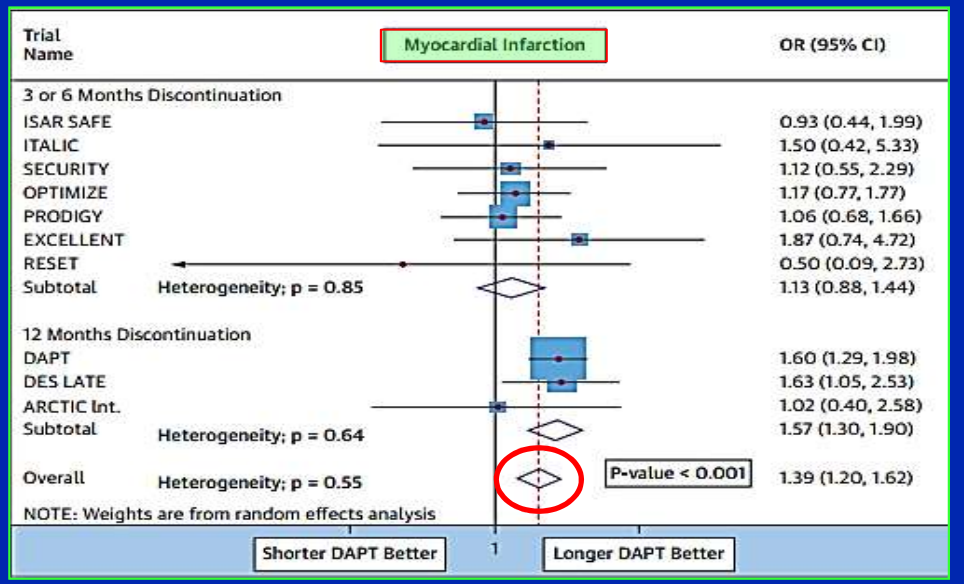
Longer DAPT is Associated with Lower Risk of Stent Thrombosis and Myocardial Infarction

A Systematic Review and Meta-Analysis of RC Trials





Giustino G, et al. JACC 2015; 65: 1298

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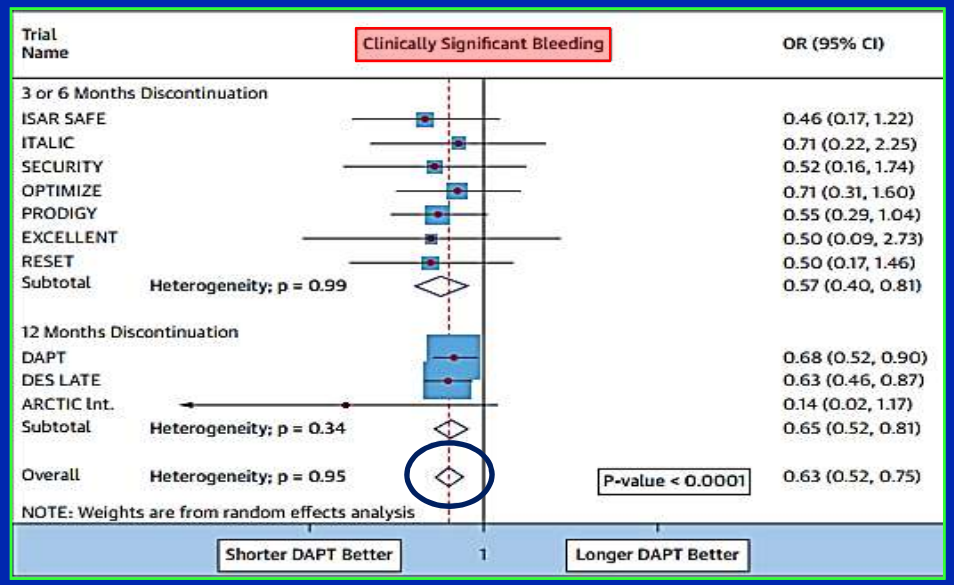
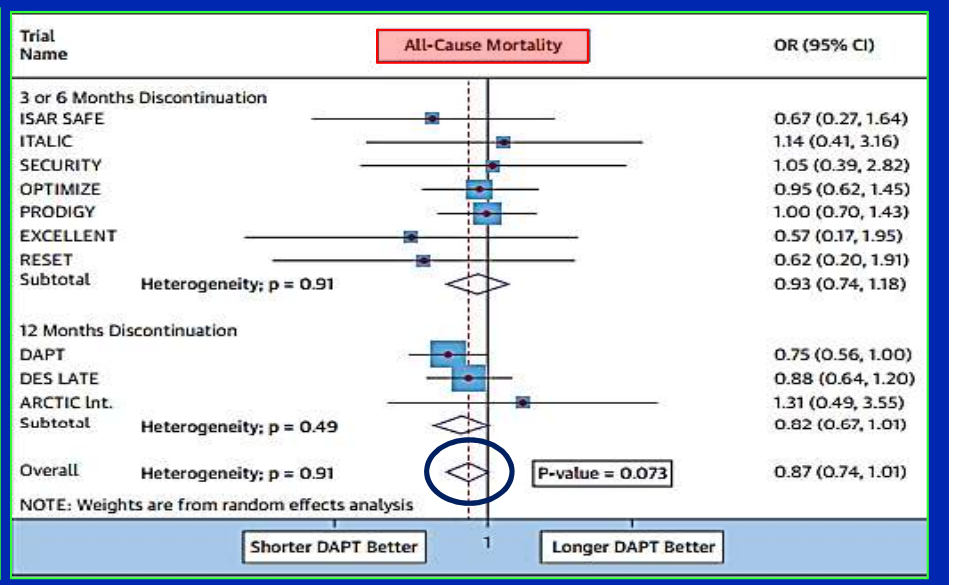
Shorter DAPT is Associated with Lower Risk of Clinically Significant Bleeding and All-Cause Mortality

A Systematic Review and Meta-Analysis of RC Trials





Giustino G, et al. JACC 2015; 65: 1298

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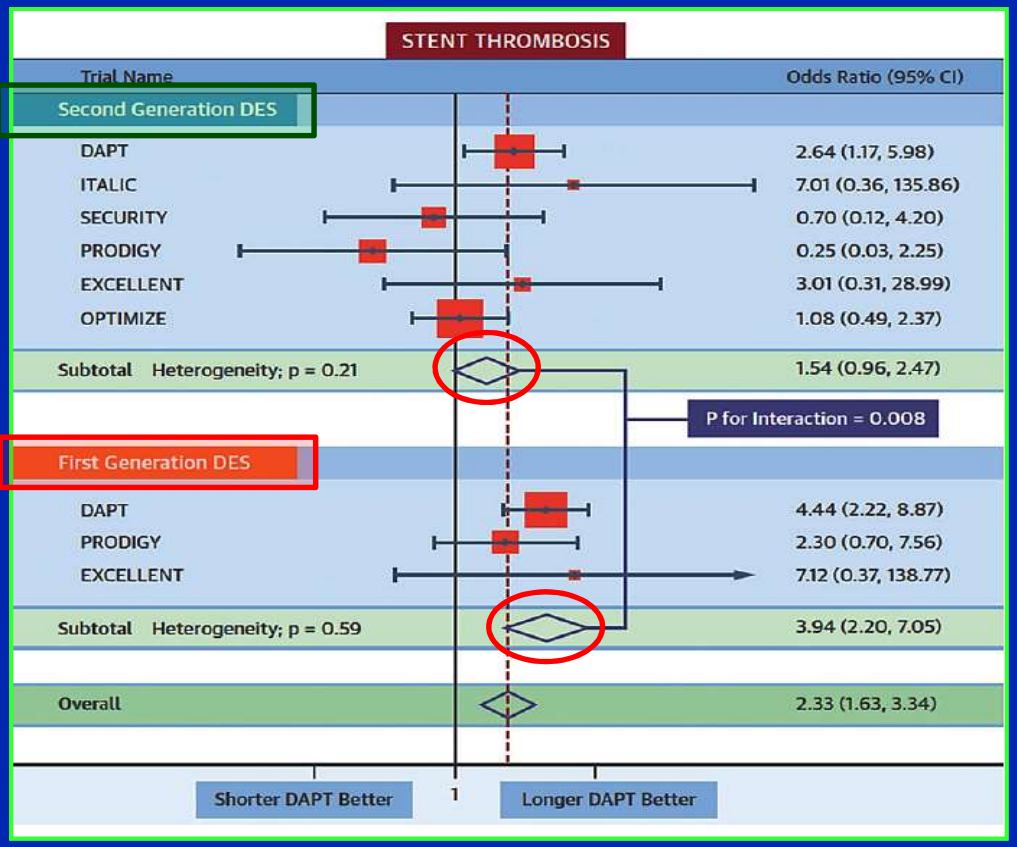
Dual Antiplatelet Therapy (DAPT), Type of DES and Stent Thrombosis



A Systematic Review and Meta-Analysis of RC Trials

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Giustino G, et al. JACC 2015; 65: 1298

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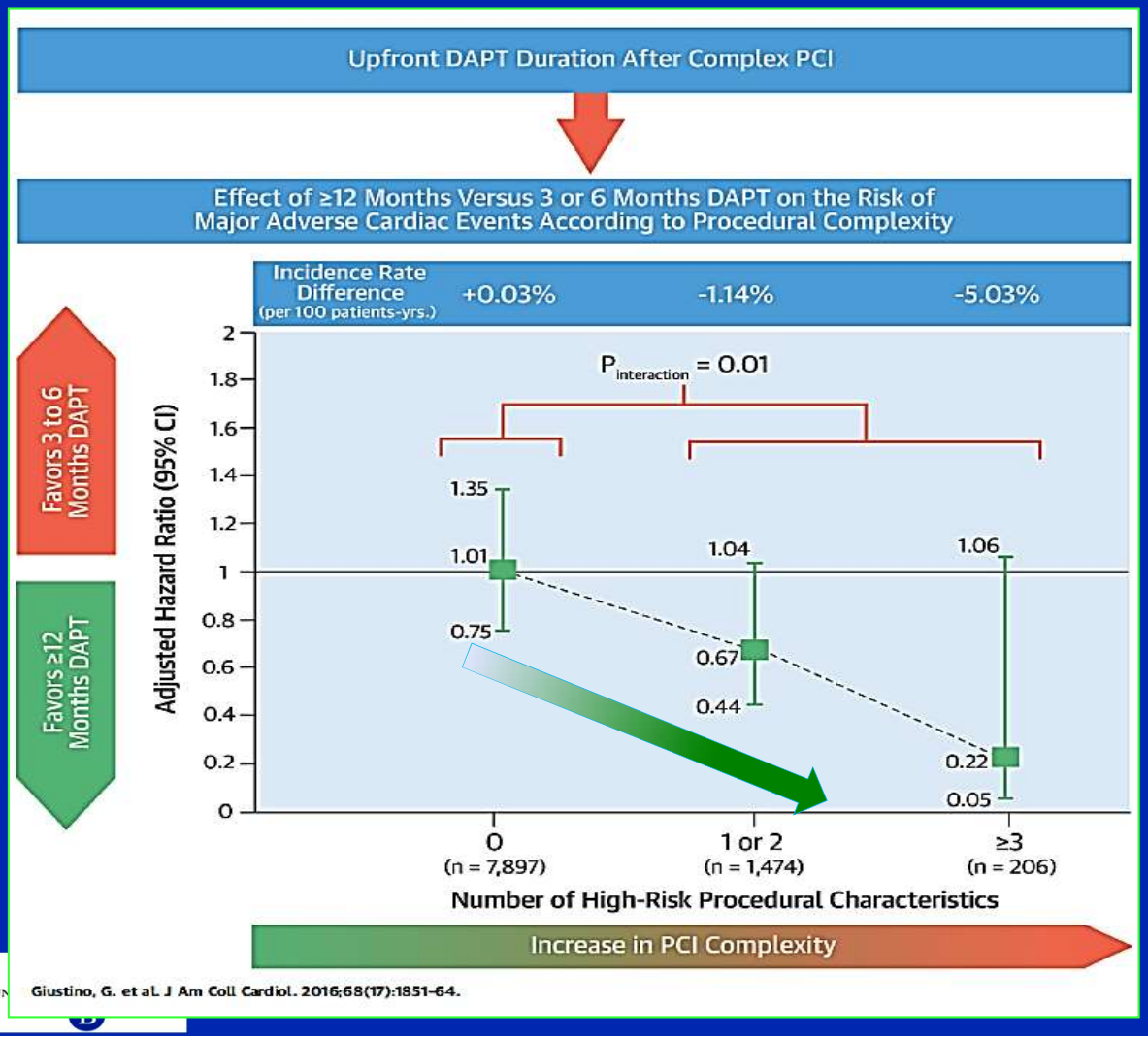
Efficacy and Safety of DAPT After Complex PCI



Complex PCI

At least 1 of the following:

- 3 vessel treated
- ≥ 3 stents implanted
- ≥ 3 lesions treated
- bifurcation + 2 stents
- stent length > 60 mm
- CTO

MACE= death, MI or stent thrombosis

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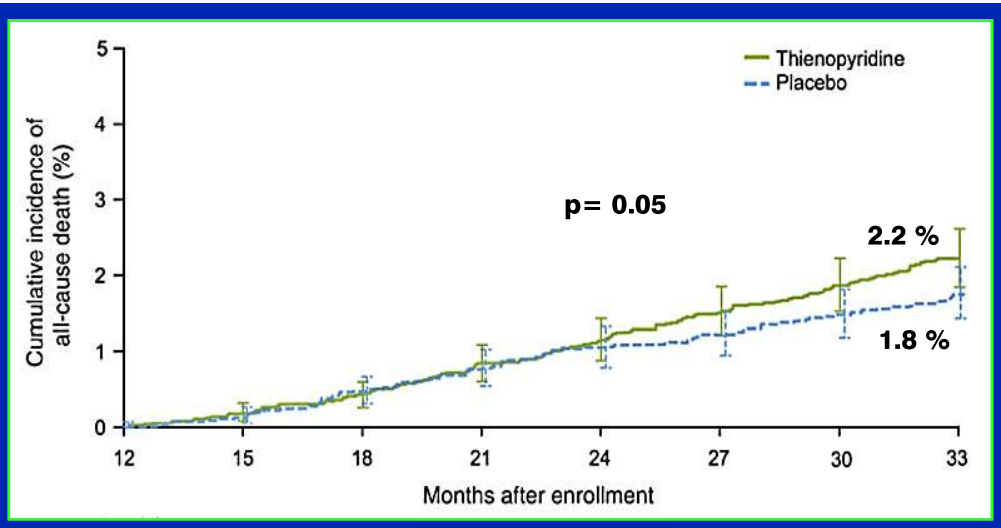
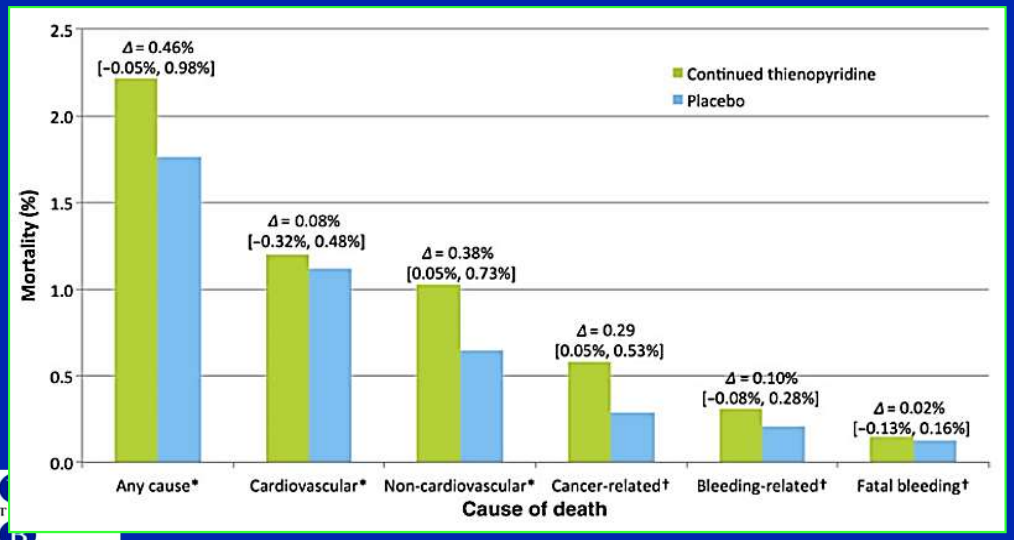
Causes of Late Mortality with DAPT after Coronary Stents

DAPT Trial





Bleeding accounted for a minority of deaths. Cancer-death was not related with bleeding (chance ?). Caution when considering DAPT in patients with advanced cancer.

Mauri L, et al. EHJ 2016; 37: 378

Tratamiento Antitrombótico en los Síndromes Coronarios Agudos

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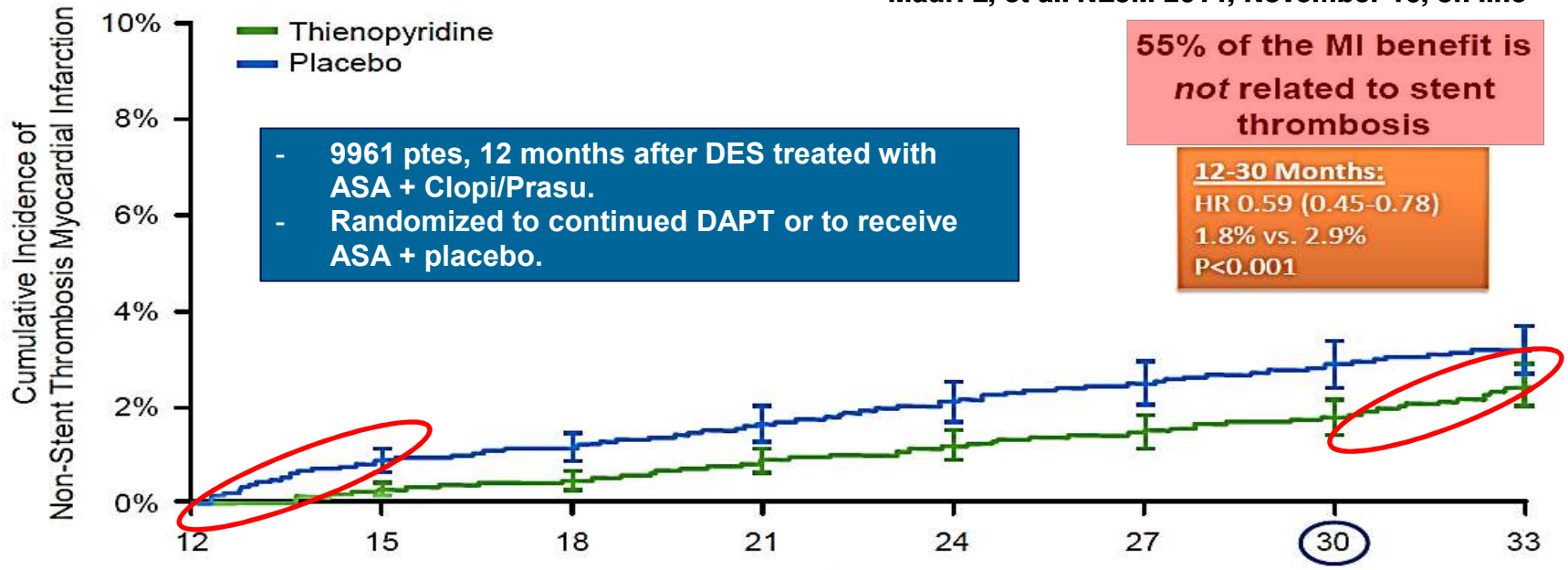
12 or 30 Months of Dual Antiplatelet Therapy after DES

Non-Stent Related Myocardial Infarction

DAPT STUDY

Mauri L, et al. NEJM 2014; November 16, on line



- 9961 ptes, 12 months after DES treated with ASA + Clopi/Prasu.
- Randomized to continued DAPT or to receive ASA + placebo.

55% of the MI benefit is *not* related to stent thrombosis

12-30 Months:
HR 0.59 (0.45-0.78)
1.8% vs. 2.9%
P<0.001

# At Risk								
Thienopyridine	5020	4920	4851	4792	4721	4641	4588	3066
Placebo	4941	4820	4751	4686	4607	4547	4491	3052

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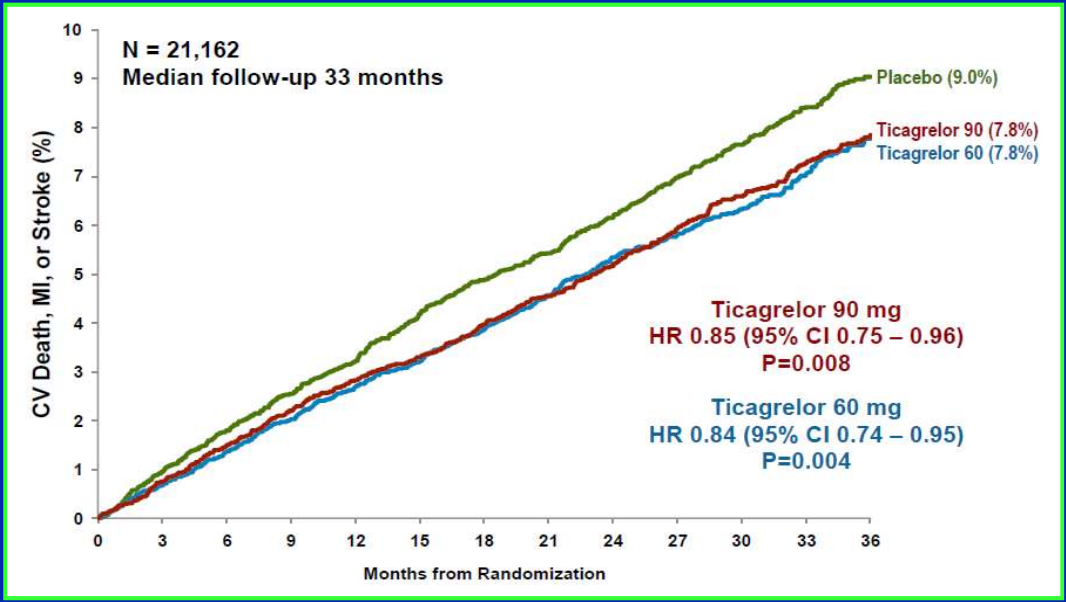
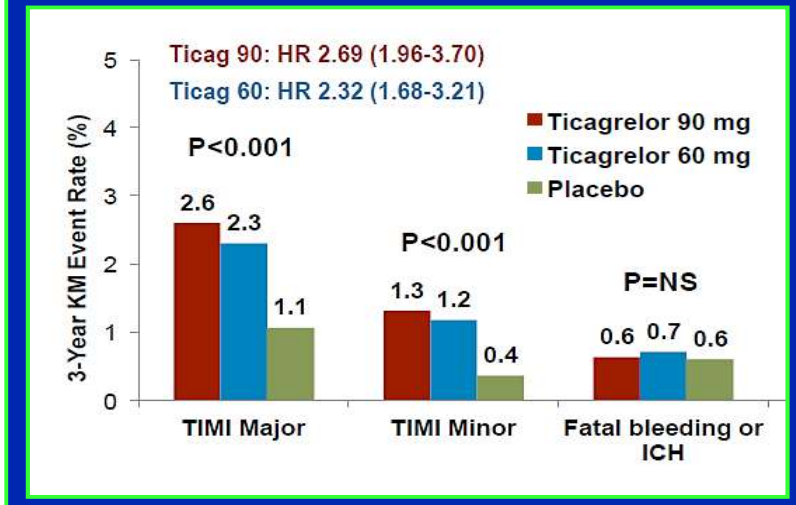
Long-Term Use of Ticagrelor in Ptes with Prior MI

PEGASUS TIMI 54

- 21162 ptes, 1-3 yrs post-MI with low dose ASA.
- ≥ 50 yo + 1 high risk factor (≥ 65 yo, diabetes, 2nd prior MI, MVD, CrCl<60mL/min)
- Randomized to ticagrelor (90mg bid or 60mg bid) vs placebo.





Conclusions: In ptes with a MI > 1 year previously, ticagrelor significantly reduced the risk of CV death, MI, or stroke and increased the risk of major bleeding.

Bonaca MP, et al. NEJM 2015; March 14, on line

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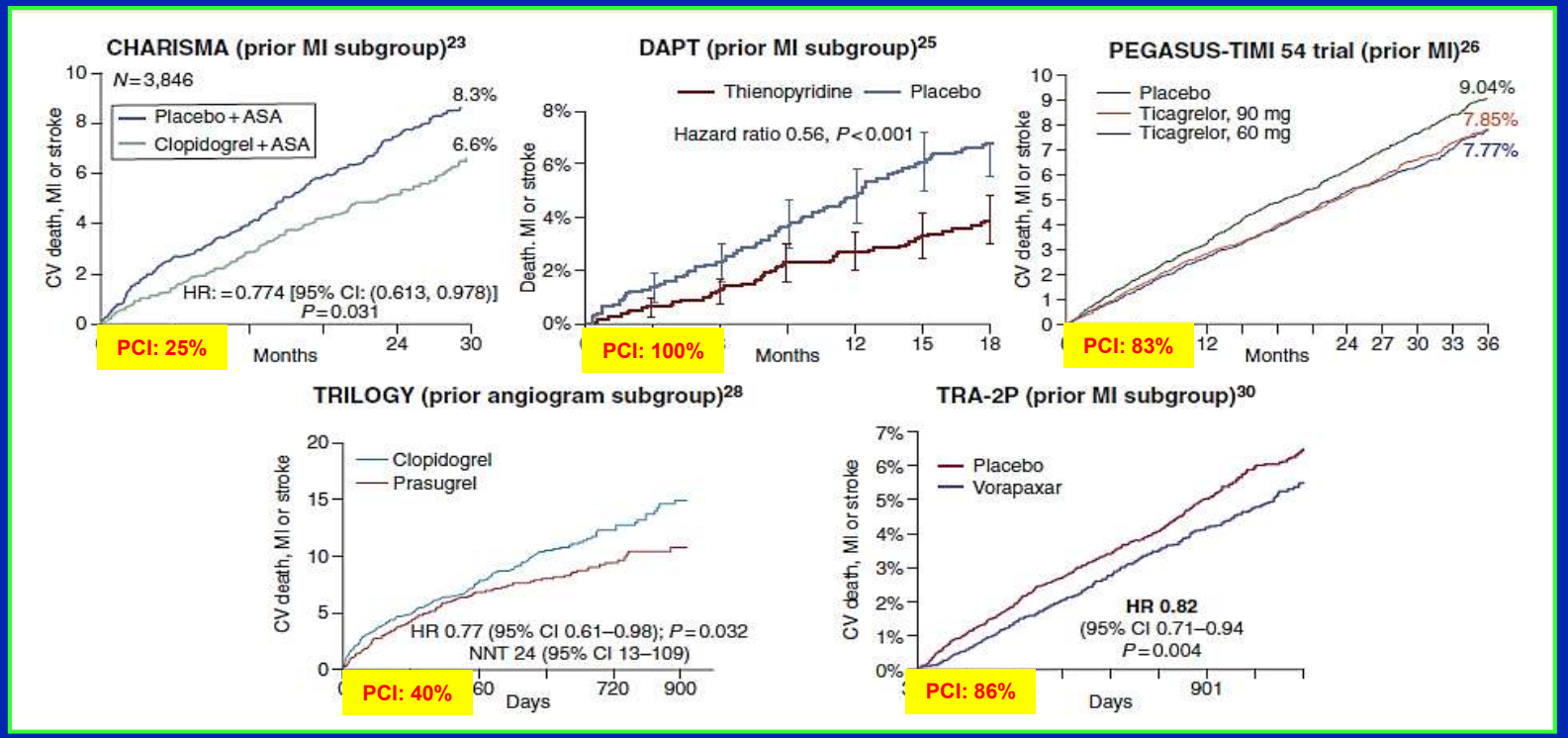
Duration of Dual Antiplatelet Therapy



Stronger antiplatelet therapy beyond 1 year vs standard care, in ptes with prior MI or angiographically proven CAD.

Montalescot G, Sabatine MS. Eur Heart J 2015; August 6.

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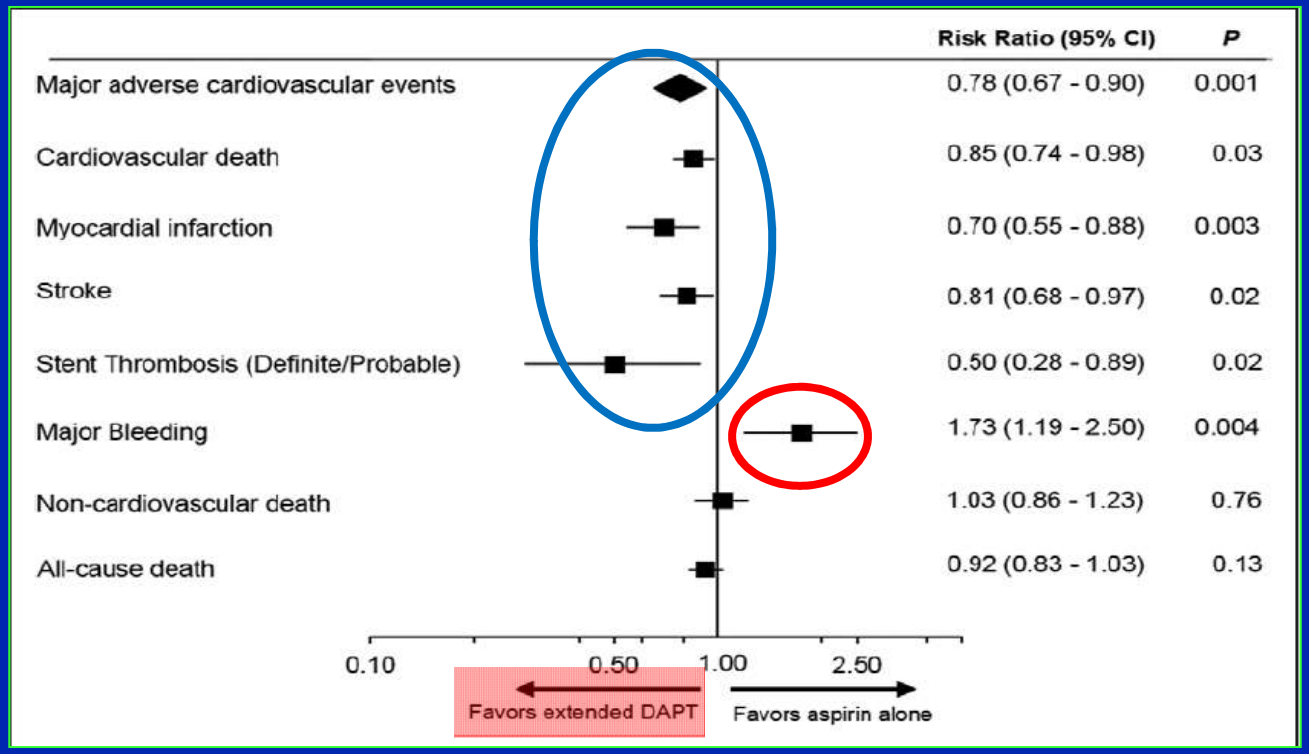
Individualizing Duration of DAPT for Secondary Prevention After ACS

Patients with Previous MI



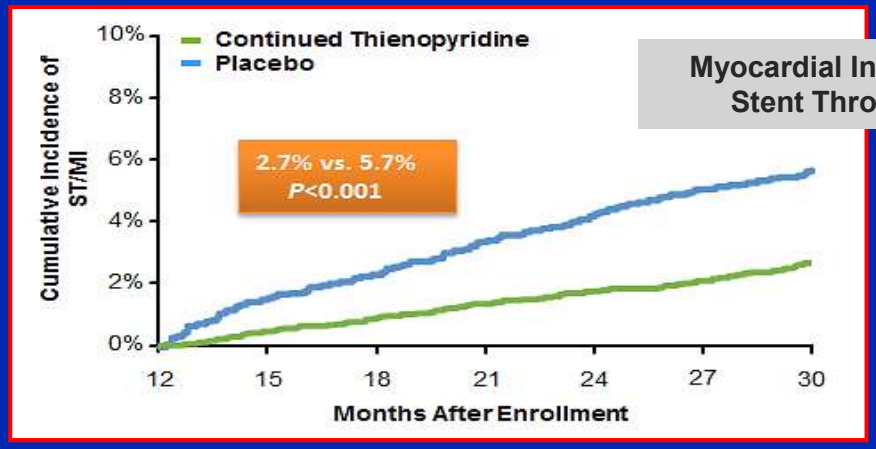
Udell JA, et al. EHJ 2016; 37:390

Continued Thienopyridine vs Placebo > 1 Year post-PCI

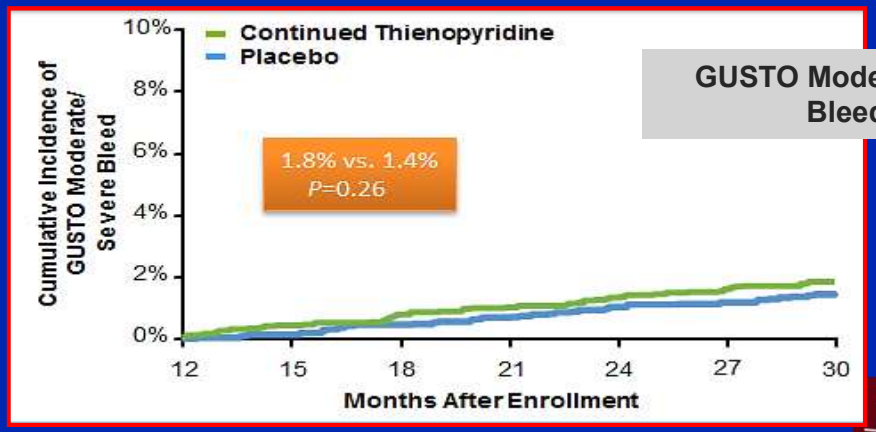
DAPT Score ≥ 2 (high)

The DAPT Score

Variable	Points
Patient	
- Age	
≥ 75	-2
65 - <75	-1
< 65	0
- Diabetes Mellitus	1
- Current Smoker	1
- Prior PCI or Prior MI	1
- CHF or LVEF < 30%	2
Index Procedure	
- MI at Presentation	1
- Vein Graft PCI	2
- Stent Diameter < 3mm	1



Myocardial Infarction or Stent Thrombosis



GUSTO Moderate/Severe Bleeding

Yeh RW, et al.
JAMA 2016; 315: 1735

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Contemporary Risk Scores for Tailoring Antiplatelet Therapy Duration

	Number of variables	Development cohort (patients, design)	Setting	Predicted outcome	Validation cohort (patients, c-index)
DAPT	Five clinical, Three procedural	11 648 patients, multicentre randomised clinical trial	PCI patients on DAPT who were event-free for 12 months	Ischaemia and bleeding between 12 and 30 months after PCI	8136 patients, 0·64 for both ischaemia and bleeding
PARIS	Coronary thrombosis risk score: six clinical; major bleeding risk score: six clinical	4190 patients, multicentre registry	PCI patients on DAPT	Ischaemia and bleeding at 24 months after PCI	8665 patients, 0·65 for ischaemia and 0·64 for bleeding
PRECISE-DAPT	Five clinical	14 963 patients, pooled analysis of randomised clinical trials	PCI patients on DAPT	Bleeding at 12 months after PCI	8595 patients, 0·70; N=6172 patients, 0·66

DAPT=dual antiplatelet therapy. PCI=percutaneous coronary intervention.

Capodanno D, Angiolillo D. Lancet 2017; 389: 987

Recommended Duration of Dual Antiplatelet Therapy

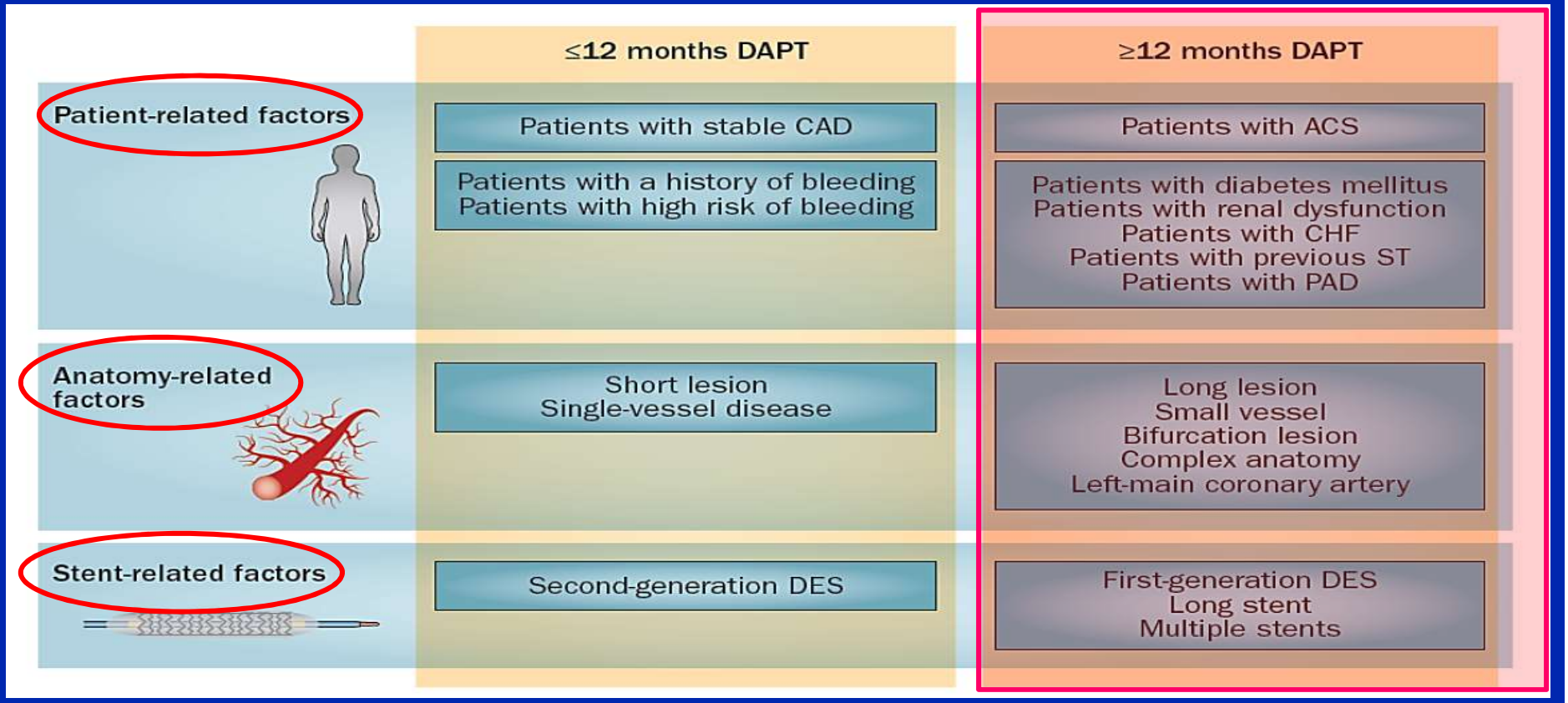
- **Dual antiplatelet therapy for >1 year:**

  - Several predictors of stent thrombosis
  - Multiple hospitalizations for ACS
  - Broad atherosclerotic burden
  - Last patent vessel / PCI in LM
  - Prior MI ++
  - No options for coronary revascularization

(+++ if > 1 factor)

(Not applicable if prior bleeding, prior stroke, or high risk of bleeding)

Individualizing Duration of DAPT



Meisen A, Bhatt DL. Nature Review Cardiology 2015

Benefit vs Risk: Fragil Balance