

ΒΕΛΤΙΣΤΟΠΟΙΗΣΗ ΤΗΣ ΑΝΤΙΘΡΟΜΒΩΤΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΗΝ ΕΠΕΜΒΑΤΙΚΗ ΚΑΡΔΙΟΛΟΓΙΑ

ΘΩΜΑΣ ΠΑΠΑΔΟΠΟΥΛΟΣ MBCIS FACC FSCAI

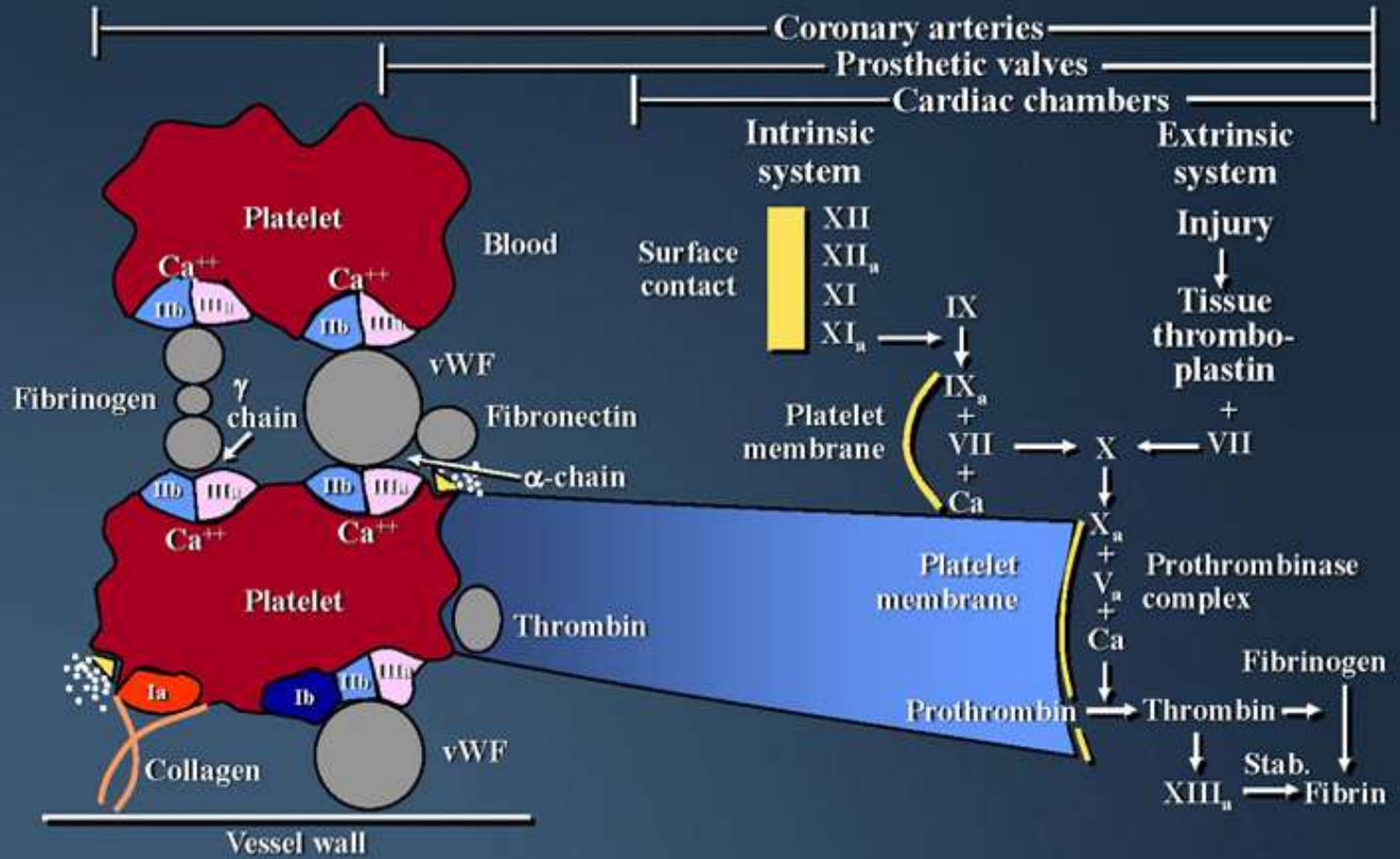
ΕΠΕΜΒΑΤΙΚΟΣ ΚΑΡΔΙΟΛΟΓΟΣ

ΙΑΤΡΙΚΟ ΔΙΑΒΑΛΚΑΝΙΚΟ ΚΕΝΤΡΟ

ΣΤΕΦΑΝΙΑΙΑ ΘΡΟΜΒΩΣΗ

- Αποτελεί σοβαρό πρόβλημα κατά τη διάρκεια της Διαδερμικής Στεφανιαίας Αγγειοπλαστικής
- Τρεις παράγοντες συμμετέχουν
 - *Το αγγειακό τοίχωμα*
 - *Οι πρωτεΐνες πήξεως του πλάσματος*
 - *Τα αιμοπετάλια*
- Οι παράγοντες αυτοί δρούν ανεξάρτητα ενώ η **Θρομβίνη** παίζει βασικό ρόλο στην μεταξύ τους αλληλεπίδραση

Platelets & Coagulation



ΑΝΤΙΘΡΟΜΒΩΤΙΚΗ ΑΓΩΓΗ

- ΑΝΤΙΑΙΜΟΠΕΤΑΛΙΑΚΗ ΑΓΩΓΗ
- ΑΝΤΙΠΗΚΤΙΚΗ ΑΓΩΓΗ ΚΑΤΑ ΤΗ ΔΙΑΡΚΕΙΑ ΤΗΣ ΑΓΓΕΙΟΠΛΑΣΤΙΚΗΣ

ΣΤΕΦΑΝΙΑΙΑ ΝΟΣΟΣ

- ΧΡΟΝΙΑ ΣΤΑΘΕΡΗ ΣΤΗΘΑΓΧΗ
- ΟΞΥ ΣΤΕΦΑΝΙΑΙΟ ΣΥΝΔΡΟΜΟ

ΧΡΟΝΙΑ ΣΤΑΘΕΡΗ ΣΤΗΘΑΓΧΗ

- ΟΙ ΟΔΗΓΙΕΣ ΟΥΣΙΑΣΤΙΚΑ ΠΑΡΑΜΕΝΟΥΝ ΟΙ ΙΔΙΕΣ
- ΤΑ ΝΕΩΤΕΡΑ ΦΑΡΜΑΚΑ ΧΡΗΣΙΜΟΠΟΙΟΥΝΤΑΙ ΟΤΑΝ ΥΠΑΡΧΕΙ ΑΔΥΝΑΜΙΑ ΧΟΡΗΓΗΣΗΣ ΤΩΝ ΠΑΛΑΙΩΤΕΡΩΝ ΦΑΡΜΑΚΩΝ

ΑΝΤΙΘΡΟΜΒΙΝΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ

- ΚΛΑΣΙΚΗ ΗΠΑΡΙΝΗ
- ΗΠΑΡΙΝΗ ΧΑΜΗΛΟΥ ΜΟΡΙΑΚΟΥ ΒΑΡΟΥΣ
- ΑΜΕΣΟΙ ΑΝΑΣΤΟΛΕΙΣ ΤΗΣ ΘΡΟΜΒΙΝΗΣ

Old and New Antithrombotic Drugs

A

	Unfractionated Heparin (UHF)	Low Molecular Weight Heparin (Enoxaparin)	Fondaparinux	Bivalirudin
Half-Life	3 Hrs	6 Hrs	4 Hrs	0.3 Hrs
Dose/Kg	30-120 mg/Kg	1 mg/Kg	2.5 mg sc	STEMI/PCI: 0.75 mg/kg bolus followed by infusion 1.75 mg/kg/h NSTE-ACS: 0.1 mg/kg bolus followed by infusion 0.25 mg/kg/h (if PCI, additional 0.5 mg/kg IV bolus followed by infusion 1.75 mg/kg/h)
Monitoring	ACT/aPTT	Factor X (not required)	Not required	ACT (not required)
Inactivation	Protamine Sulphate	n.a.	n.a.	n.a.

Stable angina - Bivalirudin

- Replacement for UFH/Enoxaparin (\pm Gp II/IIIa inhibitors) to reduce bleeding complications
- Replacement for UFH in HIT
(Heparin Induced Thrombocytopenia)

ASA + clopidogrel 300 mg + bivalirudin

bivalirudin 0.75 mg/kg bolus & infusion 1.75 mg/kg/h





Safety and Efficacy of Intravenous Enoxaparin in Elective Percutaneous Coronary Intervention: An International Randomized Evaluation

"This slide is provided solely for your personal
medical information"

Primary Objective

- **To demonstrate the safety of IV enoxaparin (0.5 mg/kg and 0.75 mg/kg) compared with IV UFH in patients undergoing non-emergent PCI**
 - **Definition of safety: non-CABG-related major and minor bleeding up to 48 hours following index PCI**

Conclusions / Clinical Implications

- **Use of IV enoxaparin in patients scheduled to undergo elective PCI is associated with significantly less major bleeding**
- **The efficacy of IV enoxaparin is non-inferior to UFH in elective PCI patients**
- **The clinical benefit observed with enoxaparin came with superior ease of use compared with UFH**
 - **Single IV bolus before the start of PCI**
 - **Similar dose with or without GP IIb/IIIa inhibitors**
 - **No anticoagulation monitoring**
- **IV enoxaparin offers an attractive alternative to the uncertain ACT-driven UFH anticoagulation used in the catheterization laboratory**

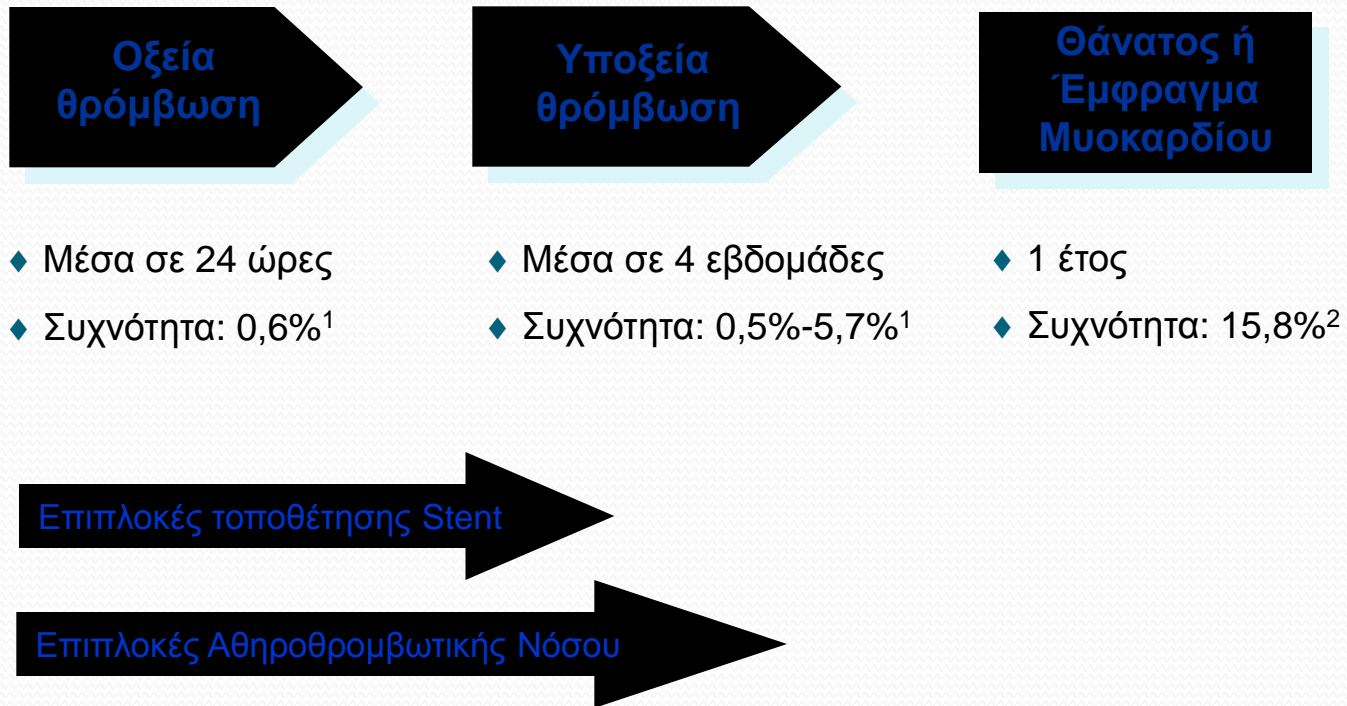


ΑΝΤΙΑΙΜΟΠΕΤΑΛΙΑΚΑ

ΑΝΤΙΑΙΜΟΠΕΤΑΛΙΑΚΟΙ ΠΑΡΑΓΟΝΤΕΣ ΧΟΡΗΓΟΥΜΕΝΟΙ ΑΠΟ ΤΟ ΣΤΟΜΑ

- Ασπιρίνη
- P₂Y₁₂ blockers

Ενεργοποίηση Αιμοπεταλίων Μετά από την PCI Βραχυπρόθεσμος και Μακροπρόθεσμος Κίνδυνος Ισχαιμικών Επεισοδίων



¹Mak K-H et al. J Am Coll Cardiol. 1996; 27: 494-503

²Steinhubl S et al. Circulation. 1999; 100: 18 (suppl): 1-380. Abstract 1993

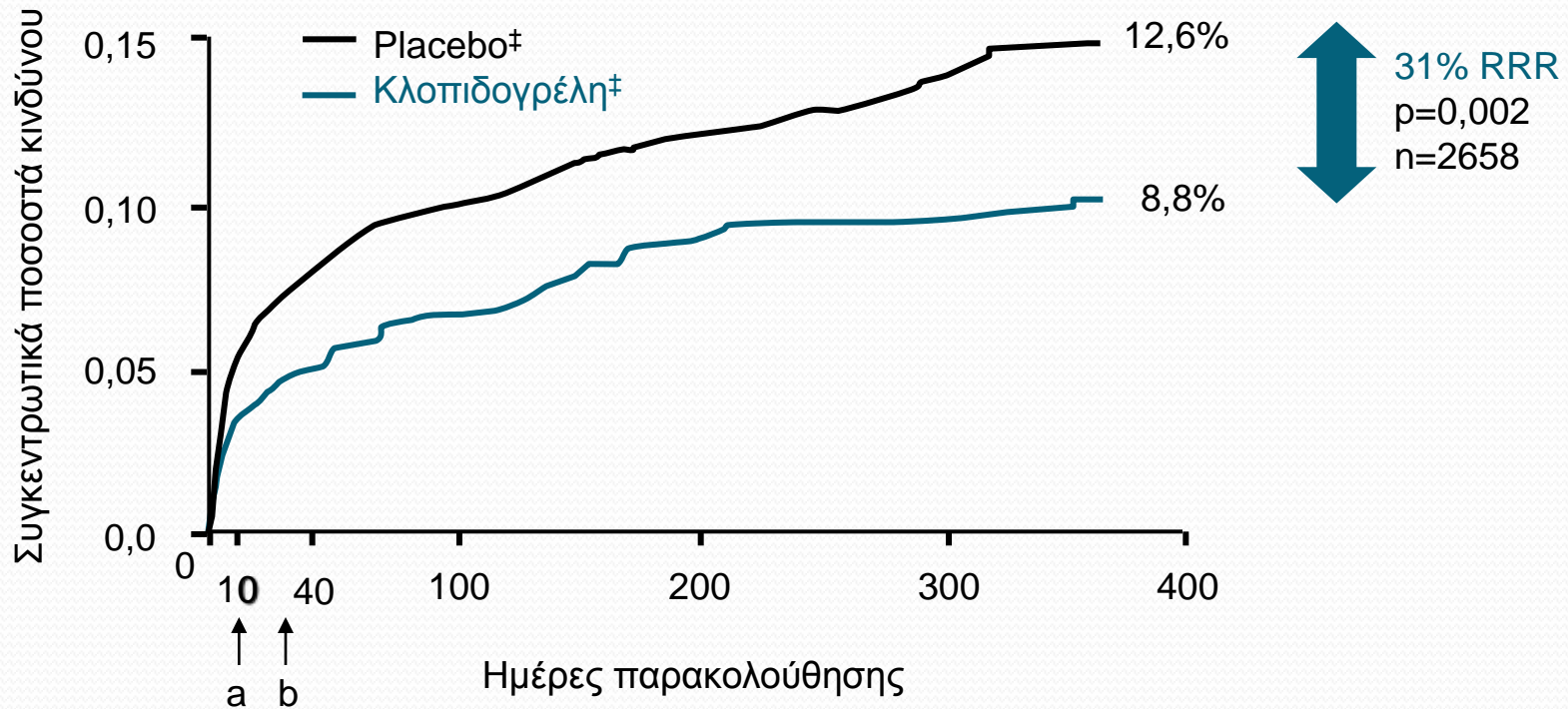
Aspirin: The least expensive and still one of the most effective drugs available in cardiology



Antithrombotic Trialists' Collaboration. *BMJ*. 2002;324:71-86.

PCI-CURE – Μακροχρόνια Αποτελεσματικότητα της Κλοπιδογρέλης

Σύνθετο σημείο θανάτου καρδιαγγειακής αιτιολογίας ή Εμφράγματος
Μυοκαρδίου από την τυχαιοποίηση ως το τέλος της παρακολούθησης†



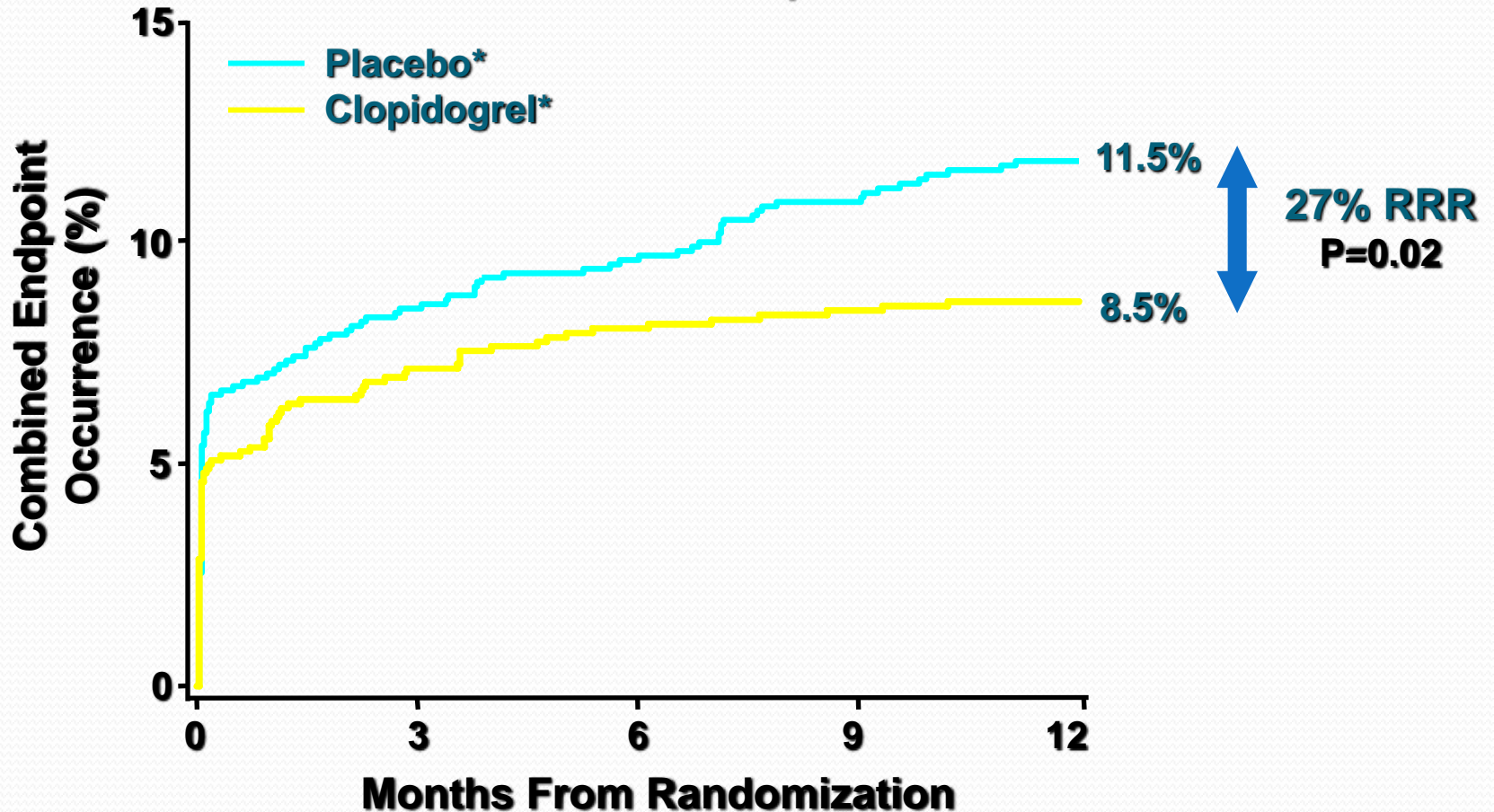
a = μέσος όρος χρόνου από την τυχαιοποίηση ως την PCI (10 ημέρες)
b = 30 ημέρες μετά από το μέσο χρόνο από την PCI
†έως 12 μήνες ‡επιπλέον της συνήθους θεραπείας που περιλαμβάνει ΑΣΟ

CREDO

- Η Μελέτη CREDO
Clopidogrel for the Reduction of Events
During Observation
(η κλοπιδογρέλη για τη μείωση των επεισοδίων
κατά τη διάρκεια μακρόχρονης παρακολούθησης)

Long-Term (1 Year) Benefits of Clopidogrel in PCI Patients

Mi, Stroke, or Death – ITT Population

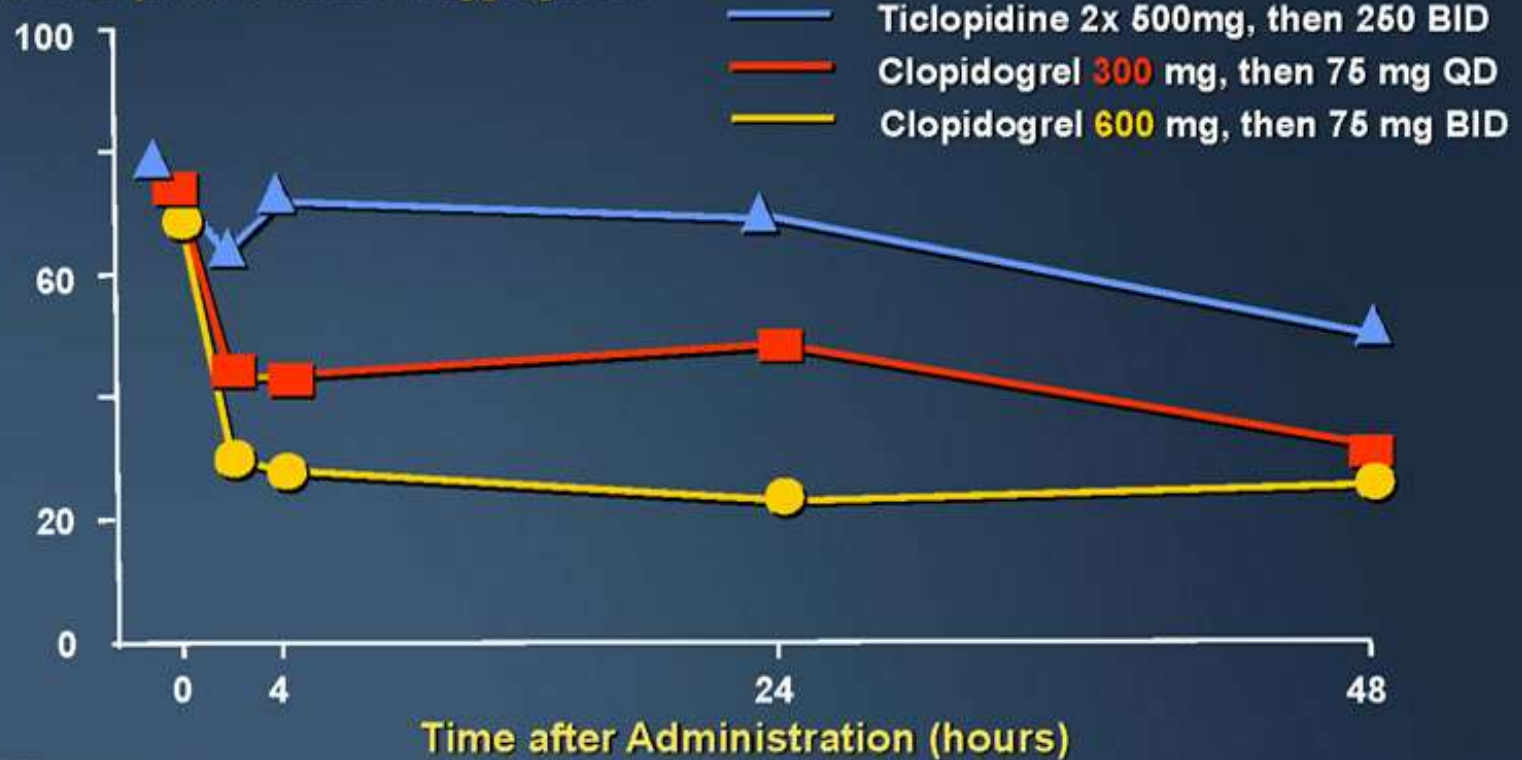


* Plus ASA and other standard therapies

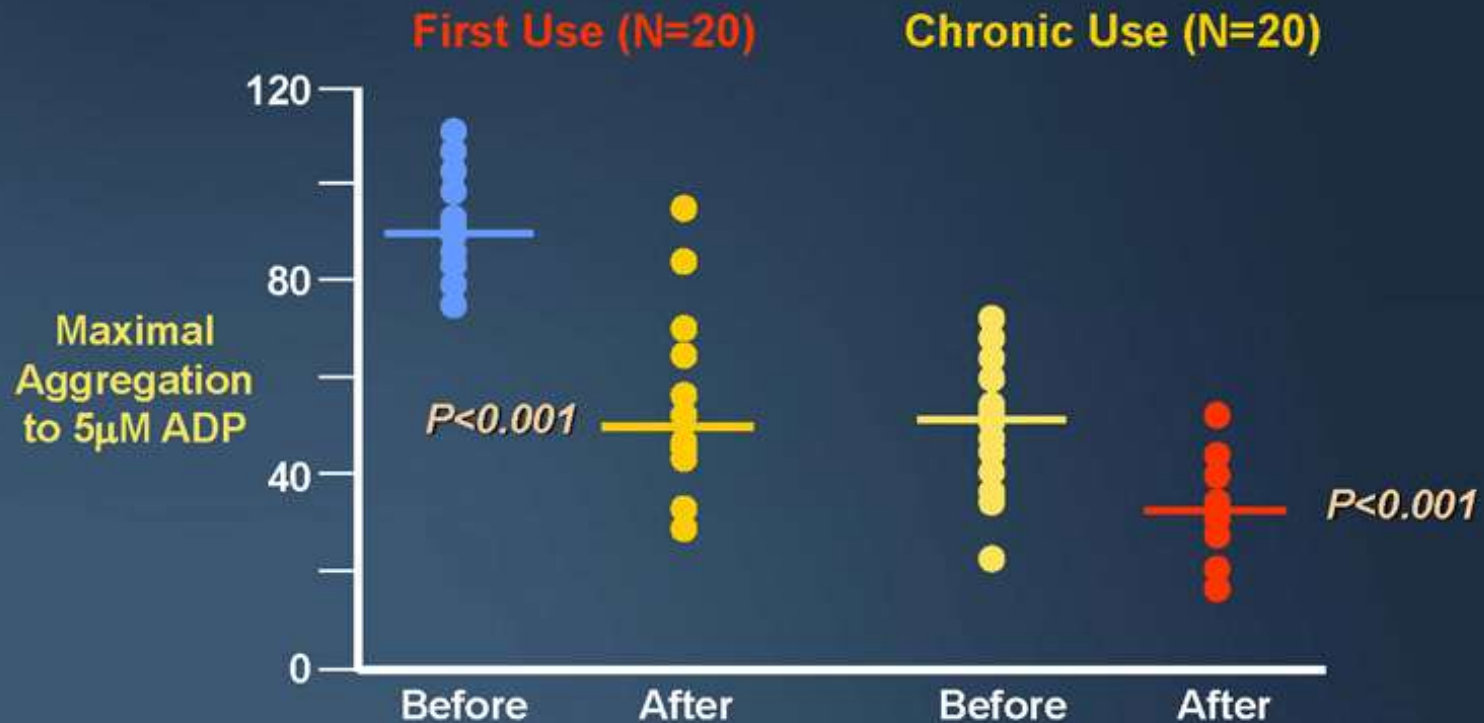
Steinhubl S, Berger P, Tift Mann III J et al. *JAMA*. 2002;Vol 288,No 19:2411-2420.

Clopidogrel LD: Is Higher Dosage Better?

% of 20 μ M ADP-induced aggregation



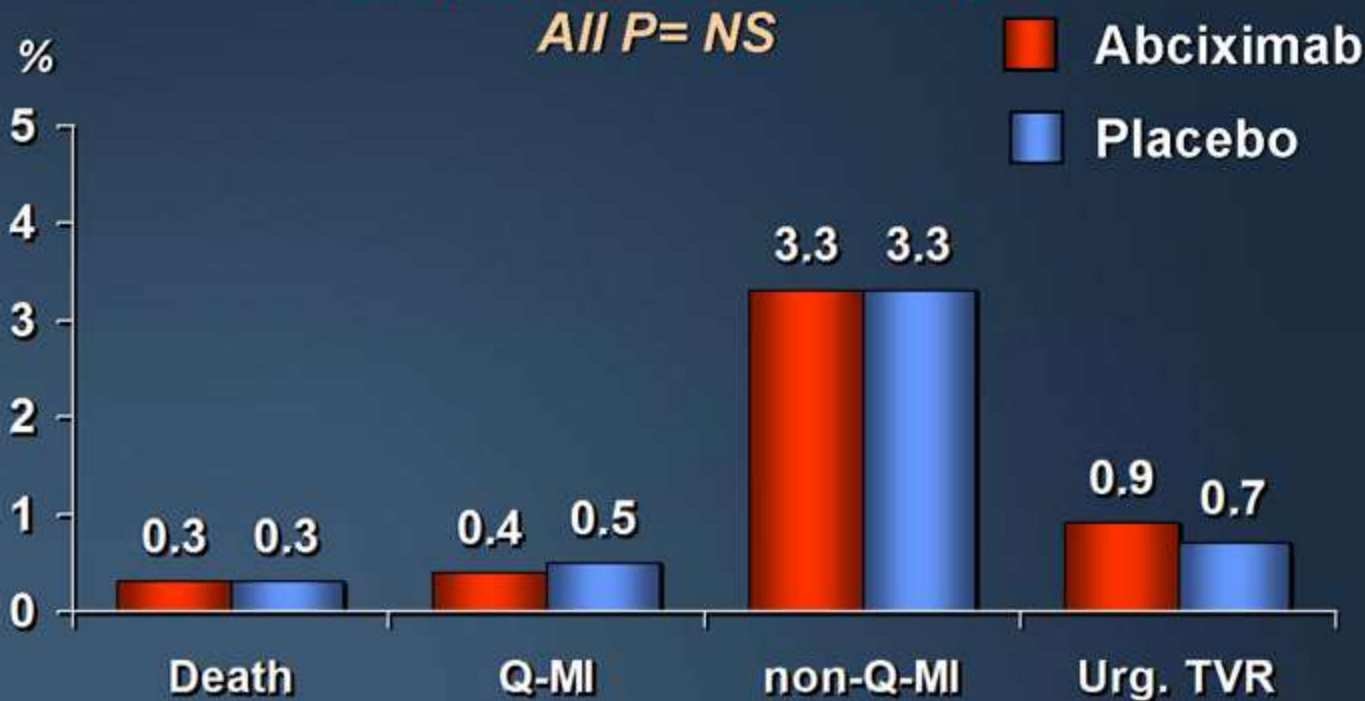
600mg Loading Dose in Patients on Chronic Clopidogrel Therapy



ISAR-REACT

*Elective PCI-stent, 600 mg
Clopidogrel, stable pts*

All P= NS

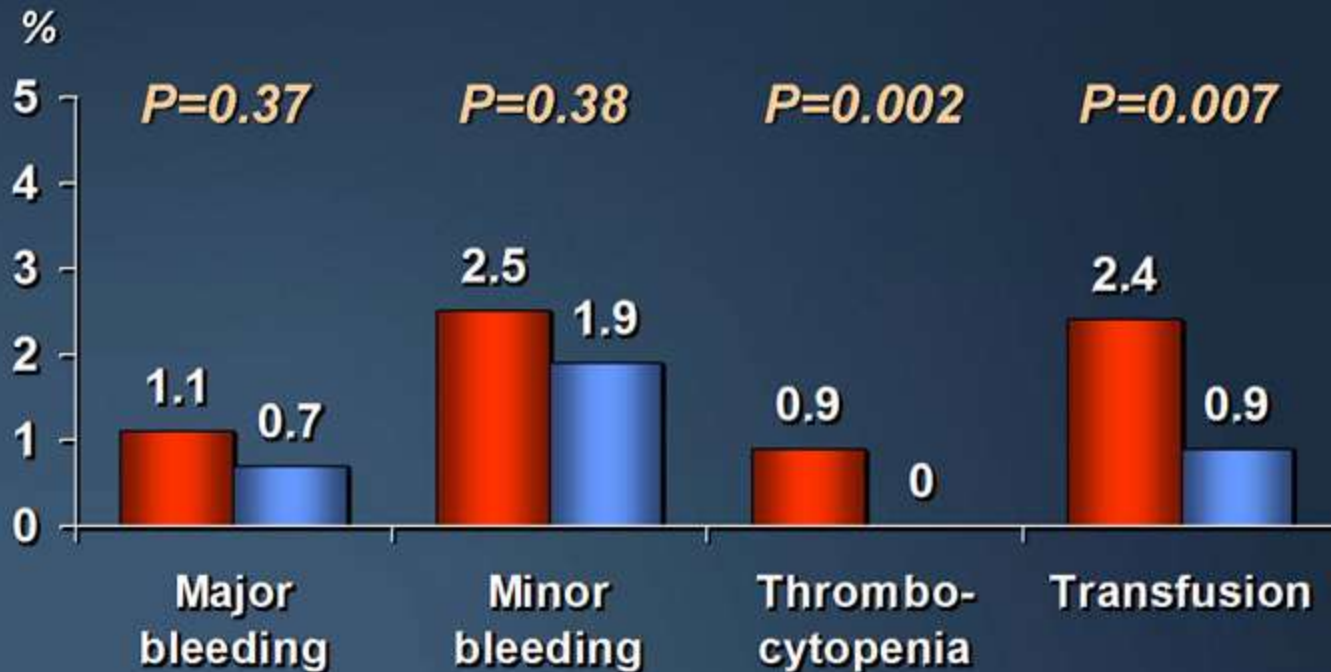


Kastrati et al, 2003

ISAR-REACT

Safety Analysis

Abciximab
Placebo



ΟΞΕΑ ΣΤΕΦΑΝΙΑΙΑ ΣΥΝΔΡΟΜΑ

- ΑΣΤΑΘΗΣ ΣΤΗΘΑΓΧΗ
- ΕΜΦΡΑΓΜΑ ΧΩΡΙΣ ΑΝΑΣΠΑΣΗ ΤΟΥ ST
- ΕΜΦΡΑΓΜΑ ΜΕ ΑΝΑΣΠΑΣΗ ΤΟΥ ST

Milestones in ACS management

Anti-thrombin Rx

Heparin

LMWH

Bivalirudin

Fondaparinux

Antiplatelet Rx

Aspirin

GP IIb/IIIa
blockers

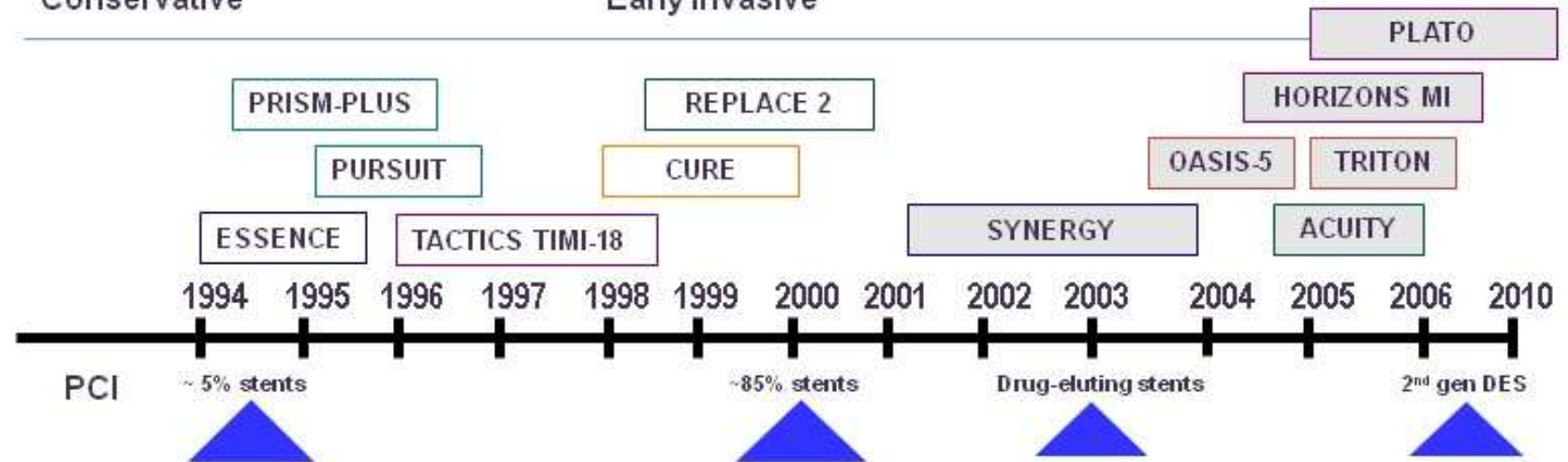
Clopidogrel

Prasugrel Ticagrelor

Treatment Strategy

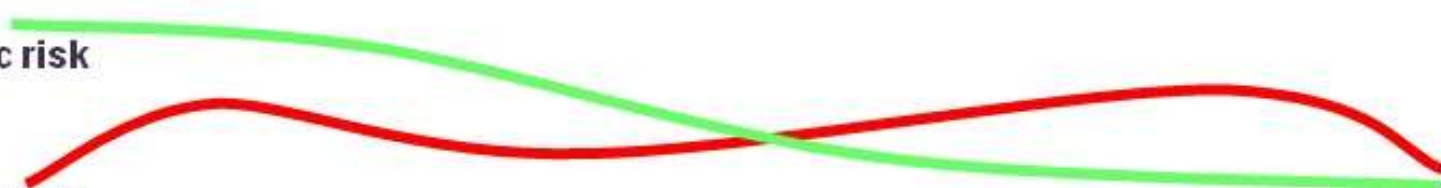
Conservative

Early invasive



Ischaemic risk

Bleeding risk



Pharmacological options in pPCI patients

Aspirin:

150-325 mg

No pPCI
data

I B*

Clopidogrel:

3/600 mg LD

No pPCI
data

I C*

UFH:

100 U/Kg (50-70U/kg if GPI)

No pPCI
data

I C*

2b/3a blockers:

Abciximab
Tirofiban
Eptifibatide

pPCI
Data: YES

IIaA*

IIbB*

IIbC*

Bivalirudin:

0.75mg/kg
1.75mg/kg/h

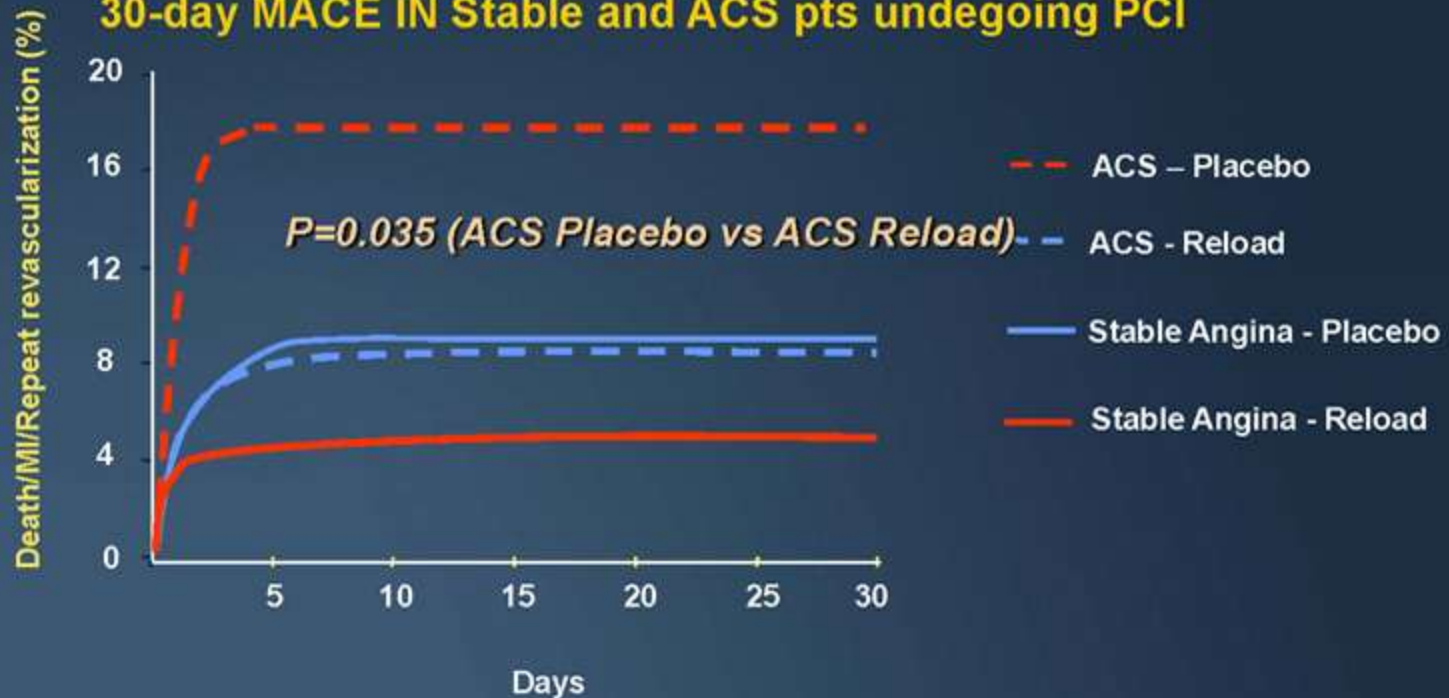
pPCI
Data: YES

IIaB*

ARMYDA-Reload: Clinical Outcomes

Evaluation of 600mg clopidogrel dose in pts who are already on chronic clopidogrel therapy

30-day MACE IN Stable and ACS pts undegoing PCI



Bivalirudin Monotherapy in NSTEACS with aspirin and clopidogrel preloading

- The simplest regimen :
 - GP IIb/IIIa inhibitors were required in only **9%** of patients in ACUTY during PCI for ischemia/thrombus
 - IV bivalirudin infusion is discontinued after cath
 - Monitoring of aPTT and ACT possible but not necessary
- Provides similar protection from ischemic complications as heparin (UFH or enoxaparin) + GP IIb/IIIa inhibitors with markedly less bleeding, and less cost

ASA + clopidogrel 300/600 mg + bivalirudin

bivalirudin 0.75 mg/kg bolus & infusion 1.75 mg/kg/h



TIMI 30: The PROTECT Trial

High-risk UA/NSTEMI for PCI of a native coronary artery with either
DM; or + Troponin; or $ST\downarrow \geq 0.5$ mm; or TRS ≥ 3

N = 857

TRANSFER TO CATH LAB, DIAGNOSTIC ANGIOGRAM

CONFIRM ELIGIBLE FOR PCI OF CULPRIT IN NATIVE ARTERY

Eptifibatide

180/180 ug/kg +
2 ug/kg/min

+

+

Low Dose UFH
50 U/kg IVB
ACT 200-250

Low Dose
Enoxaparin
0.5 mg/kg IV

Bivalirudin

0.75 mg/kg IVB +
1.75 mg/kg/h

Randomization stratified by Clopidogrel pretreatment >6 h and ≤ 6 h

If not pretreated, then 300 mg Clopidogrel immediately prior to starting. All tx'd with ASA



TIMI 30: The PROTECT Trial

TIMI Myocardial Perfusion Grade 3 Post-PCI

O.R. 1.44 (95% CI 1.003-2.06)

p = 0.048 pre-specified adjustment for baseline TMPG



HORIZONS AMI Trial

3400 patients with STEMI within 12^o onset
at 200 international sites

Consent

Aspirin 324 mg chewed

Clopidogrel 300 or 600 mg po load or Ticlopidine 500 mg



1:1

**UFH
+ IIb/IIIa inhibitor**

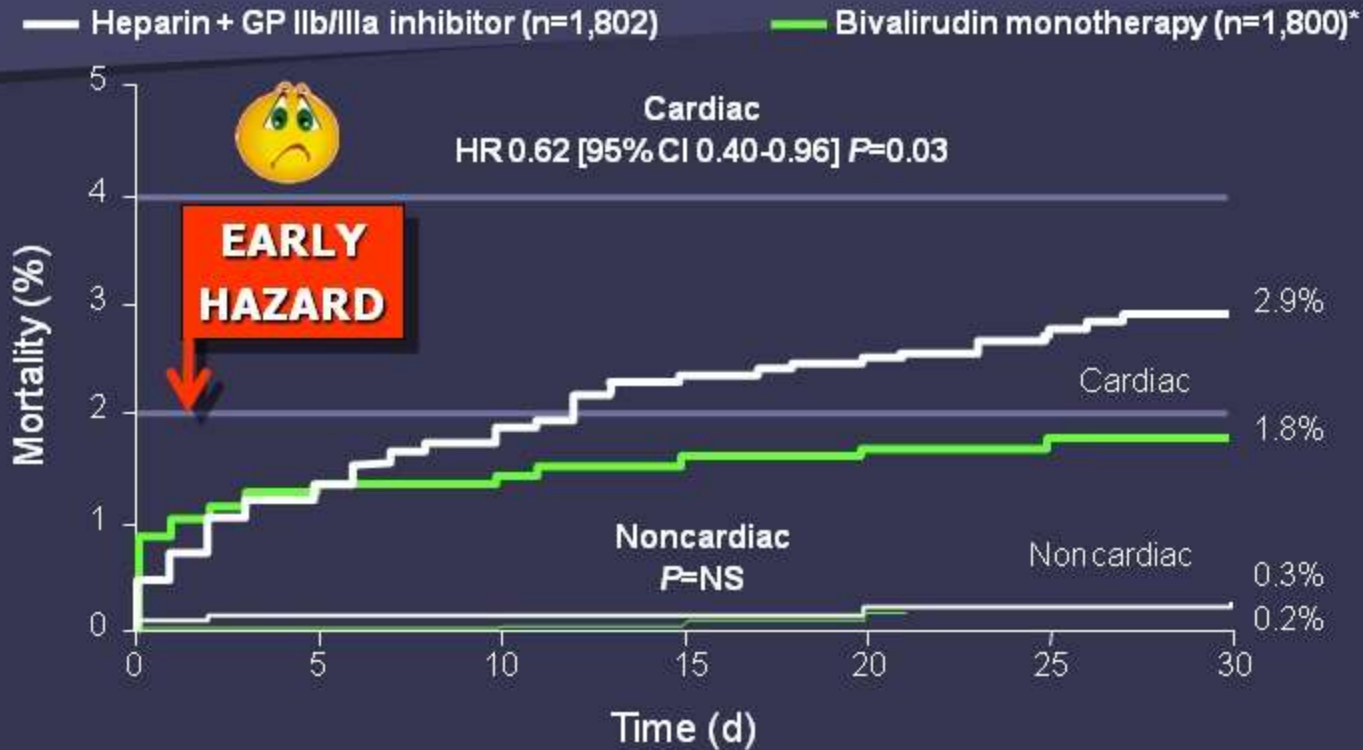
**Bivalirudin
+ bail-out IIb/IIIa**

Cath lab

left ventriculography and coronary arteriography

30-day mortality

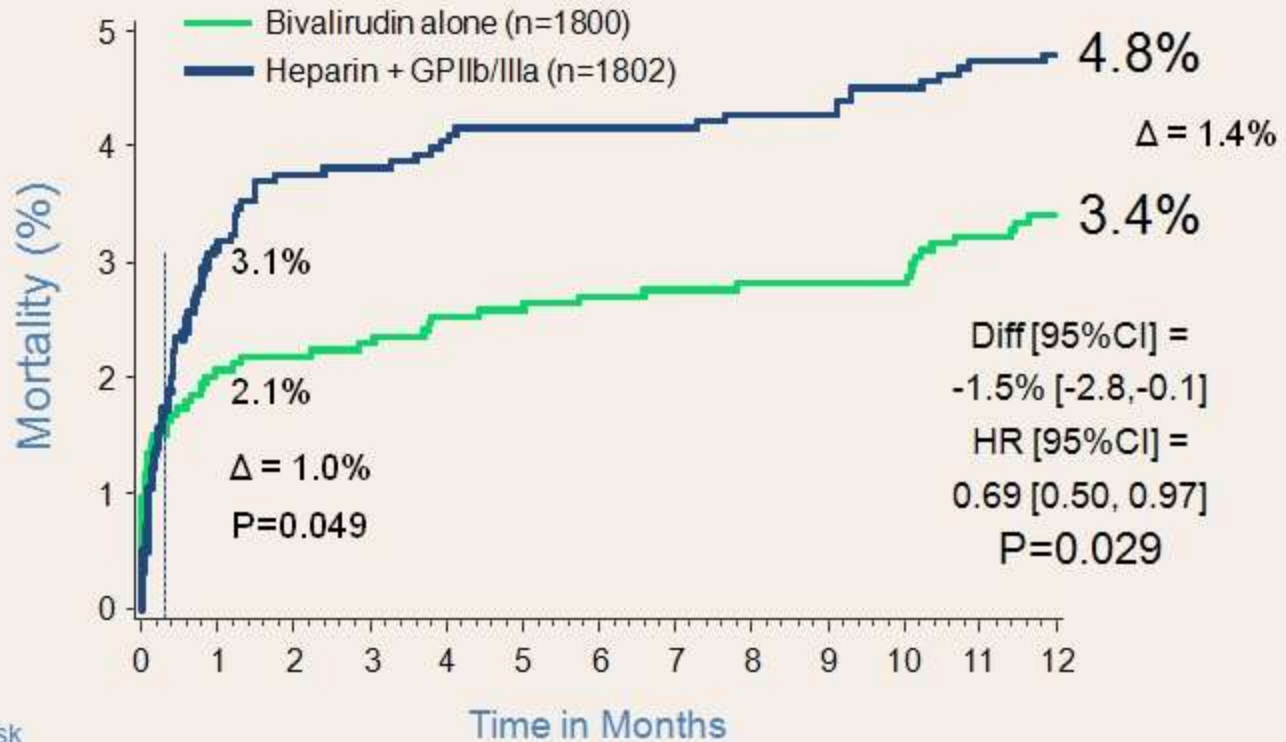
30-Day Cardiac and Noncardiac Mortality



*In HORIZONS AMI, 93% of bivalirudin patients received monotherapy, without provisional GP IIb/IIIa.

Stone GW. *NEJM* 2008; 358:2218-30

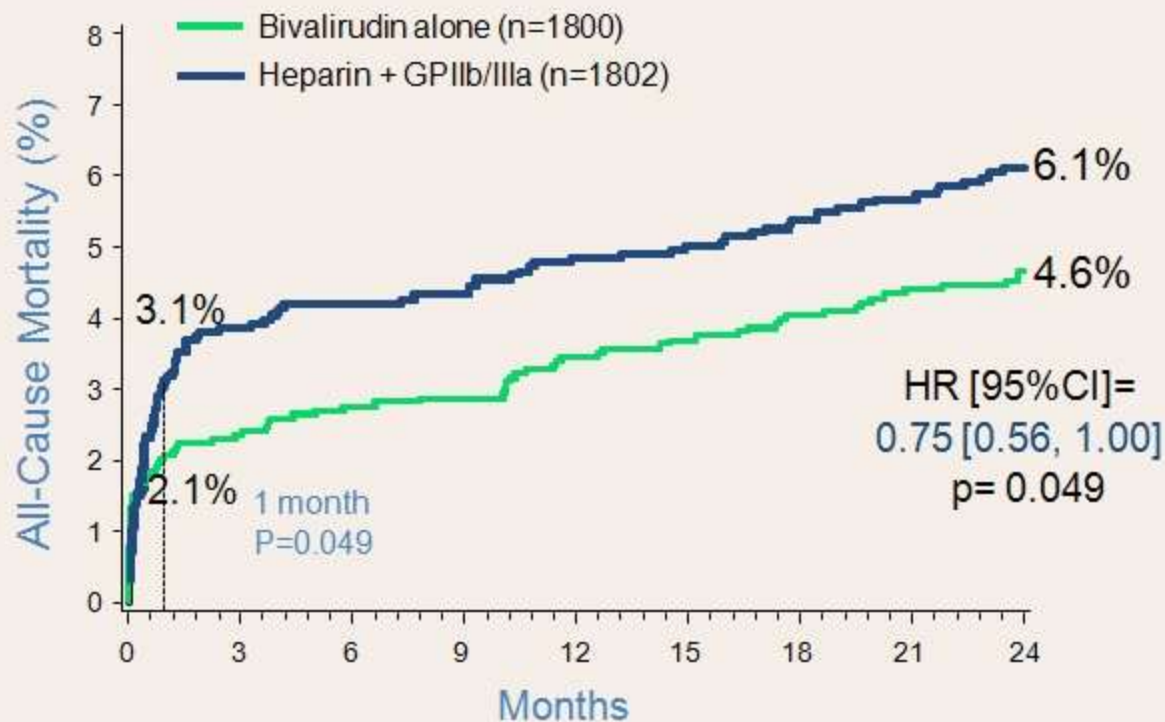
1-Year All-Cause Mortality



Number at risk

	0	1	2	3	4	5	6	7	8	9	10	11	12
Bivalirudin alone	1800	1705	1684	1669	1669	1669	1669	1669	1669	1669	1669	1520	1520
Heparin+GPIIb/IIIa	1802	1678	1663	1646	1646	1646	1646	1646	1646	1646	1646	1486	1486

Two-Year All-Cause Mortality



Number at risk

Bivalirudin alone	1800	1690	1658	1627	1359
Heparin+GPIIb/IIIa	1802	1669	1637	1579	1324

Non-Access Related Bleeding

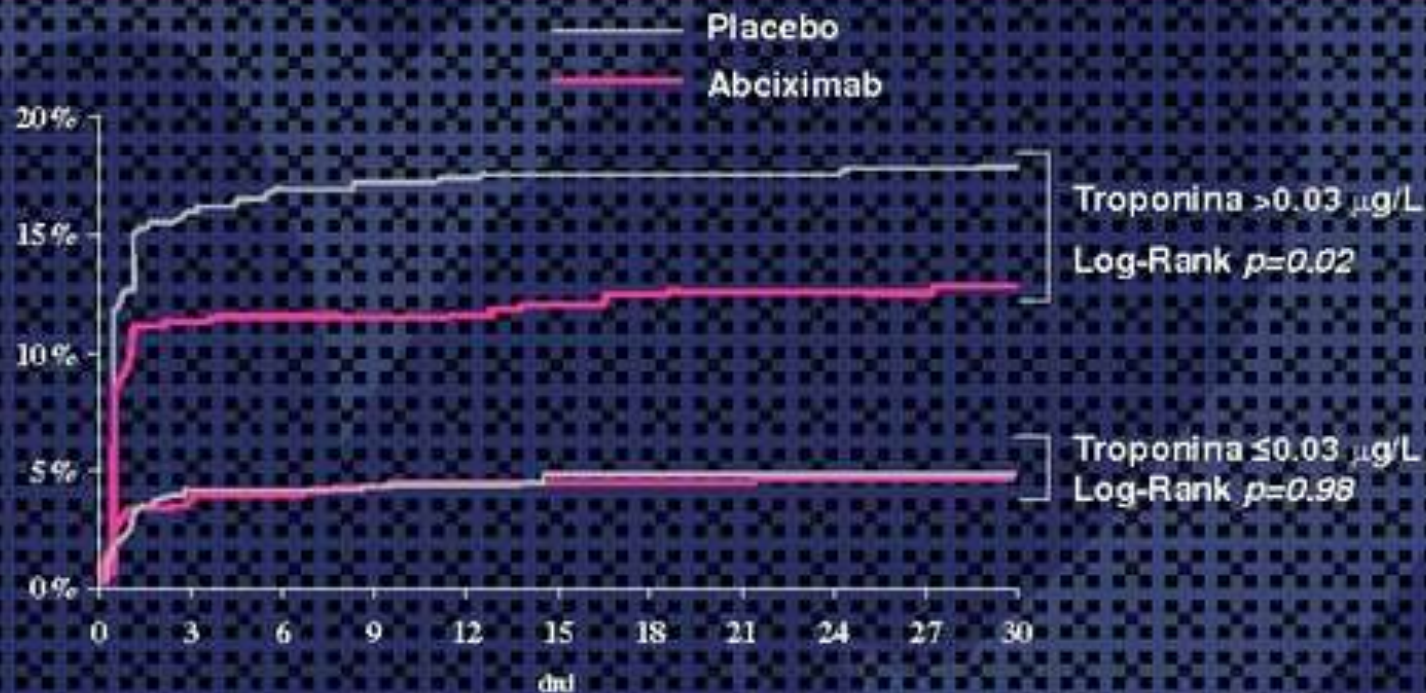


Intracranial bleeding, intraocular bleeding, or a reduction in haemoglobin concentration of ≥ 4 g/dL without an overt source of bleeding



ISAR-REACT 2

– death, MI, urgent PCI

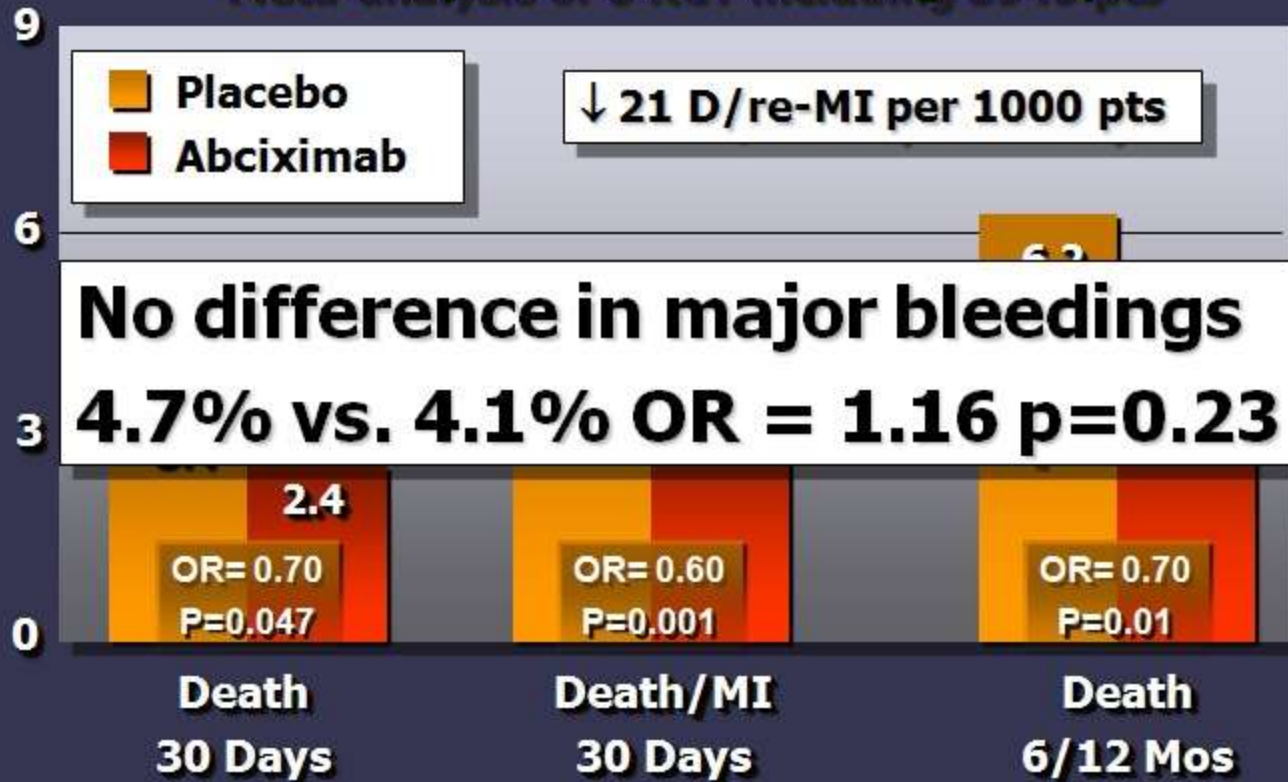


JAMA, 2006;295 (doi:10.1001/jama.295.13.joc60034)



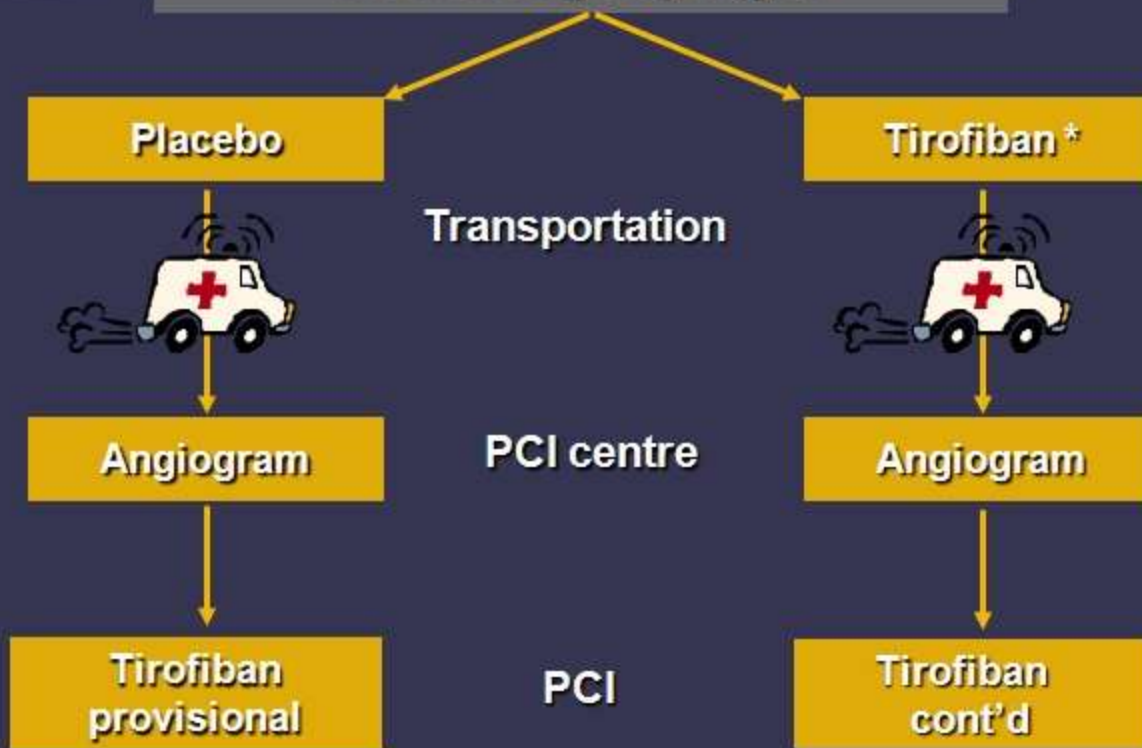
Abciximab in primary PCI: Early and Sustained benefit

Meta-analysis of 8 RCT including 3949 pts



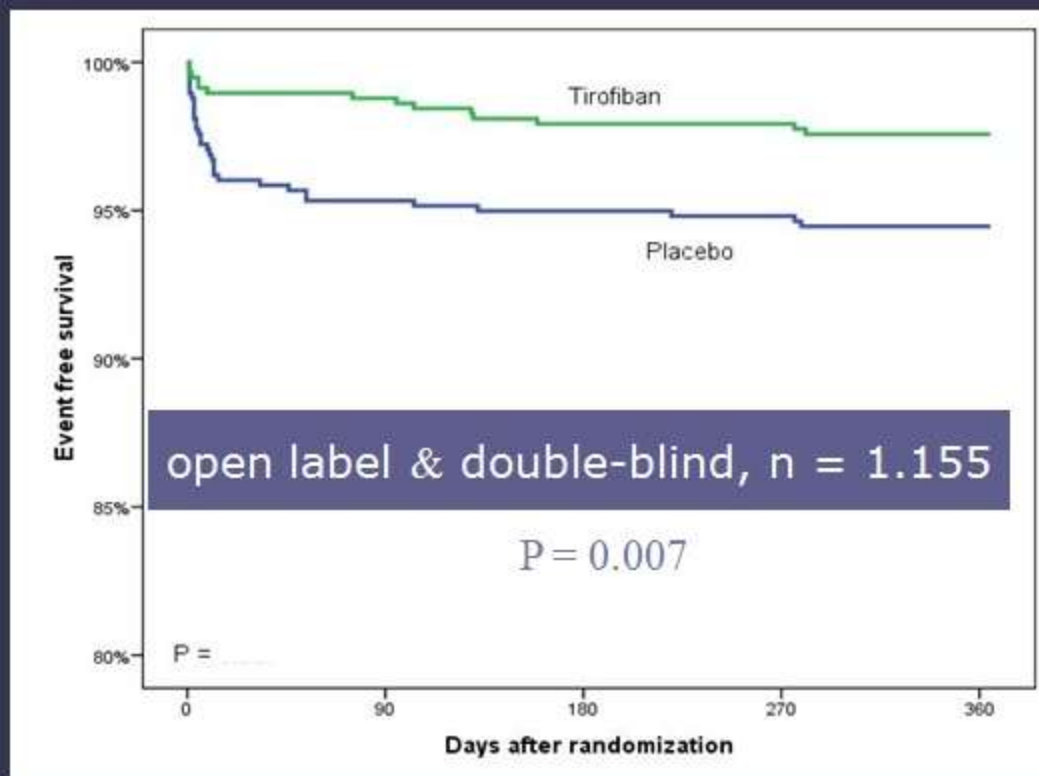
ON-TIME 2 Trial

Acute myocardial infarction
diagnosed in ambulance or referral center
ASA+600 mg Clopidogrel



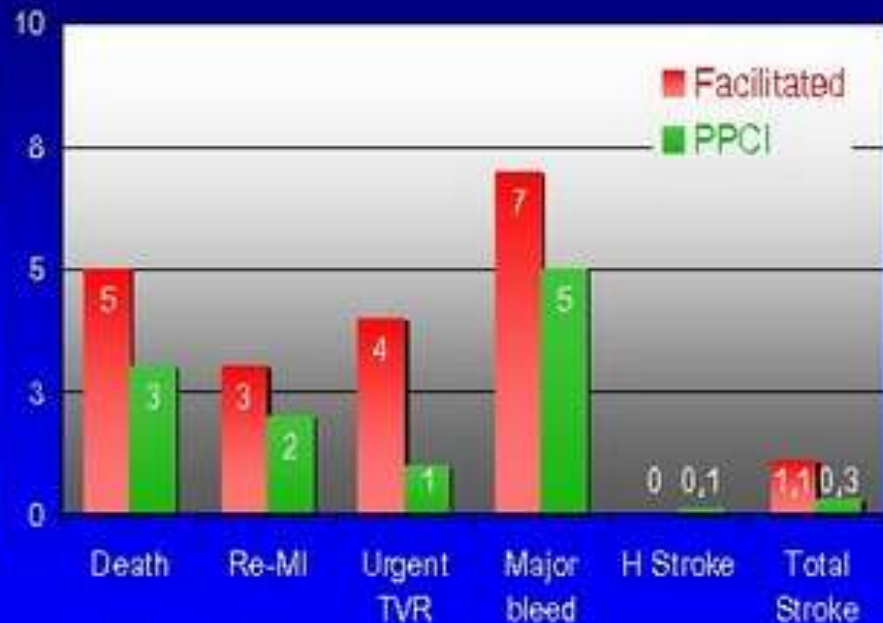
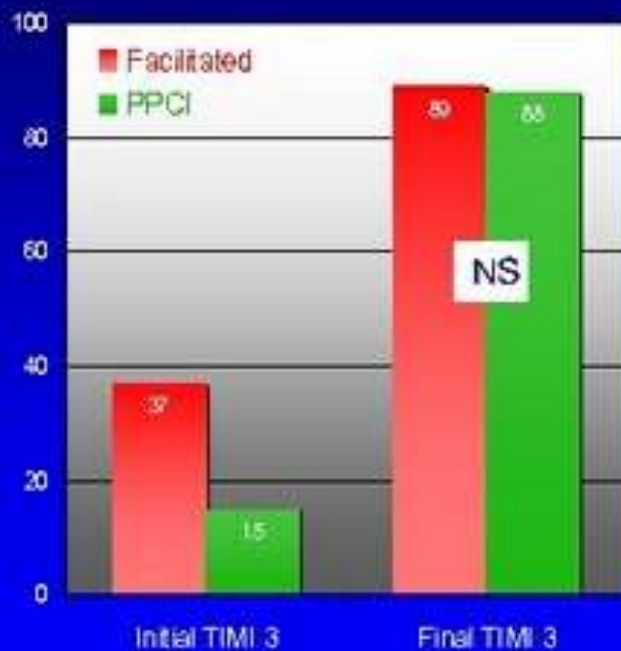
**Bolus: 25 $\mu\text{g}/\text{kg}$ & 0.15 $\mu\text{g}/\text{kg}/\text{min}$ infusion*

1 Year Survival: Patients with Primary PCI



Lytic-facilitated PCI – Review

All comparisons are significant except final TIMI 3



Keeley EC, Boura JA, Grines CL. *The Lancet online*, Feb 14, 2006

TRITON 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

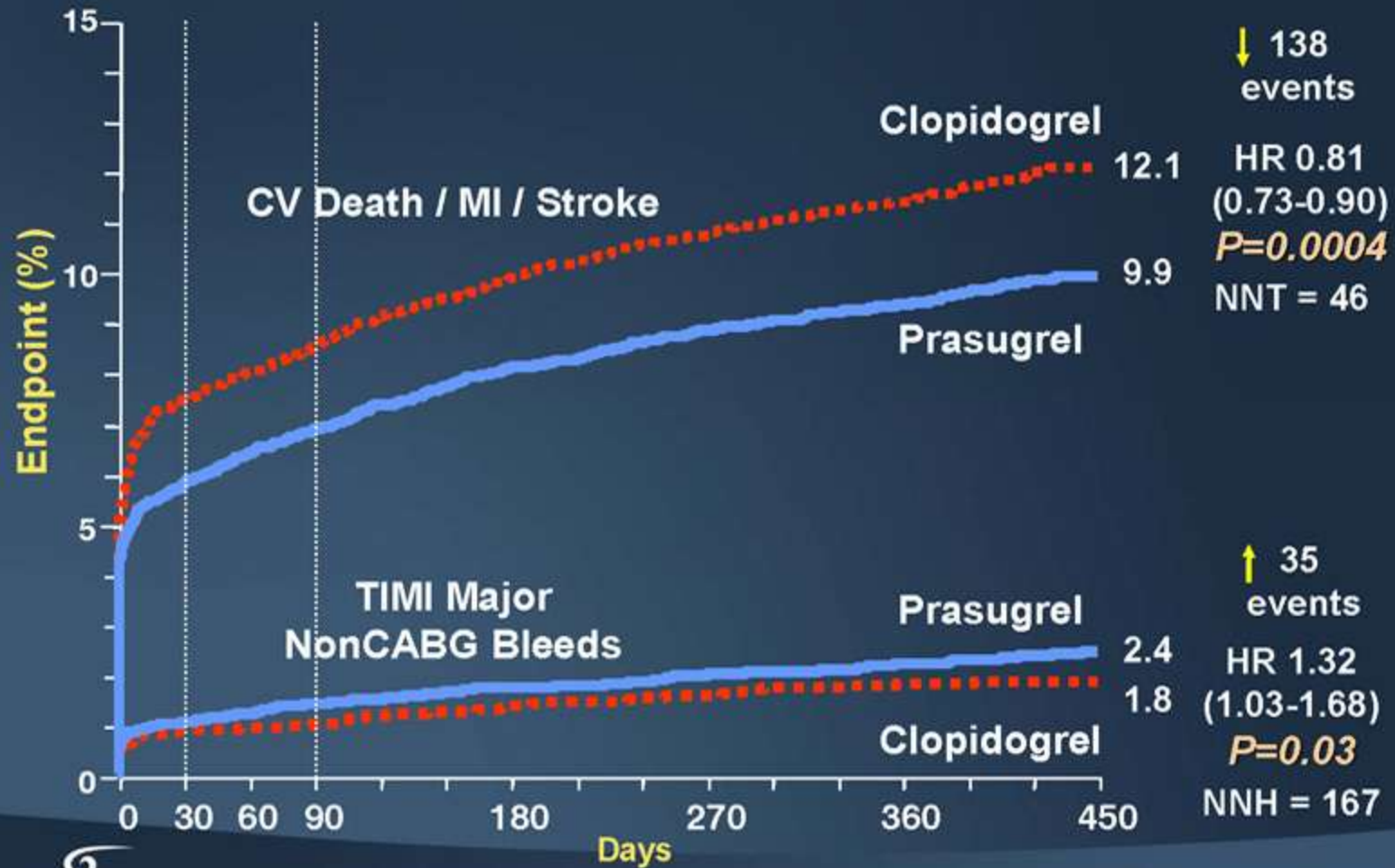
CV death, MI, UTVR

Stent Thrombosis (ARC definite/prob.)

Safety endpoints: TIMI major bleeds, Life-threatening bleeds

Key Substudies: Pharmacokinetic, Genomic

Balance of Efficacy and Safety



TIMI-38 STENT ANALYSIS

Definite/Probable ST: DES Only (N=5743)

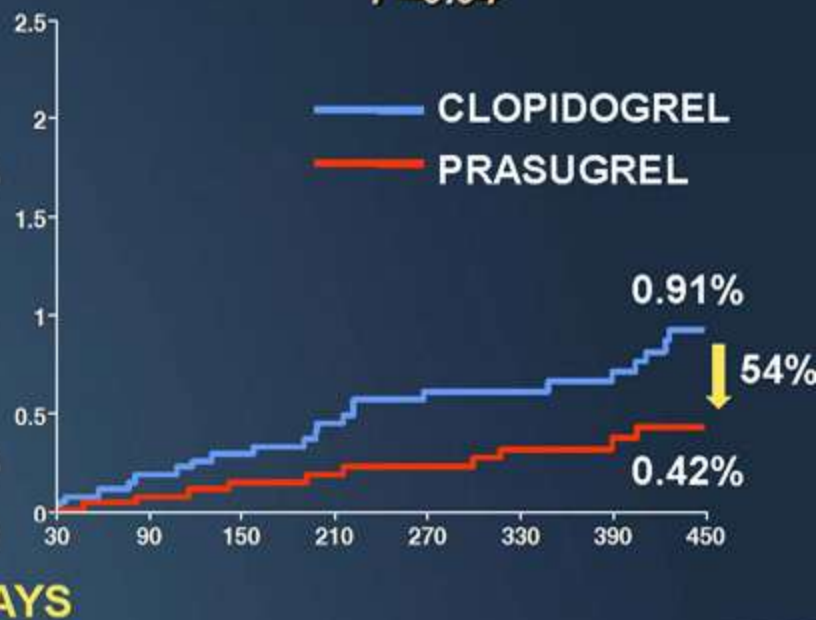
EARLY ST

HR 0.29 [0.15-0.56]
P=0.0001



LATE ST

HR 0.46 [0.22-0.97]
P=0.04

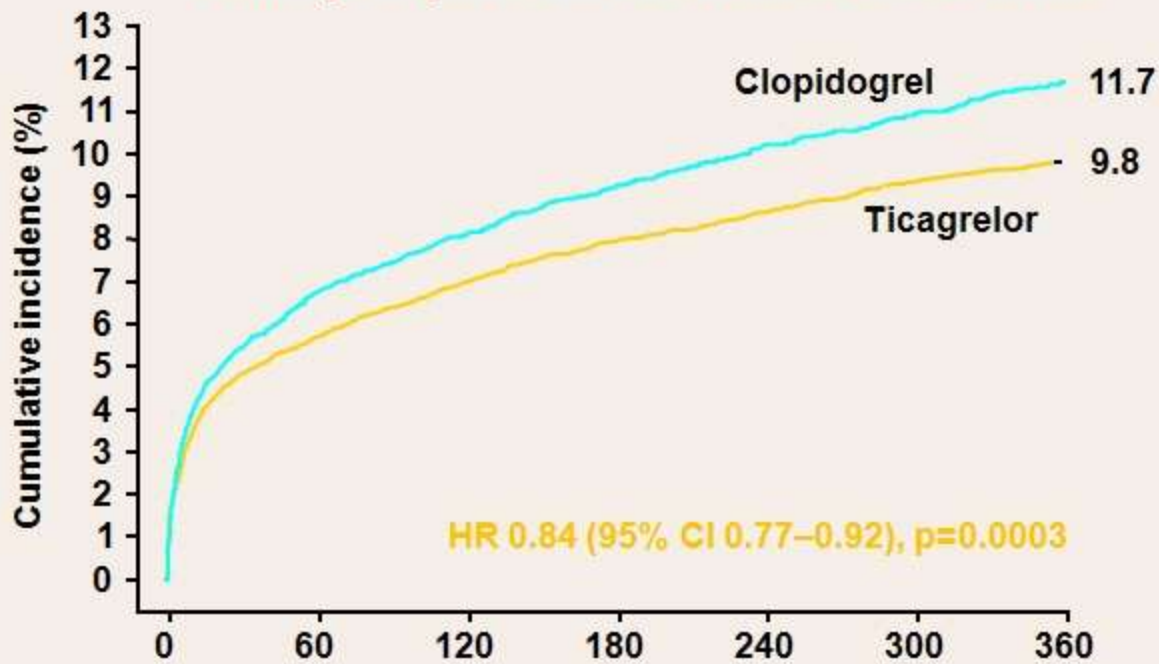


Antiplatelet Therapy Summary

- **<100 mg Aspirin** (300 mg loading dose)
- **600 mg Clopidogrel > 6 hrs before PCI** (300 mg >24 h)
- Reloading 3-600 mg pts on chronic Clopidogrel therapy
- **150 mg Clopidogrel** in the initial periprocedural phase
- Prasugrel 60 mg loading/10 mg maintenance dose probably reserved to high risk patients
- Abciximab in pts with no previous Clopidogrel loading
- **Abciximab in Troponin positive ACS patients undergoing PCI**
- **Tirofiban/eptifibatide in high-risk ACS patients who cannot be rapidly treated with ACS**
- Cilostazol for patients allergic to aspirin and/or thienopyridines

PLATO: ticagrelor vs clopidogrel in all types of ACS

Primary endpoint time to CV death, MI or stroke



No. at risk

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

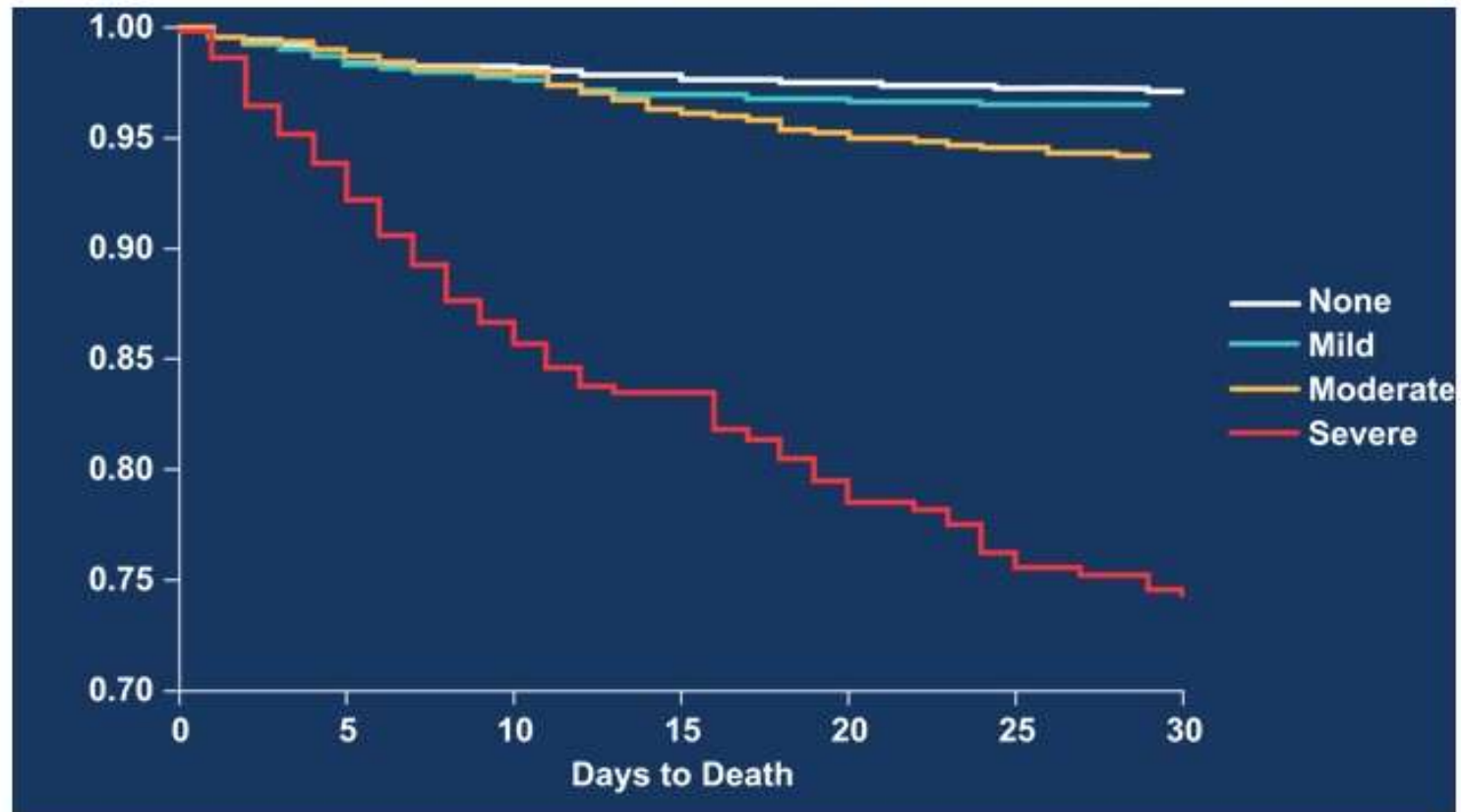
K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

Wallentin et al NEJM 2009

PLATO: summary of bleeding

- The PLATO study evolved bleeding definitions to better capture events occurring in both the chronic and acute settings
- As expected with a more potent antiplatelet therapy, there was an increase in bleeding with ticagrelor compared to clopidogrel; and, PLATO-defined minor and minimal bleeding was greater with ticagrelor than clopidogrel in this study
- Importantly, ticagrelor had no increase in overall major or fatal bleeding compared to clopidogrel

Kaplan Meier Curves for 30-Day Death, Stratified by Bleed Severity



Rao SV, et al. *Am J Cardiol.* 2005



**It is tough to keep
the balance
between efficacy
and safety of
antithrombotics !**

Antiplatelets

Elective PCI				
Antiplatelet therapy		Class ^a	Level ^b	Ref. ^c
	ASA	I	B	55
	Clopidogrel	I	A	55
	Clopidogrel - pretreatment with 300 mg loading dose >6 h before PCI (or 600 mg >2 h before)	I	C	—
	+ GPIIb-IIIa antagonists (bailout situation only)	IIa	C	—

NSTEMI-ACS				
Antiplatelet therapy				
	ASA	I	C	—
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C	—

+ GPIIb-IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)				
	Abciximab (with DAPT)	I	B	
	Tirofiban, Eptifibatide	IIa	B	
	Upstream GPIIb-IIIa antagonists	III	B	

STEMI				
Antiplatelet therapy				
	ASA	I	B	55, 94

+ GPIIb-IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)				
	Abciximab	IIa	A	
	Eptifibatide	IIa	B	
	Tirofiban	IIb	B	
	Upstream GPIIb-IIIa antagonists	III	B	

Guidelines on myocardial revascularization.
Eur Heart J (2010) 31 (20): 2501-2555.

Adjunctive antithrombotic Rx for STEMI PCI

STEMI			
Antiplatelet therapy			
	ASA	I	B
	Clopidogrel ^f (with 600 mg loading dose as soon as possible)	I	C
	Prasugrel ^d	I	B
	Ticagrelor ^d	I	B
	+ GPIIb-IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)		
	Abciximab	IIa	A
	Eptifibatide	IIa	B
	Tirofiban	IIb	B
	Upstream GPIIb-IIIa antagonists	III	B
Anticoagulation			
	Bivalirudin (monotherapy)	I	B
	UFH	I	C
	Fondaparinux	III	B

ΣΑΣ ΕΥΧΑΡΙΣΤΩ

IICE 2011

ΘΕΣΣΑΛΟΝΙΚΗ