Antiplatelet therapy and Coronary Interventions

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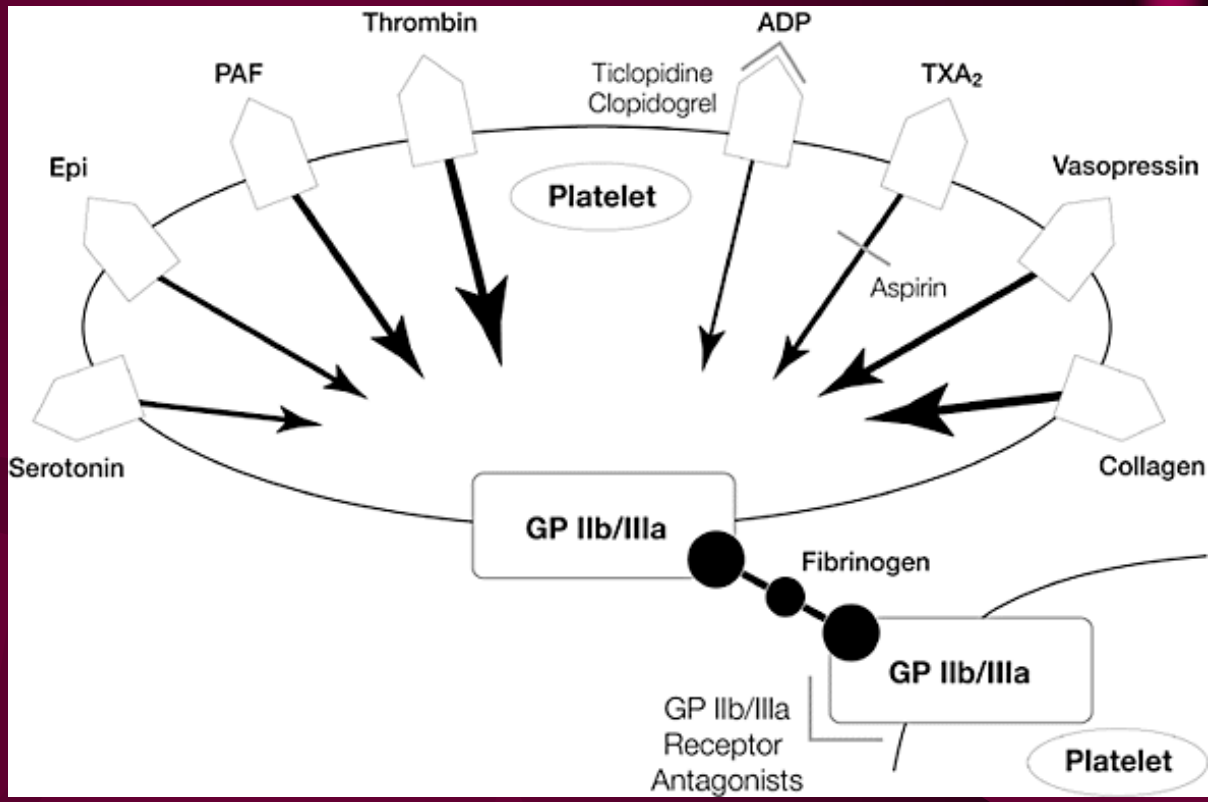
Objectives

- Pharmacology of GP IIb/IIIa inhibitors and Monitoring of Platelet Inhibition
- Appropriate Use of GP IIb/IIIa inhibitors during PCI
- The Thienopyridines
- PCI Algorithm

Platelet activation and aggregation

- Hemostasis and Thrombosis
- (GP) Ib – vWF interaction
- Activation of GP IIb/IIIa receptors
- Ligand binding* and platelet aggregation



*** Fibinogen, vWF, fibronectin, vitronectin**

GP IIb/IIIa Antagonists

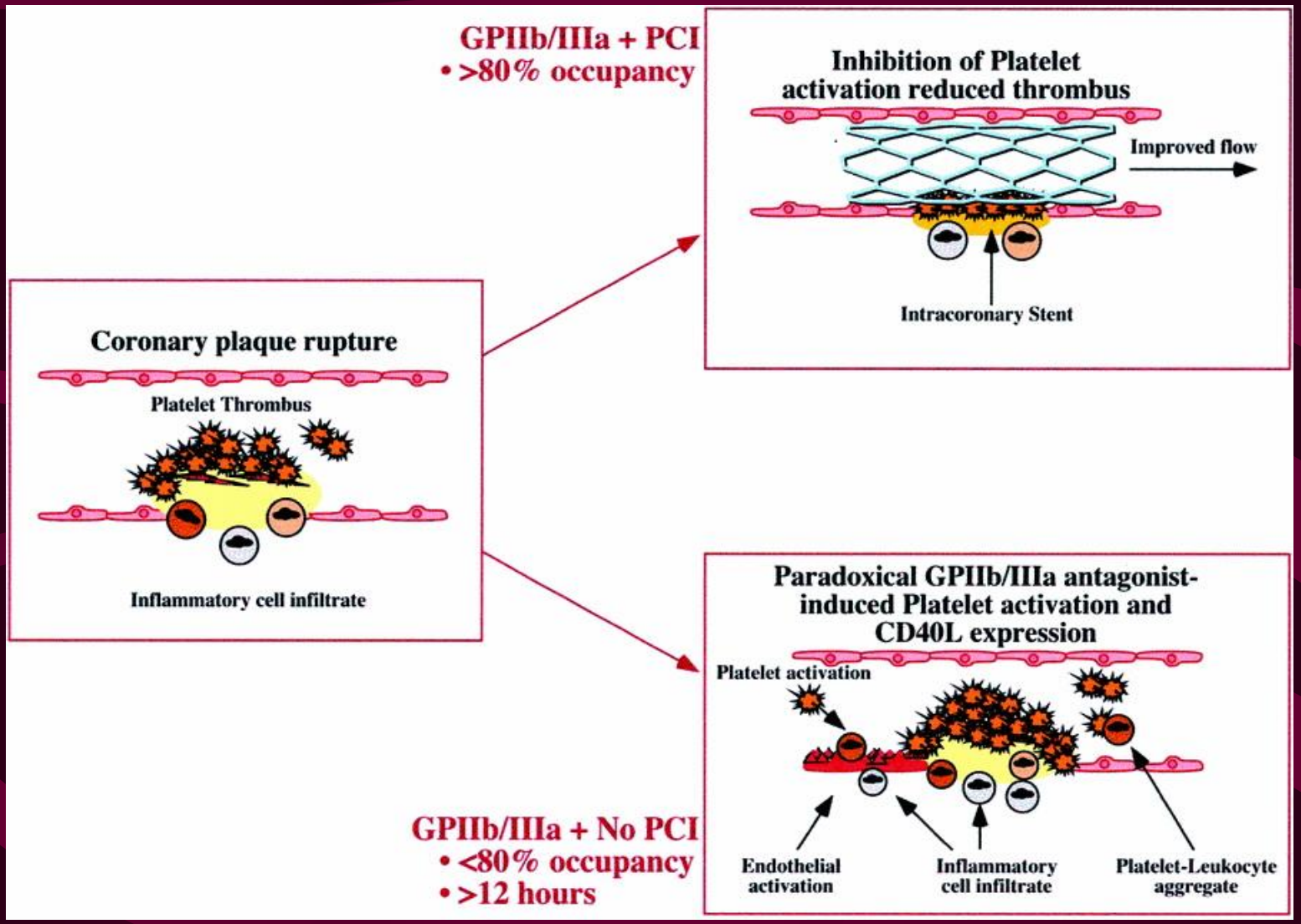
- Abciximab
  - Murine Monoclonal Antibody
  - Binds rapidly – dissociates slowly
  - Not IIb/IIIa integrin-specific (Mac-1, Vitronectin)
  - Inhibits Thrombin generation
  - 6% anti-abciximab antibodies

- Eptifibatide - Tirofiban
  - Synthetic peptide (Sistrurus M. Barbouri - Echistatin)
  - Binds and dissociates rapidly
  - GP IIb/IIIa Integrin specific
  - Not immunogenic

Platelet Aggregation Inhibition Essays

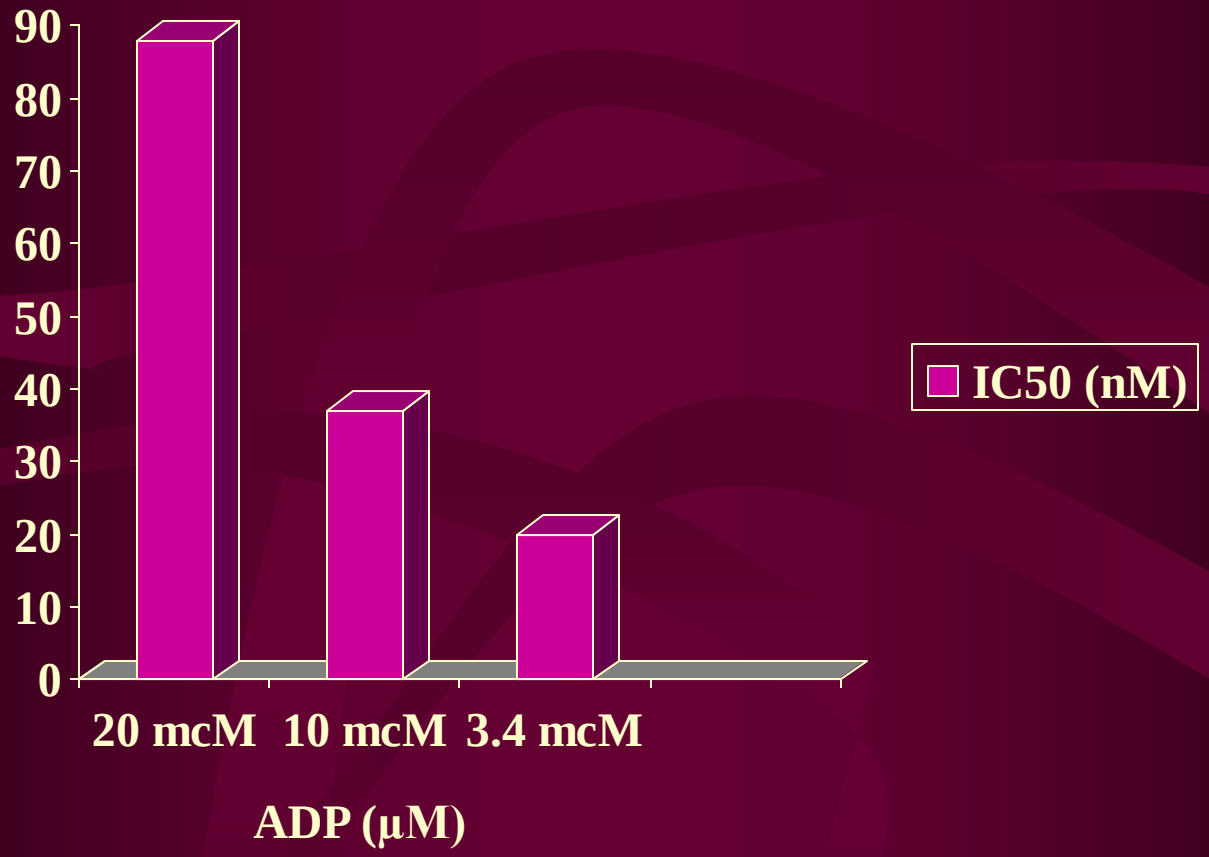
- **Light Transmission Aggregometry (LTA)**
  - **Time consuming**
  - **Linear relationship**
  - **Anticoagulants (Sodium citrate, PPACK, UFH, EDTA)**
  - **Platelet agonists (ADP, thrombin)**
  - **Tirofiban (3.4-5 μM ADP) vs. abciximab/eptifibatide (20 μM)**
  - **>80%: surrogate inhibition**
- Rapid Platelet Function Essay (RPFA)
  - **Bedside monitoring**
  - **Iso-TRAP agonist**
  - **Correlation with LTA not ideal**
  - **>80% target inhibition**
  - **>95% clinically tested**

Prolonged exposure to low levels of platelet inhibition (<80%), enables paradoxical expression of GP IIb/IIIa pro-thrombotic effect



Quinn et al. *Circulation 2002;106:379-85.*

IC50 of Tirofiban inhibition of platelet aggregation (LTA) when platelets are stimulated by increasing concentrations of ADP



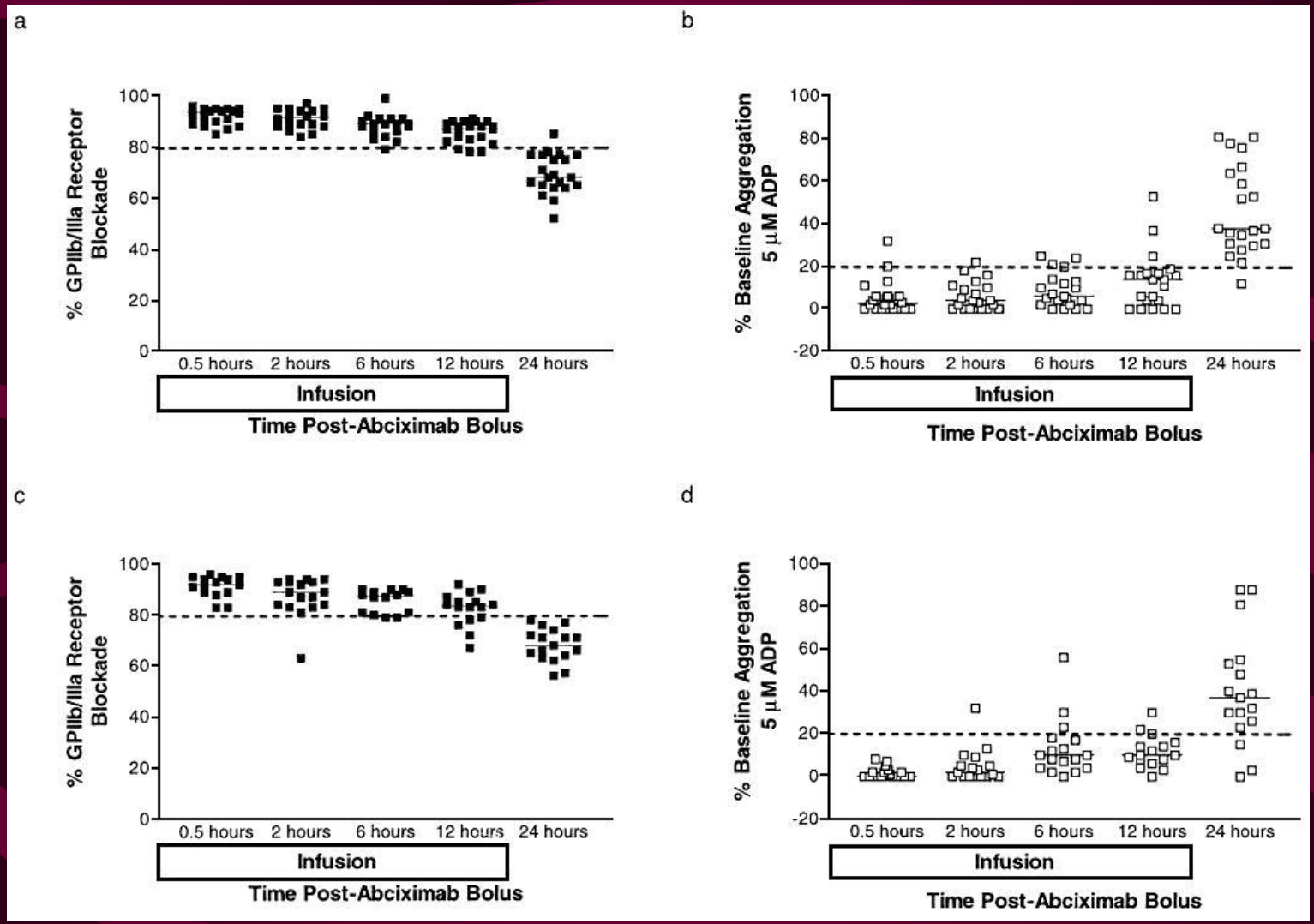
Jennings et al. *J. Interven Cardiol 2002;15:45-60.*

Lack of Correlation between Platelet Aggregation Inhibition Measurements obtained by RPFA and LTA with Tirofiban

Time	RPFA	LTA
10 min	73%	73%
2 hrs	91%	74%
6 hrs	91%	77%
18-20 hrs	92%	76%

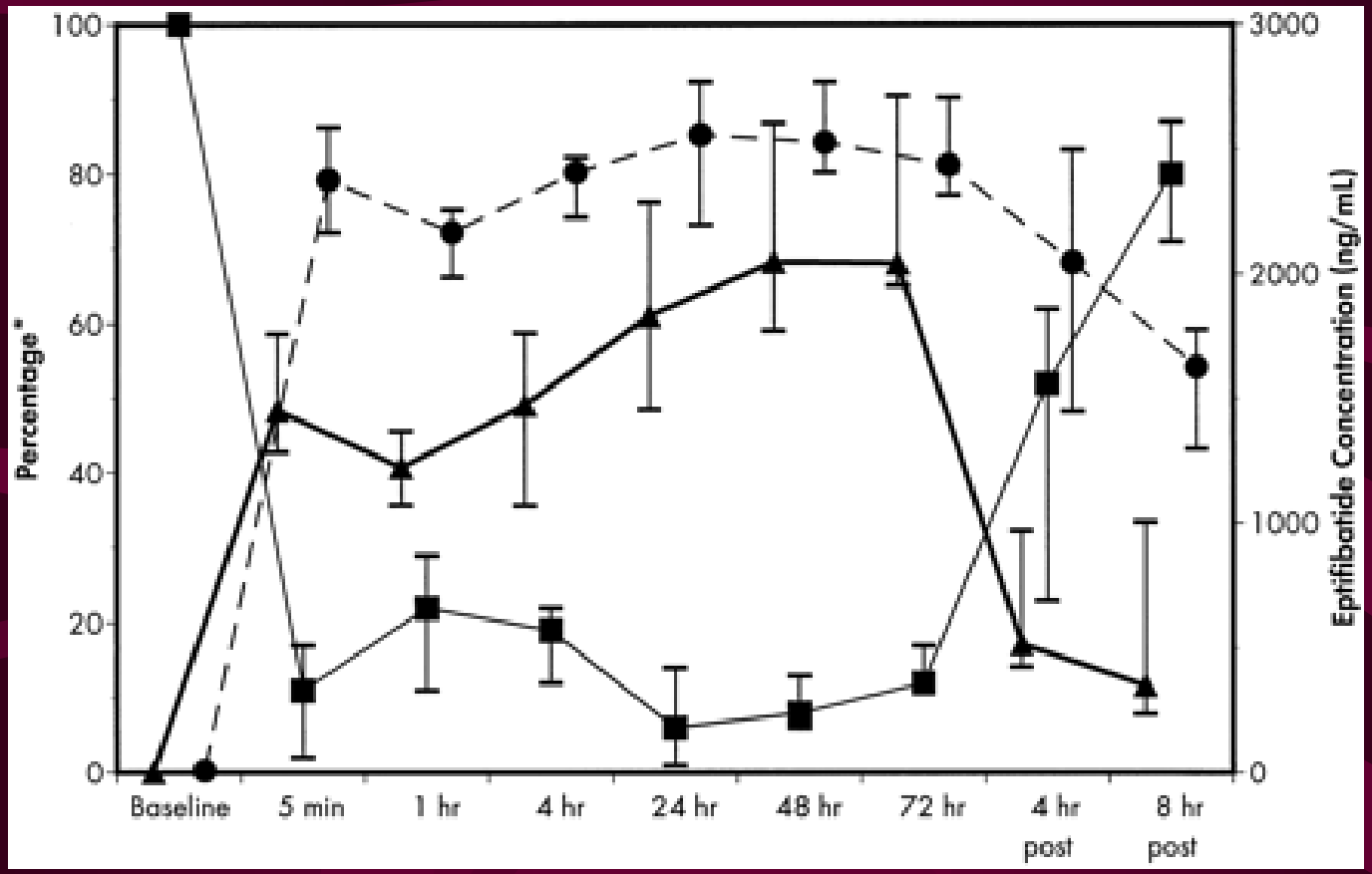
Kereiakes et al. ***Am J Cardiol 1999;94:391-5.***

Dose Selection Studies with Abciximab



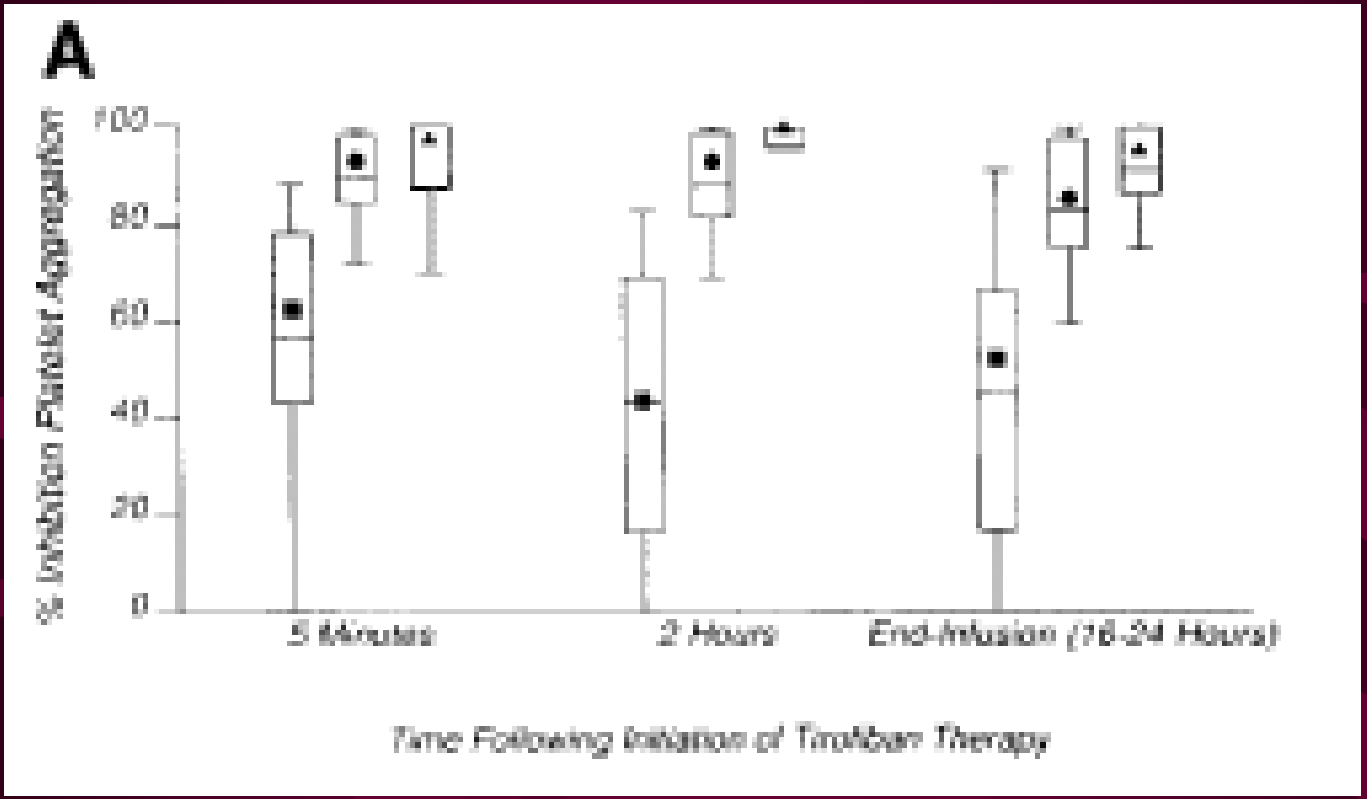
Masceli et al. Abciximab EPIC and EPILOG comparisons. ***Circulation 1998;97:1680-88.***

Dose Selection Studies with Eptifibatide (LTA)



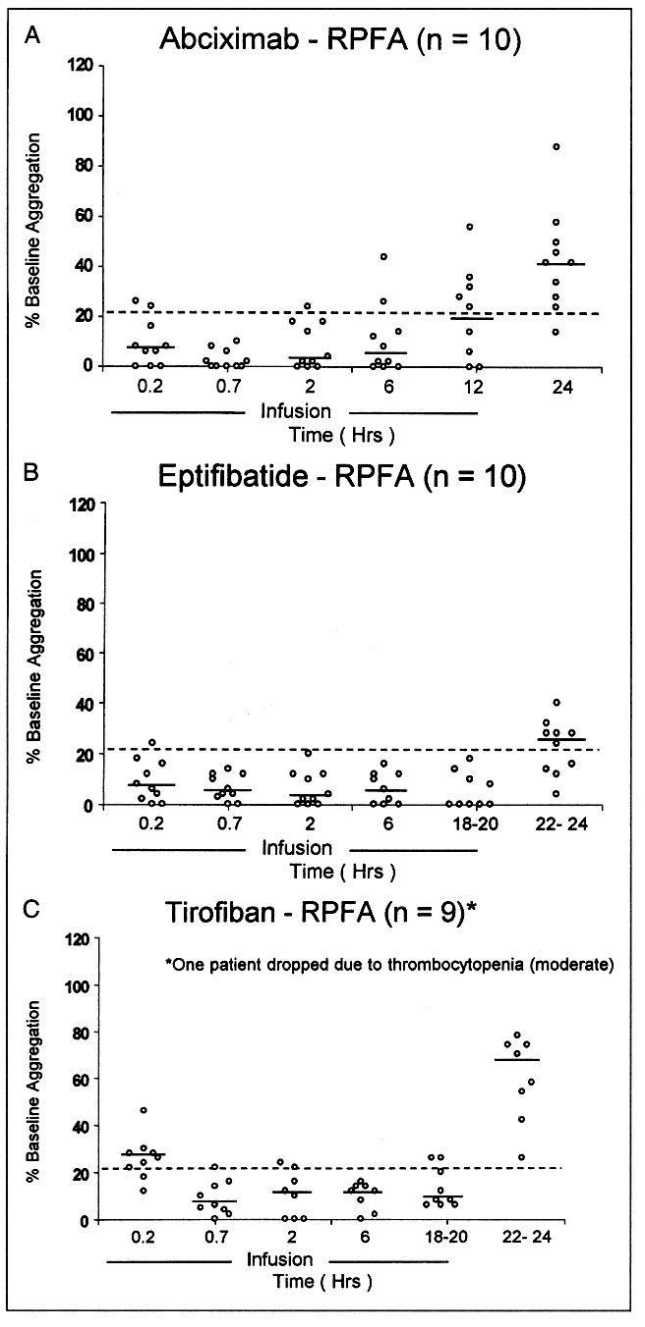
Tardiff et al. ***Circulation 2001;104:399-405***. Median normalized platelet aggregation analyzed in PPACK with ADP (■), receptor occupancy analyzed in PPACK (•), and eptifibatide concentration (4). Vertical lines indicate 25th, 75th percentiles. All results after 48 hours, n<10. **PURSUIT Trial (180/2.0)**

Dose Selection Studies with Tirofiban (LTA)



Percent Inhibition of ex vivo platelet aggregation at 5 min, 2 hrs and end of infusion. Median (symbol) and Mean (dashed lines). Dosing (Bolus + Infusion) ■:5/0.05, ●: 10/0.1, ▲: 10/0.15

Kereiakes et al. ***J Am Coll Cardiol 1996;27:536-42.***

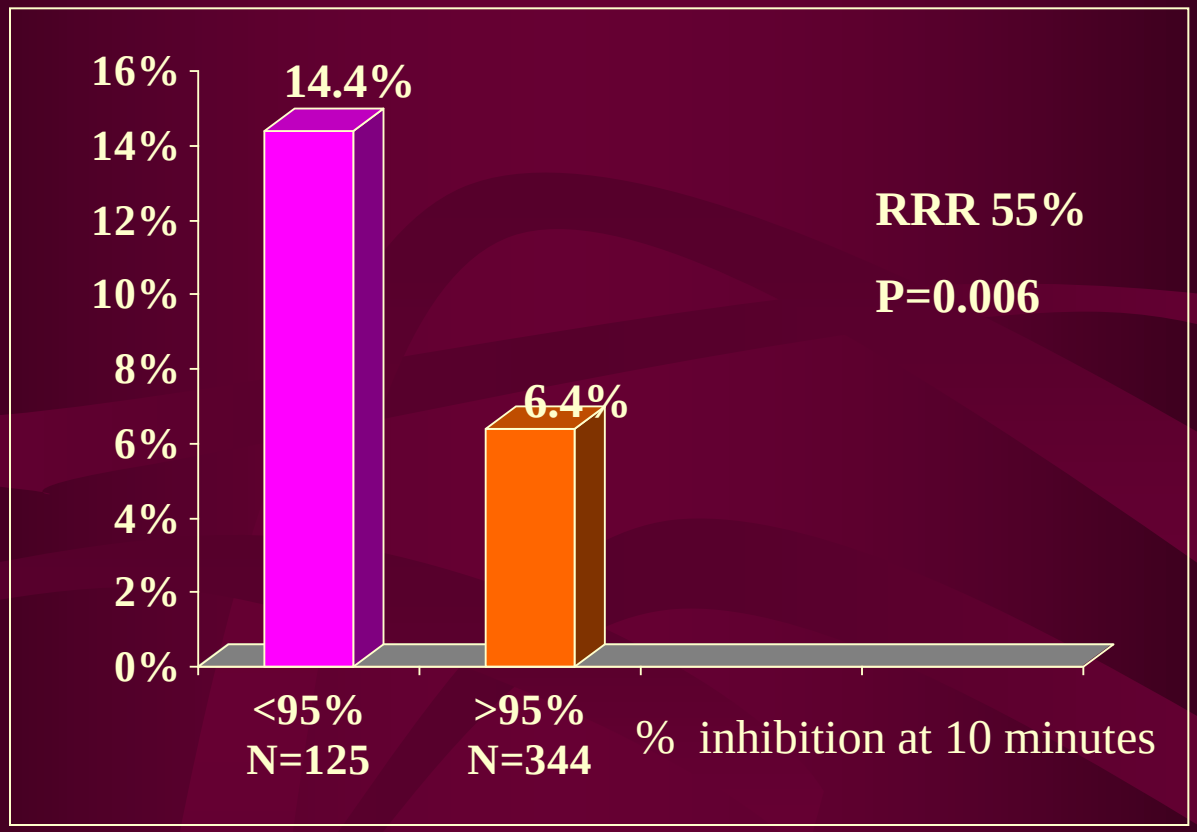


Comparison of Platelet inhibition among Abciximab (0.25 μg/kgr + 0.125 μg/kg/min for 12 hrs), Eptifibatide (180 μg/kgr + 2 μg/kgr/min for 20-24 hrs), Tirofiban (0.4 μg/kgr + 0.1 μg/kgr/min for 20-24 hrs) in patients undergoing PCI (LTA, 20 μM ADP, PPACK anticoagulant).

The **dashed lines** represent 20% residual platelet aggregation, whereas the **solid lines** reflect the median platelet aggregation values.

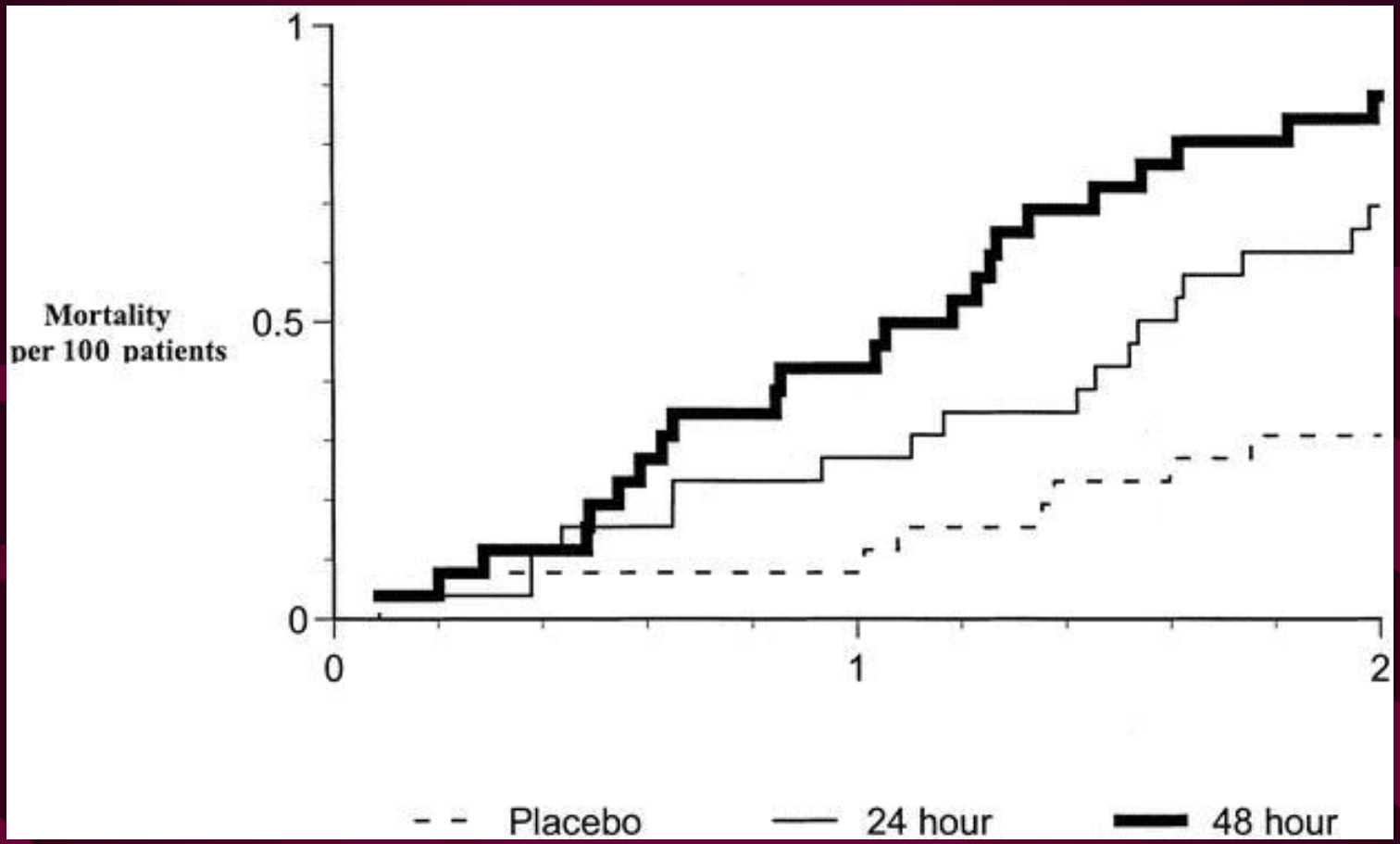
Kereiakes et al. ***Am J Cardiol 1999;84:391-5.***

MACE Versus Platelet Inhibition by RPFA



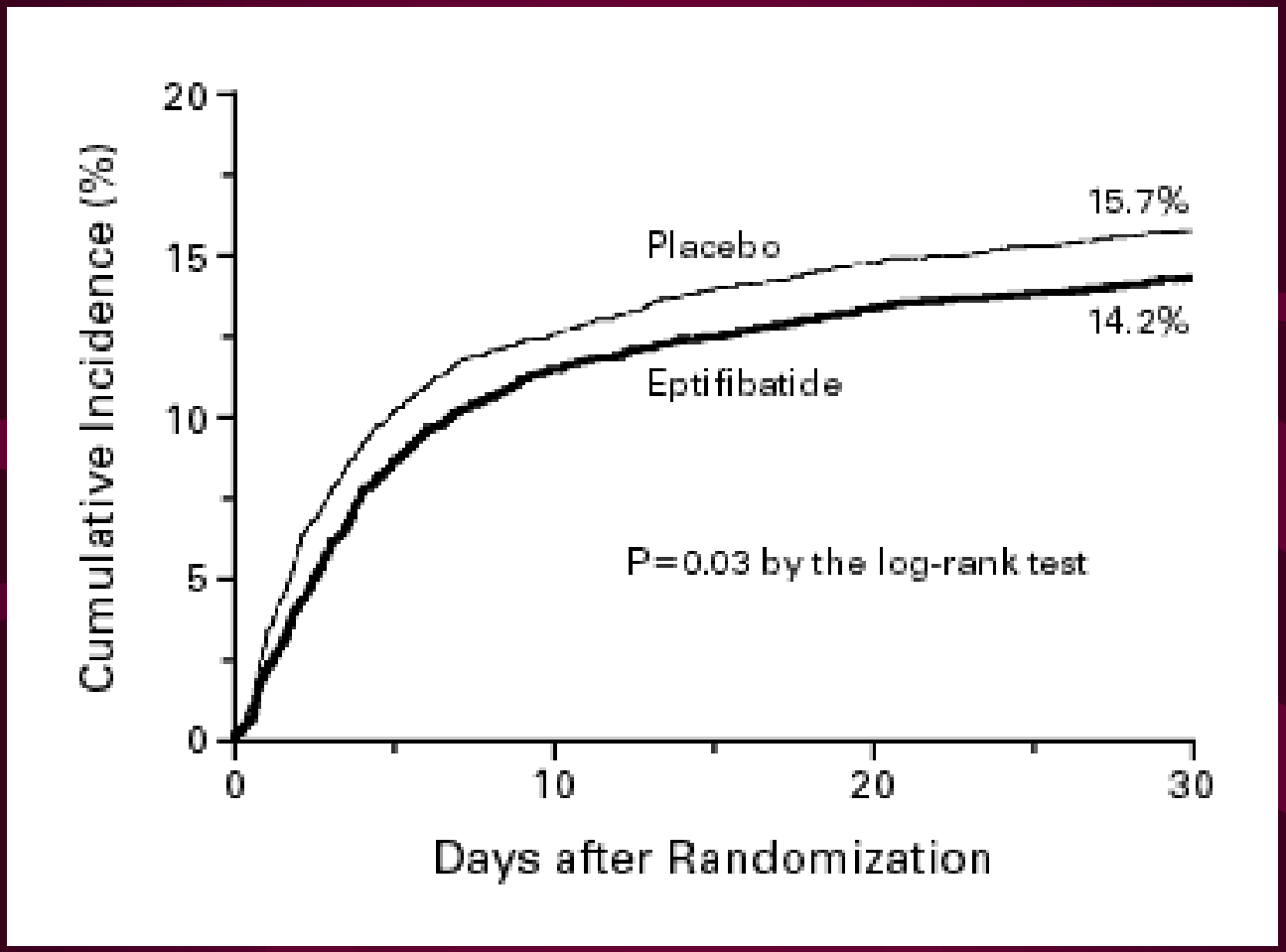
The GOLD Trial. ***Circulation 2001;103:2572-78.***

Clinical Implications: GUSTO IV-ACS



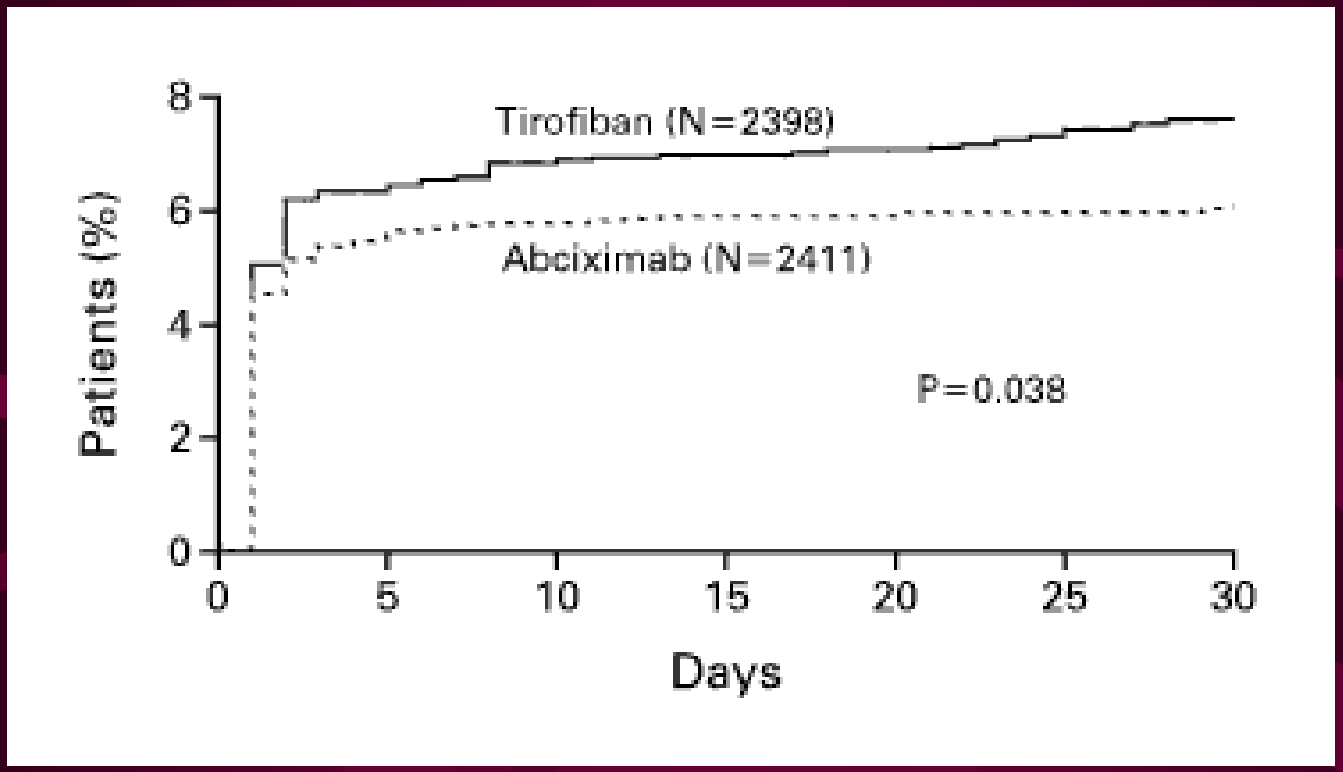
Increased mortality in the 24-hr (p=0.048) and 48-hr (p=0.007) abciximab groups. The curves separate early an continue to separate after 24 hrs. **Circulation 2002;106:379-85.**

Clinical Implications: PURSUIT (ACS)



Kaplan–Meier Curves Showing the Incidence of Death or Nonfatal Myocardial Infarction at 30 Days. **N Engl J Med 1998;339:436-443.**

Clinical Implications: TARGET



TARGET: Incidence of the Primary End Point, a Composite of Death, Nonfatal Myocardial Infarction, or Urgent Target-Vessel Revisualization, in the First 30 Days after Enrollment. **N Engl J Med 2001;344:1888-1942.**

Conclusions: Monitoring Platelet Inhibition

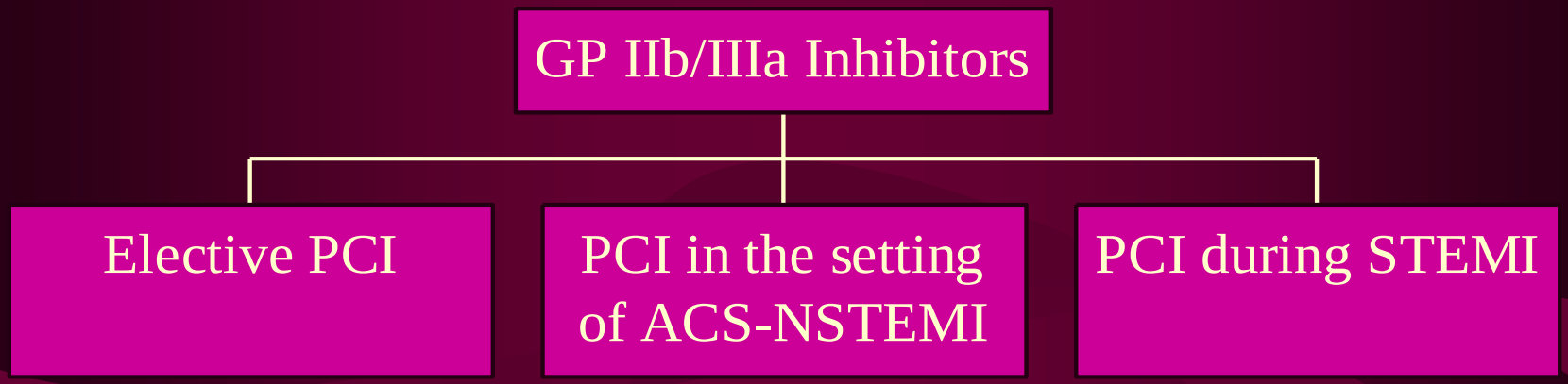
- >80% (LTA) Platelet Inhibition during PCI is desirable
- Abciximab response has substantial interpatient variability
- Eptifibatide double bolus is very efficacious and consistent (ESPRIT data)
- Tirofiban current regimen may be inadequate especially for early platelet inhibition

Objectives

- Pharmacology of GP IIb/IIIa inhibitors and Monitoring of Platelet Inhibition
- Appropriate Use of GP IIb/IIIa inhibitors during PCI
- The Thienopyridines
- PCI Algorithm

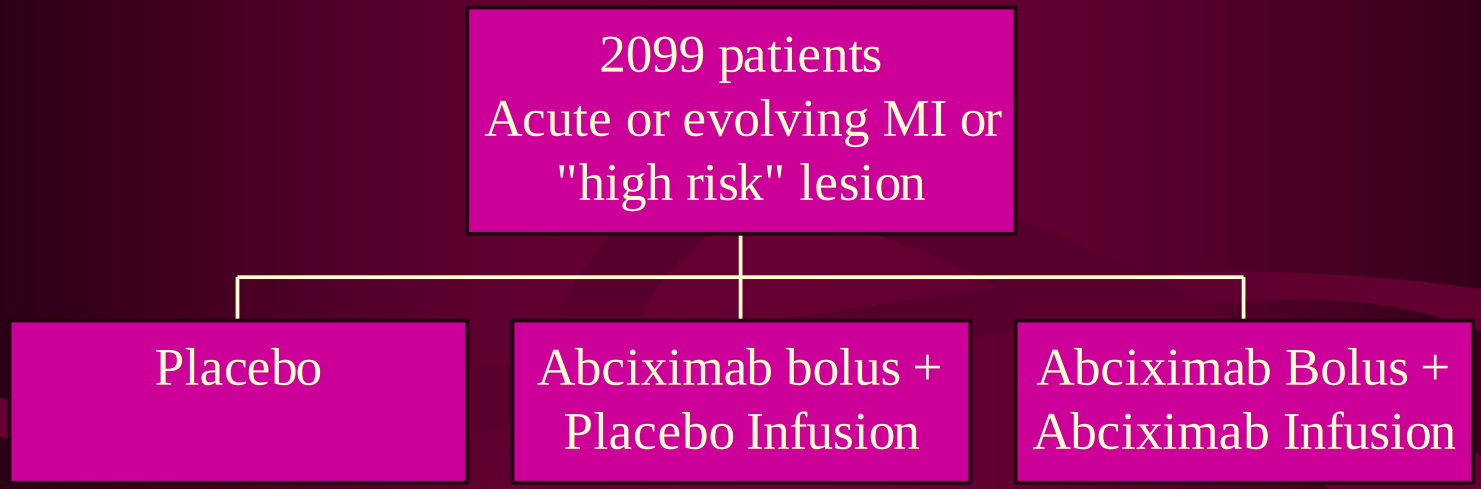
Long before fellowship!

Trials with GP IIb/IIIa Inhibitors during PCI



Modified from Karvouni et al. ***J Am Coll Cardiol 2003;41:26-32.***

GP IIb/IIIa Inhibitors during ACS + PCI (PTCA): EPIC



- ASA 325 mg PO QD
- Heparin (ACT 300-350 sec)
- No Plavix/Ticlid post PTCA

Primary Combined End Point (30-days)

- Death or non fatal MI
- CABG or repeat PCI
- Stent insertion(!) or IABP

N Engl J Med 1994;330:956-61

30-days EPIC Results (n=2099)

Event*	Placebo (N = 696)	c7E3 Fab Bolus (N = 695)	c7E3 Fab Bolus and Infusion (N = 708)	P Value for Dose Response
	no. of patients (%)			
Primary end point	89 (12.8)	79 (11.4)	59 (8.3)	0.009†
Components of primary end point				
Death	12 (1.7)	9 (1.3)	12 (1.7)	0.96
Nonfatal myocardial infarction	60 (8.6)	43 (6.2)	37 (5.2)	0.013
Q wave	16 (2.3)	7 (1.0)	6 (0.8)	0.020
Large non-Q wave	28 (4.0)	19 (2.7)	21 (3.0)	0.265
Small non-Q wave	16 (2.3)	17 (2.4)	10 (1.4)	0.239
Emergency PTCA	31 (4.5)	25 (3.6)	6 (0.8)	<0.001
Emergency CABG	25 (3.6)	16 (2.3)	17 (2.4)	0.177
Stent placement	4 (0.6)	12 (1.7)	4 (0.6)	0.98
Balloon-pump insertion	1 (0.1)	1 (0.1)	1 (0.1)	0.99

*PTCA denotes percutaneous coronary angioplasty or atherectomy, and CABG coronary-artery bypass grafting.

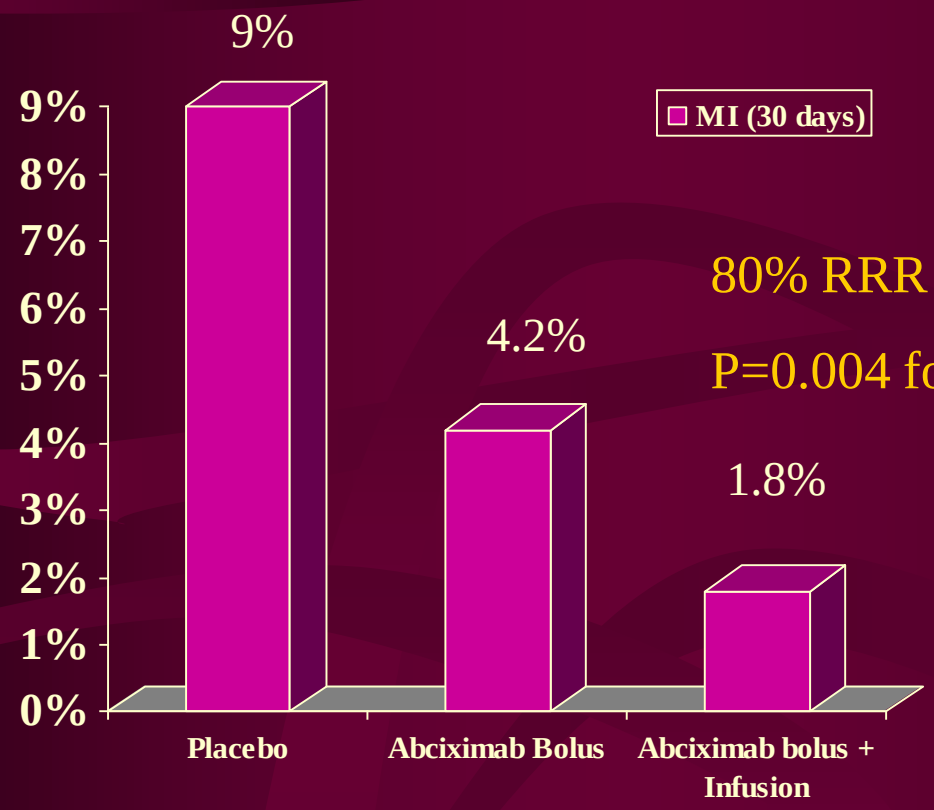
†P = 0.009 for overall test for trend, P = 0.43 for comparison of the placebo group with the group given the bolus only, and P = 0.008 for comparison of the placebo group with the group given the bolus and infusion.

35% RRR

40% RRR

N Engl J Med 1994;330:956-61.

EPIC UA Subgroup (n=489)

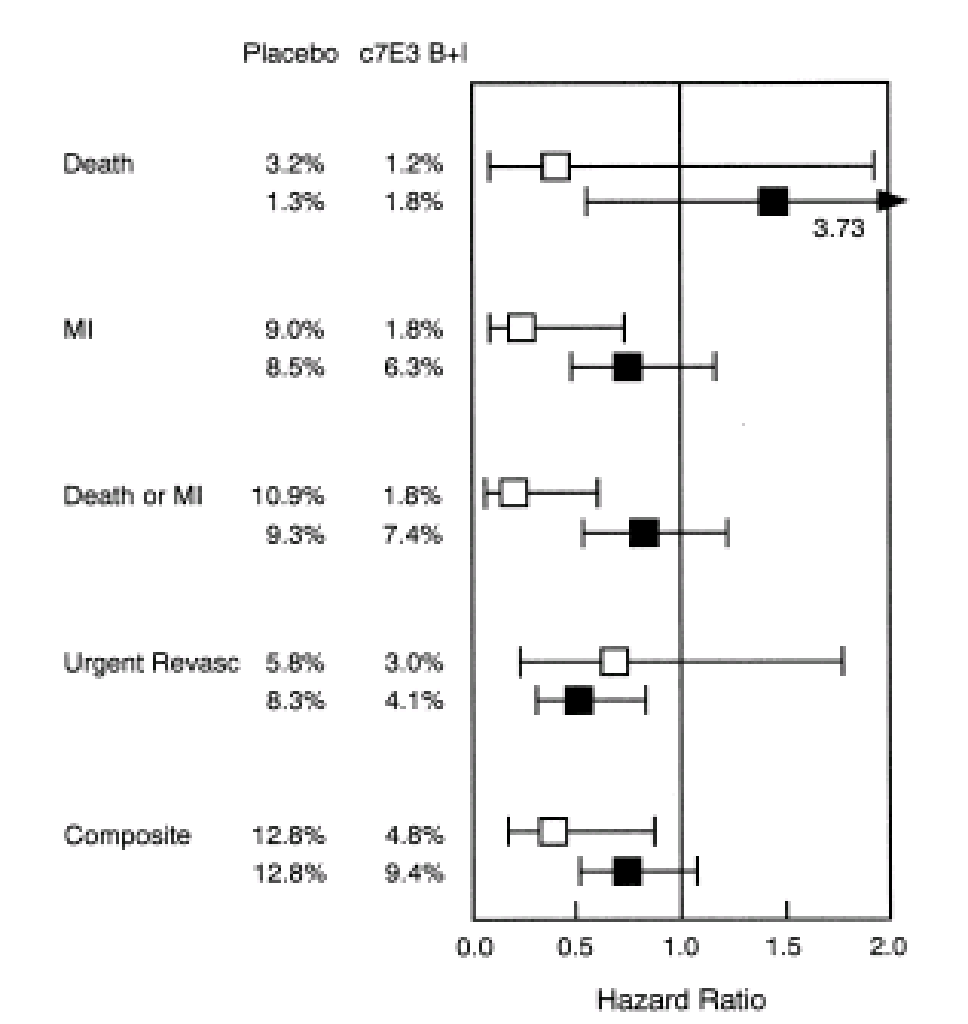


80% RRR

P=0.004 for dose response

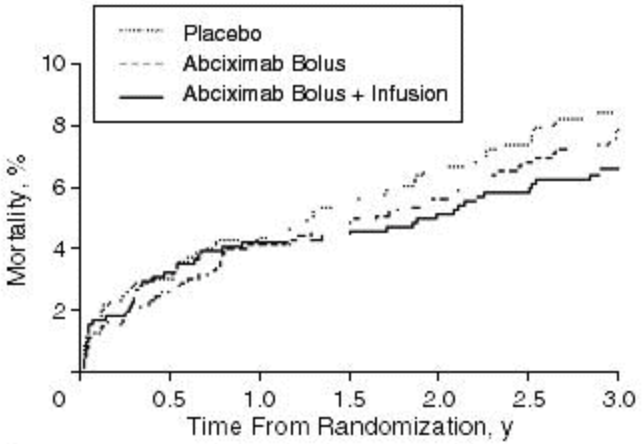
J Am Coll Cardiol 1997;30:149-56.

UA Subgroup of EPIC: Benefit of Abciximab in reducing MI in UA patients

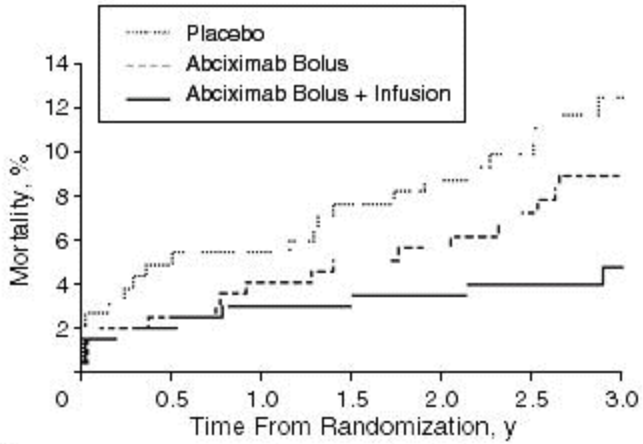


Open Squares: UA, **Solid Squares**: No UA. ***J Am Coll Cardiol 1997;30:149-56.***

3-year EPIC Results



Completed Follow-up							
Placebo	696	696	694	692	691	677	440
Bolus	695	695	691	691	688	669	436
Bolus + Infusion	708	706	704	703	701	689	439

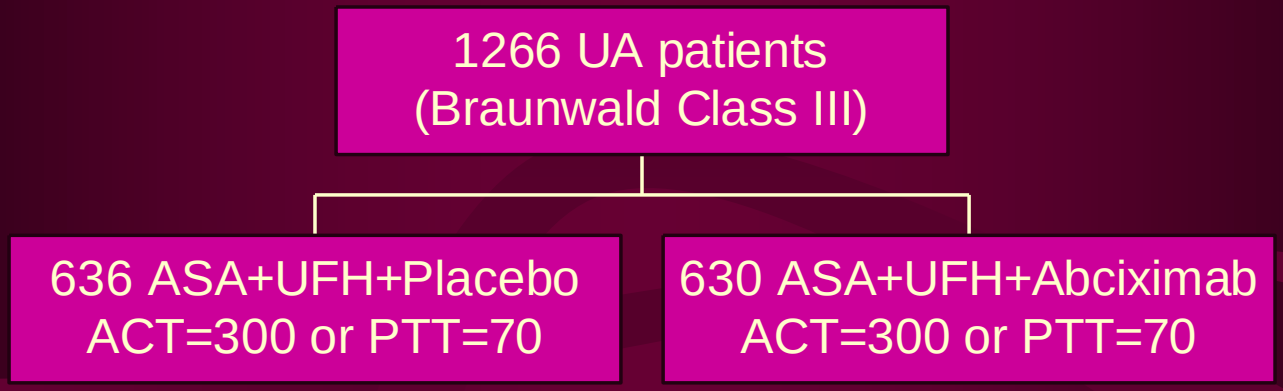


Completed Follow-up							
Placebo	179	179	178	178	178	170	101
Bolus	188	188	188	188	187	180	98
Bolus + Infusion	188	188	188	187	187	180	99

Mortality event curves for overall trial cohort by treatment assignment (Left, p=0.2) and mortality for the UA/MI subgroup (Right, p=0.01).

JAMA 1997;278:479-84.

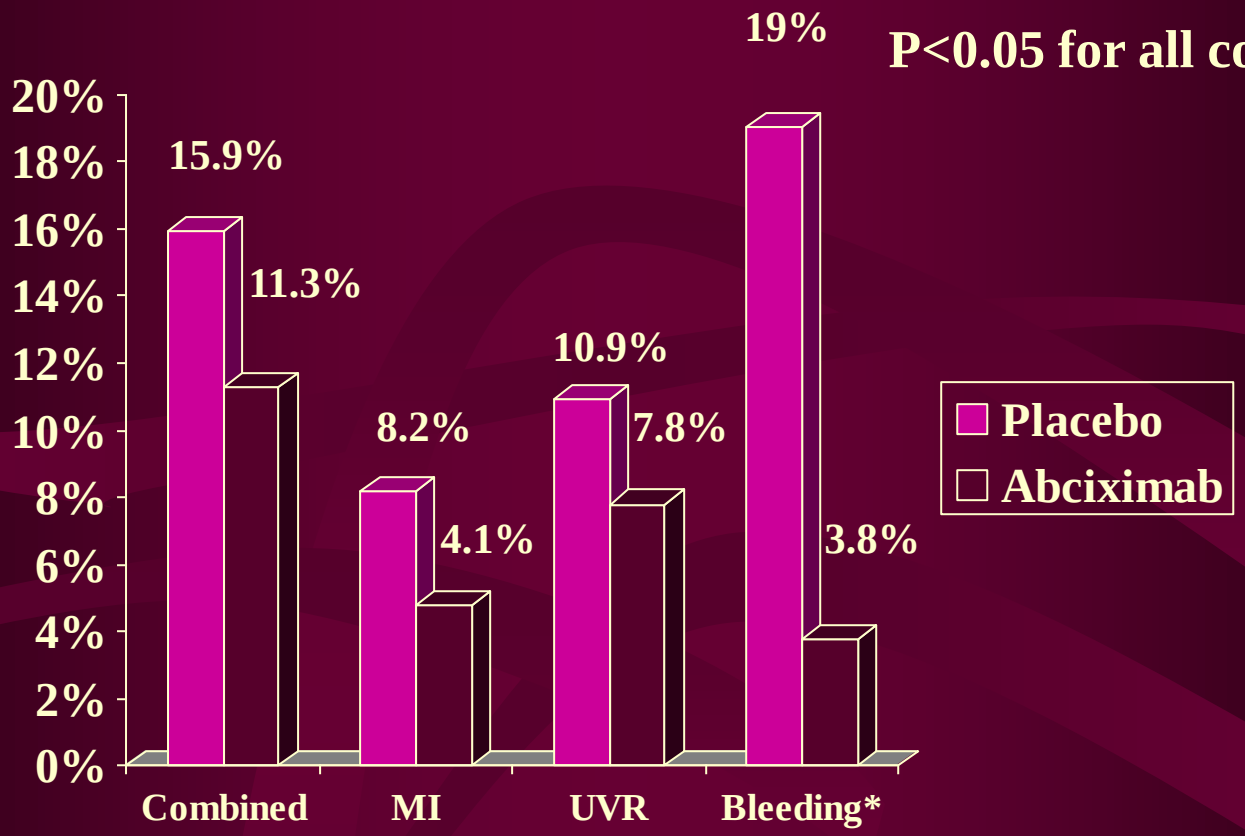
CAPTURE (ACS)



- Abciximab or Placebo infusion was given before PTCA (18-26 hours)
- Primary Endpoint: death, MI or TVR within 30 days
- Ticlodipine in 4% of patients only
- 8% of patients received stents

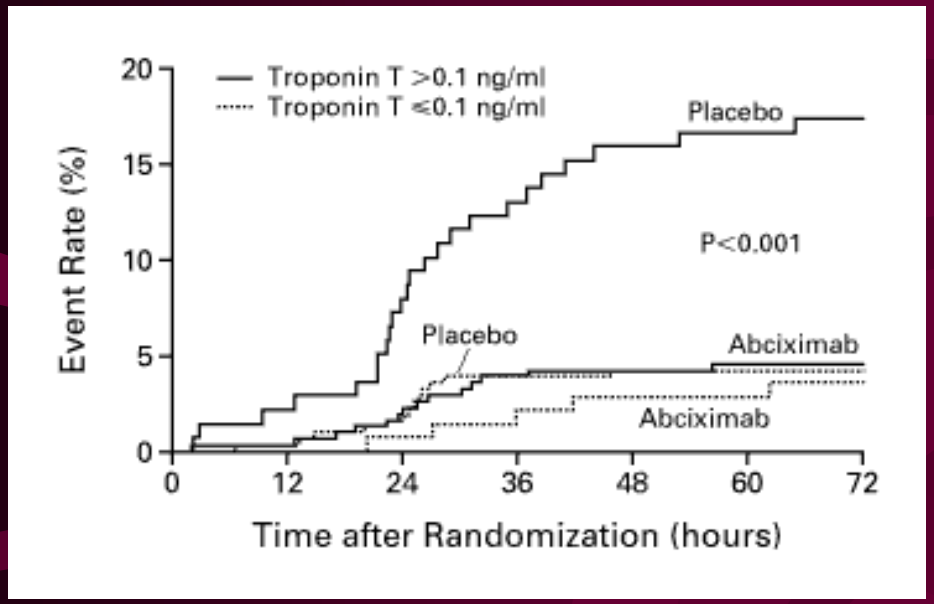
Lancet 1997;349:1429-35.

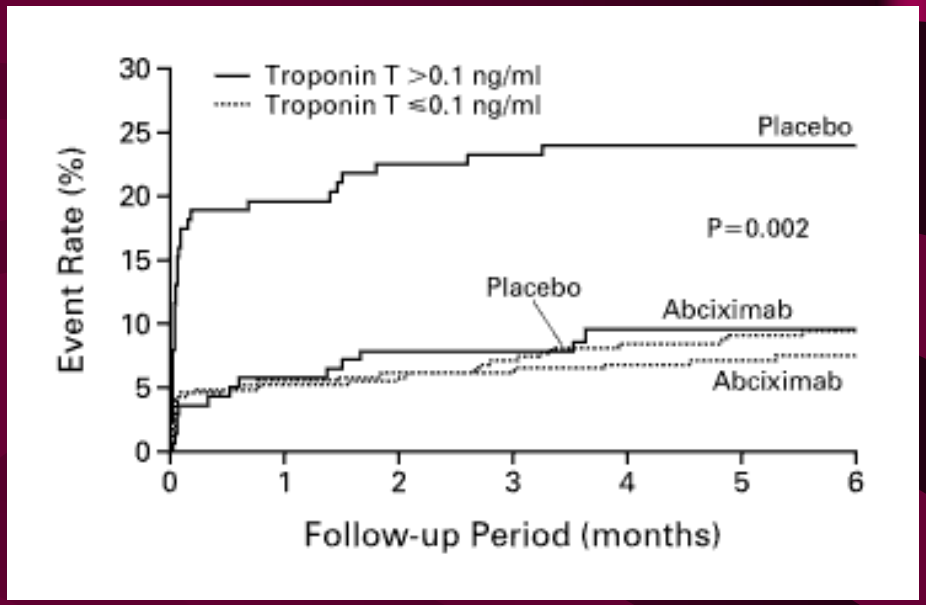
CAPTURE 30-days Results



Lancet 1997;349:1429-35. ***Major Bleeding**. MI lower rates in abciximab arm related to PTCA.*

Results based on the Troponin Status in the CAPTURE Trial

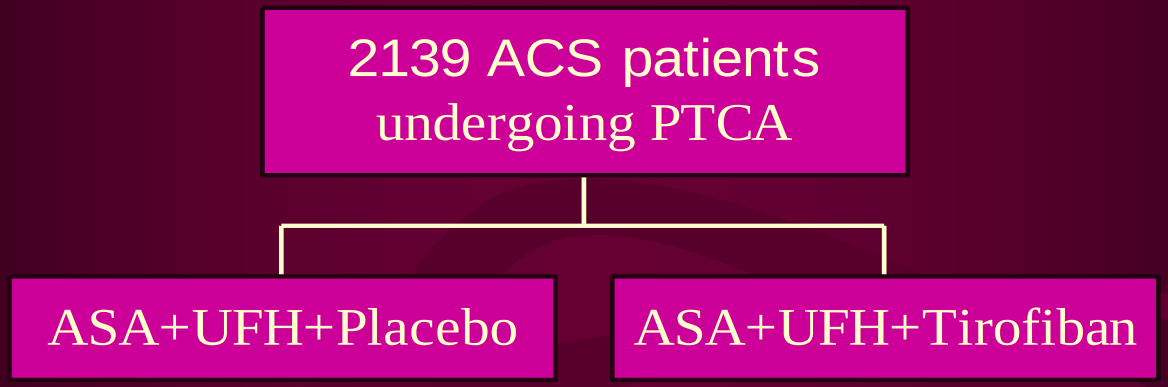




Cardiac Events (death + MI) in the Initial 72 Hours (Left) and during the 6 Months of Follow-up (Right) among Patients with Serum Troponin T Levels above and those with Levels below the Diagnostic Cutoff Point.

N Engl J Med 1999;340:1623-29.

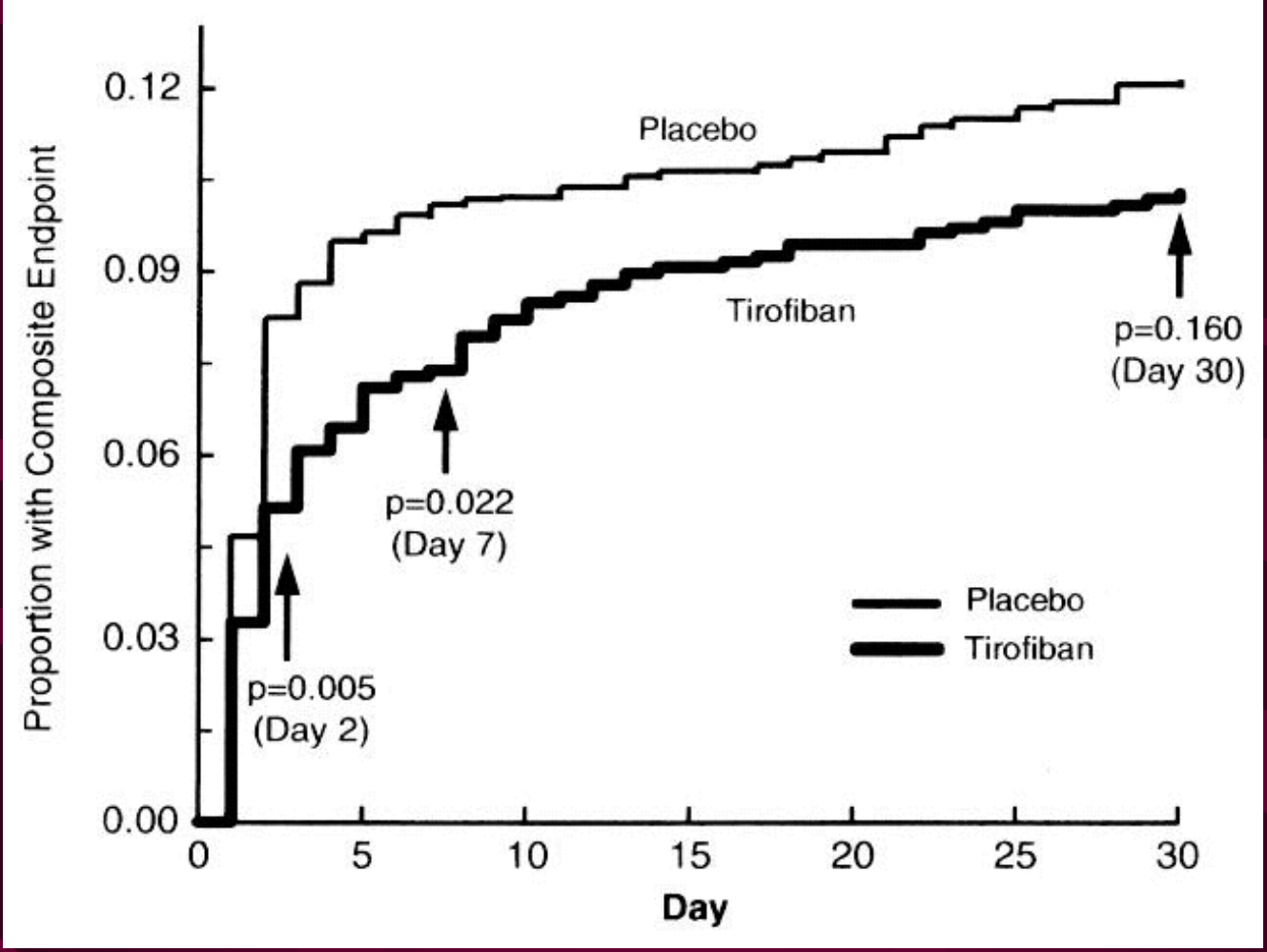
RESTORE (ACS-PCI within 72 hours)



- Composite 30-days end point: Death, MI, CABG, TVR (any), stent insertion (bailout)
- ACT>300 sec
- 2.5% stents in the placebo arm - 1.5% in the tirofiban arm 9p=0.093)
- ? Plavix and/or Ticlid

Circulation 1997;96:1445-53.

RESTORE Results

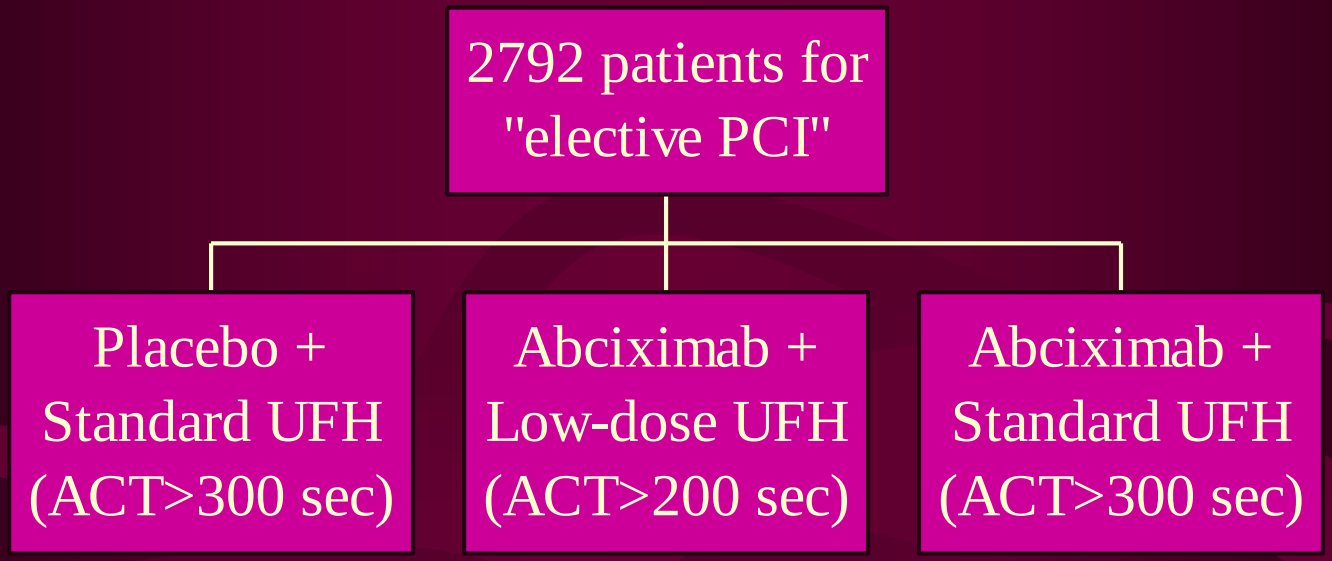


Time to composite end point: Kaplan-Meier curves. Neither of the components (including MI) of the primary end point was significant at 30 days. ***Circulation 1997;96:1445-53.***

Conclusions regarding the use of GP IIb/IIIa Inhibitors in ACS-PCI patients

- Abciximab but not Tirofiban (RESTORE) reduces non fatal MI in the setting of PTCA
- High risk UA/MI patients benefit the most (EPIC Subgroup, CAPTURE Troponin + Subgroup, Pooled data from EPIC, EPILOG, EPISTENT)
- Trials did not evaluate PCI with stenting +/- Thienopyridines

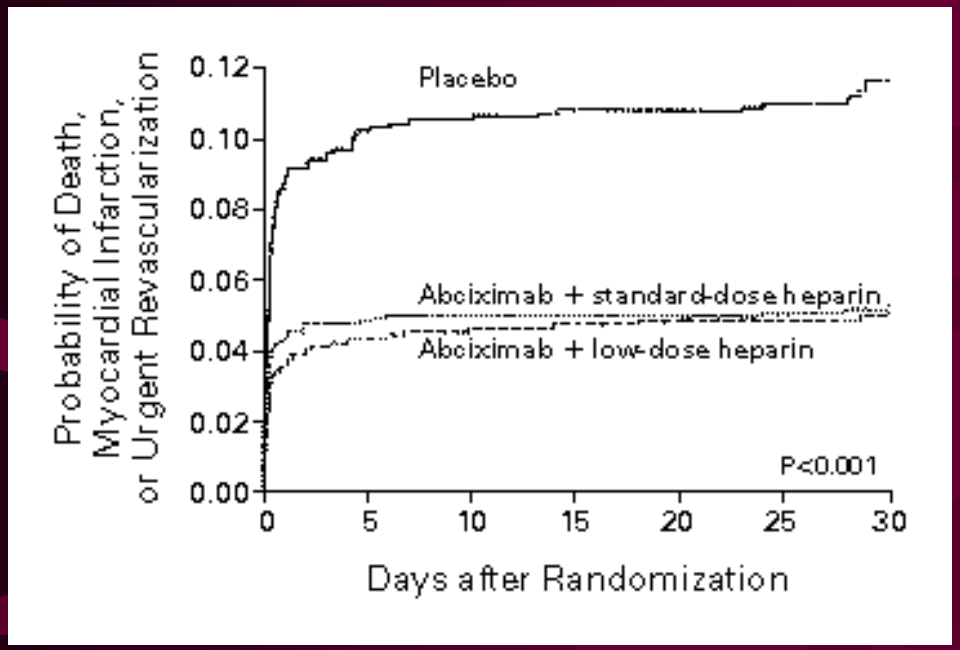
GP IIb/IIIa Inhibitors during Elective PCI: EPILOG

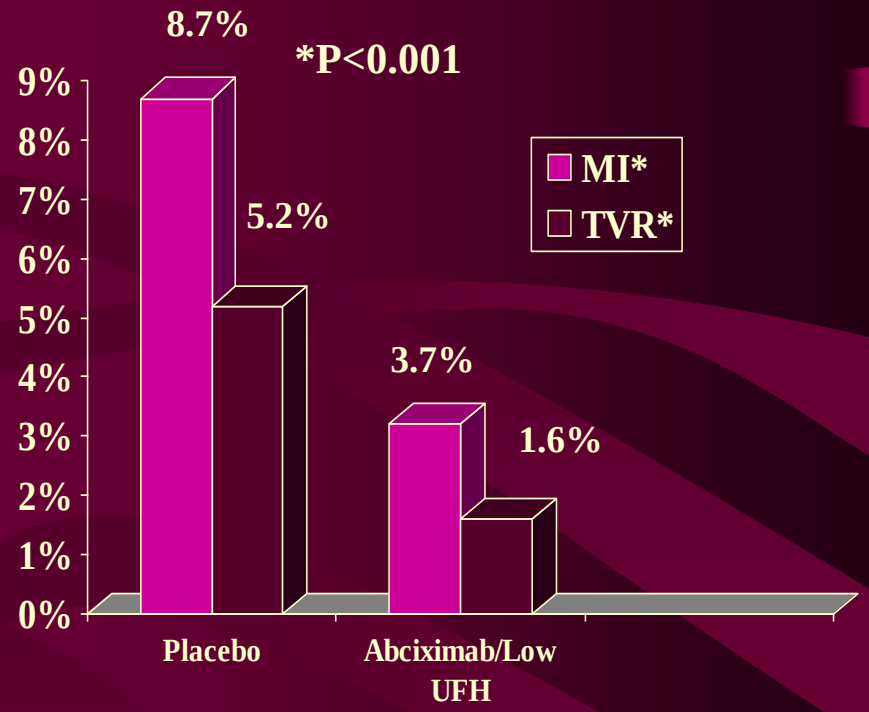


- Patients with UA or ECG changes within the last 24 hours were excluded
- ASA 325 mg, Standard versus Low-dose heparin
- Primary Efficacy End point: Death, Non fatal MI, severe ischemia (TVR) at 30 days
- No Plavix or Ticlid
- Minimal % of stenting

N Engl J Med 1997;336:1689-96.

EPILOG 30-days Results





Primary Composite End Point: 11.7% (Placebo), 5.4% (Low dose UFH) p<0.001. Heparin reduced minor but not major bleeding rates. ***N Engl J Med 1997;336:1689-96.***

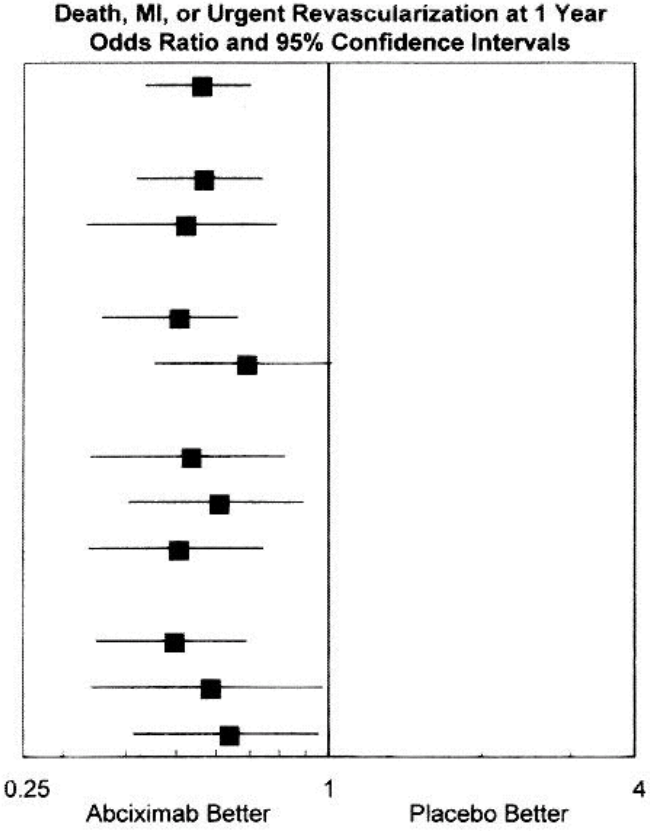
EPILOG 1-year Results: The higher the risk the greater the benefit of Abciximab during PCI

Results

Efficacy Analysis at 1 Year

The incidence of the primary composite end point of death, myocardial infarction, or urgent revascularization (the

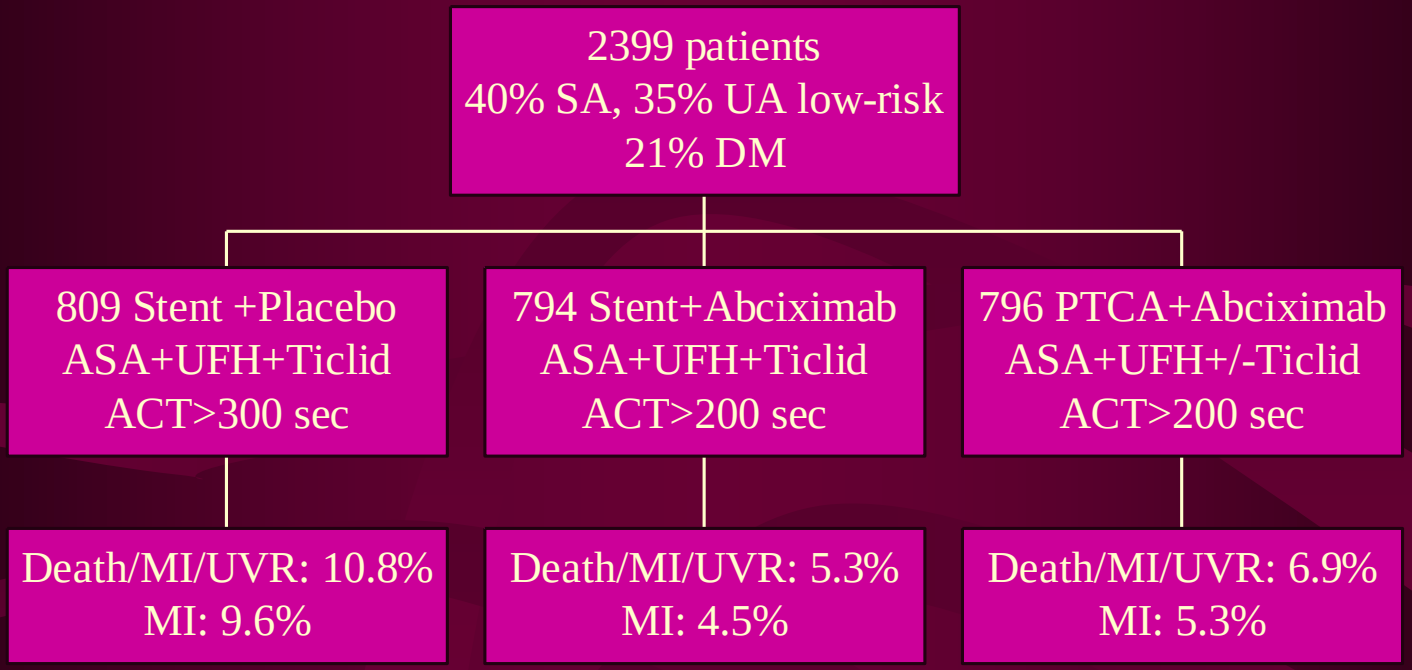
Subgroup	Placebo % (n)	Abciximab % (n)
All Patients	16.1% (939)	9.6% (1853)
Male	15.5% (674)	9.3% (1338)
Female	17.9% (265)	10.1% (515)
Age <65 years	17.5% (598)	9.4% (1174)
Age ≥65 years	13.8% (341)	9.9% (679)
Weight ≤75 kg	16.1% (282)	9.2% (510)
Weight 75-90 kg	16.2% (308)	10.4% (680)
Weight ≥90 kg	16.2% (348)	8.8% (662)
Unstable Angina	16.8% (474)	9.0% (854)
Recent MI	15.4% (189)	9.5% (390)
Stable Ischemia	15.6% (276)	10.4% (609)



Circulation 1999;99:1951-8.

I indeed was in the marines!

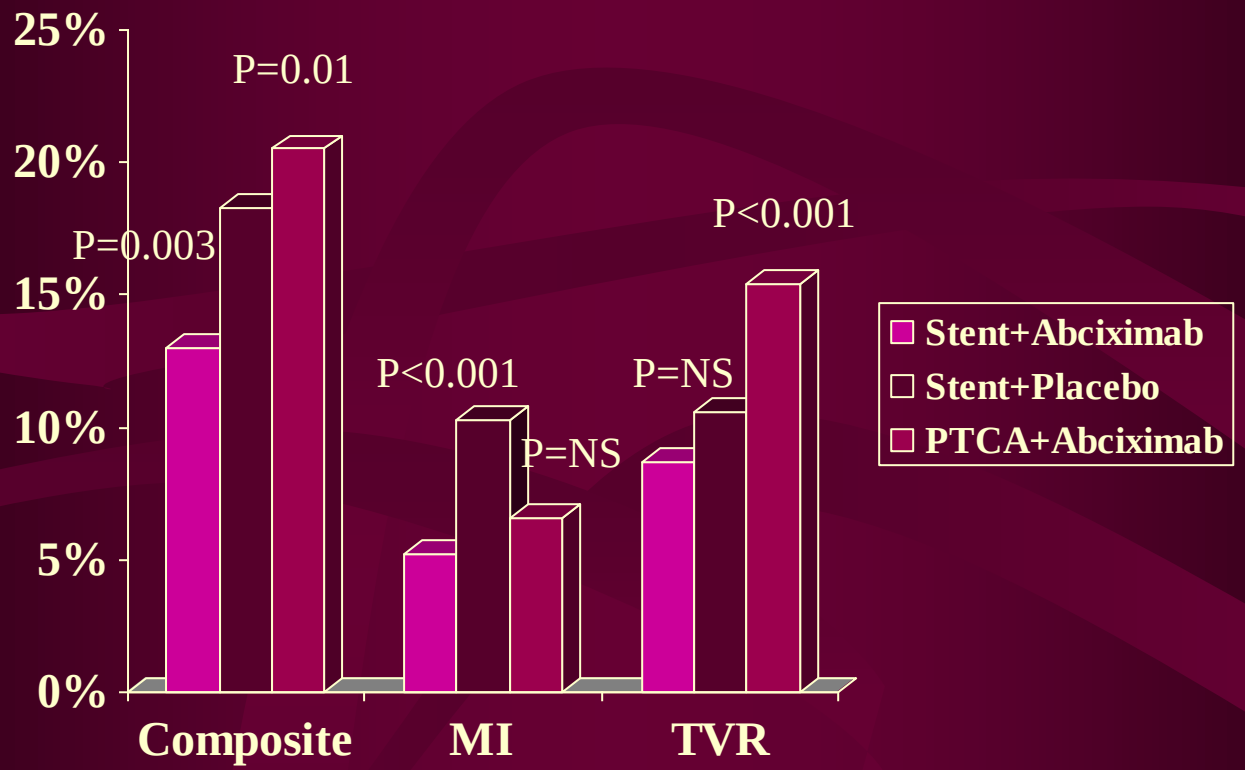
EPISTENT- 30-days Results



Conclusions: Abciximab substantially improves the safety of coronary stenting procedures. PTCA with Abciximab is safer than stenting without abciximab.

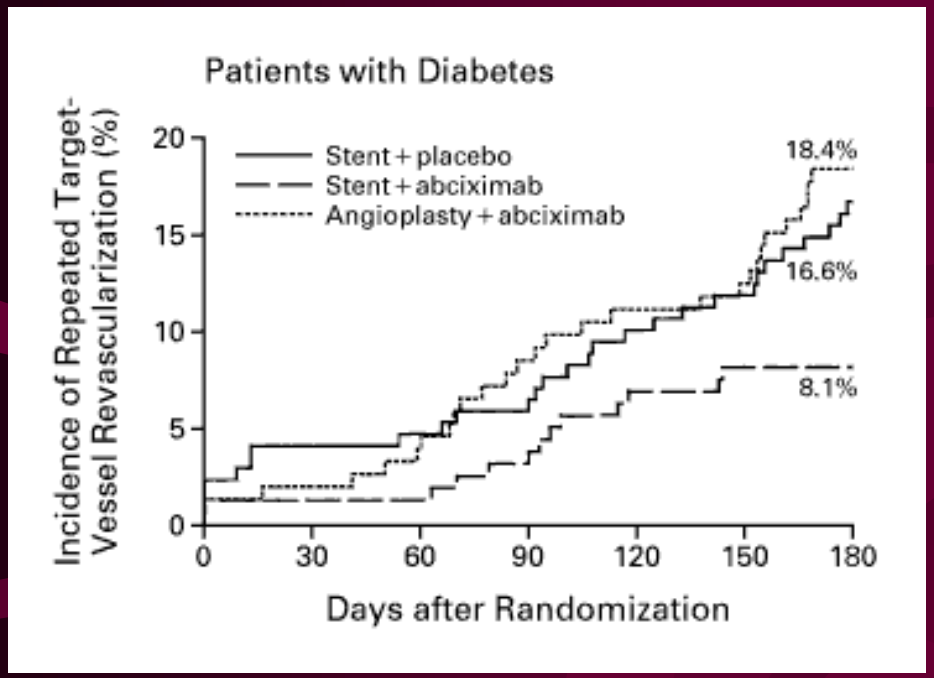
Lancet 1998;352:87-92.

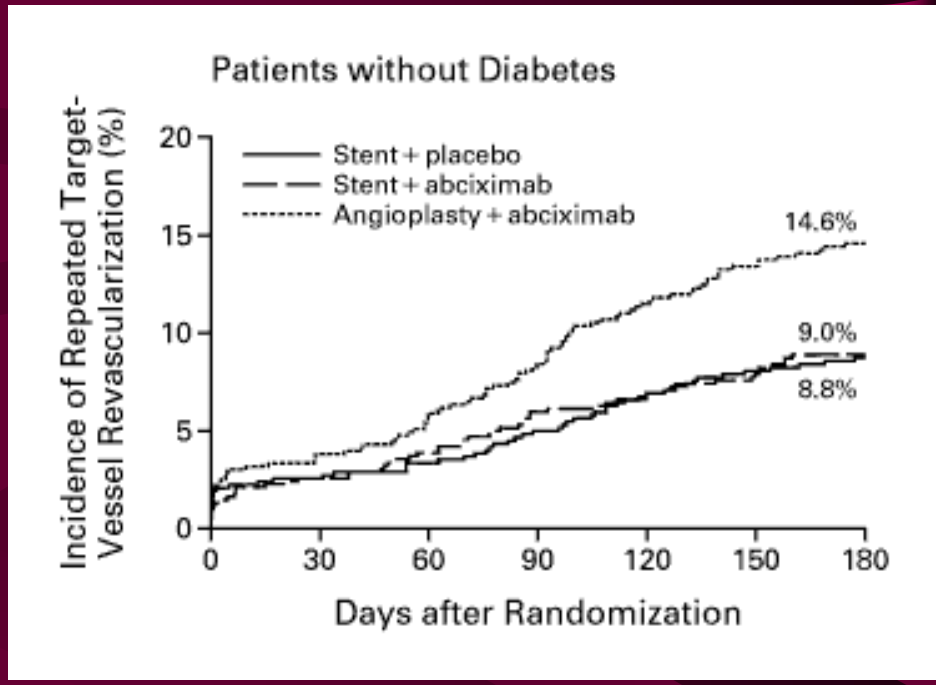
EPISTENT 6 months



Primary End Point: Death, MI or Repeated Target-Vessel Revisualization. Comparisons made between Stent+Abciximab and other groups. ***N Engl J Med 1999;341:319-27.***

EPISTENT DM Subgroup (n=491, 20%)





RRR=51%

Among patients with DM, p=0.02 for the comparison between Stent+Abciximab and Stent+Placebo. Curves diverge at 60-90 days post-stent implantation. Among patients without DM p=0.002between PTCA +Placebo and Stent+Placebo. ***N Engl J Med 1999;341:319-27.***

EPIC, EPILOG, EPISTENT DM Subgroups

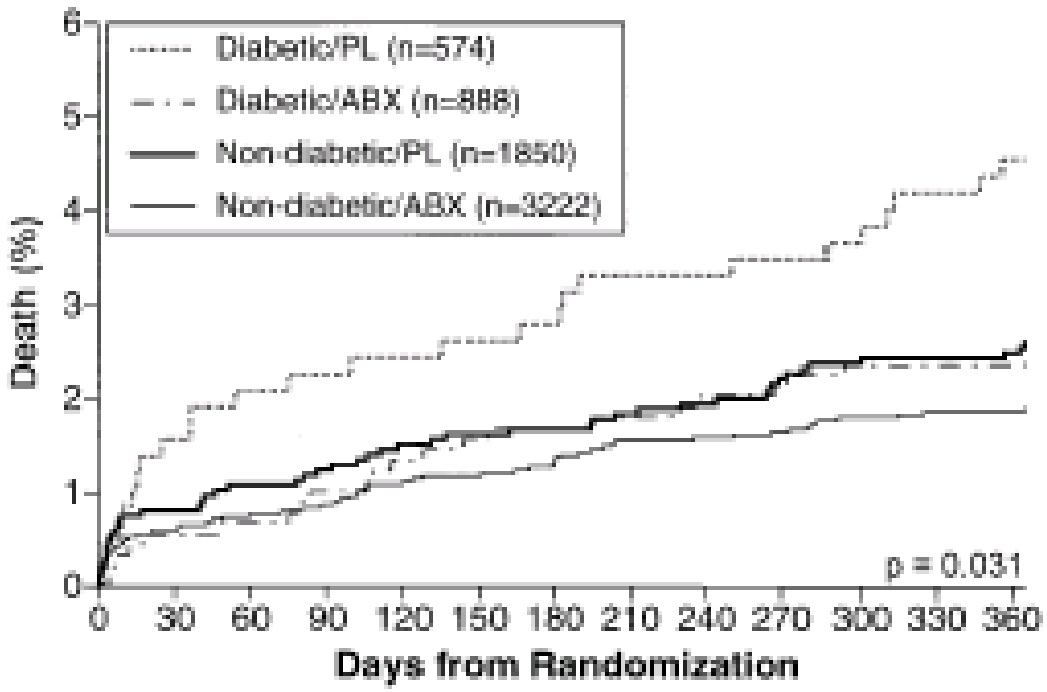


Figure 3. The Kaplan-Meier curves are shown for one-year mortality in diabetics and nondiabetics randomized to either placebo (PL) or abciximab (ABX).

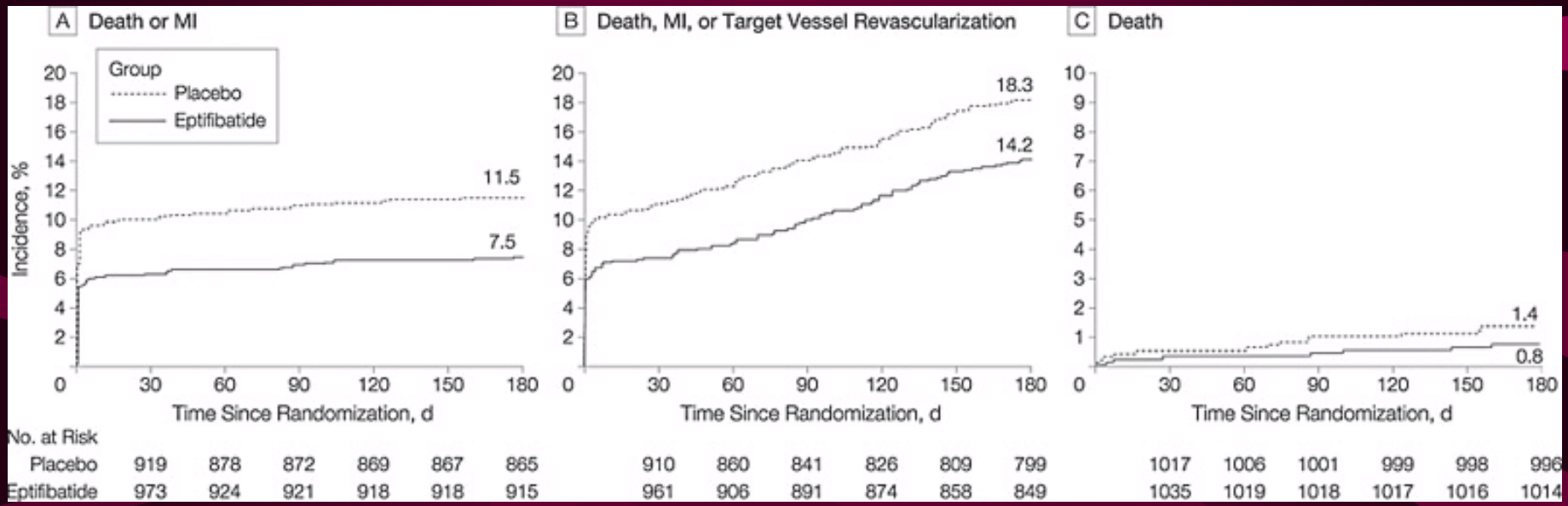
P Value refers to the comparison between DM/PL - DM/ABX Groups.

J Am Coll Cardiol 2000;35:922-28.

Impact of EPISTENT Study

- Abciximab in addition to stenting reduces the incidence of MI at 30 days and 6 months
- 1 year f/u reduced mortality (2.4% versus 1%, p=0.037)
- The benefit of TVR is restricted to diabetics in the setting of "elective PCI"
- Subgroup analysis showed a consistent effect of eptifibatide (although more profound in UA, DM population)
- *Not clear in the study design the use and duration of Ticlid (No loading dose, pretreatment at the discretion of cardiologists)*

Following IMPACT-II: The ESPRIT Trial (“non-urgent PCI”)

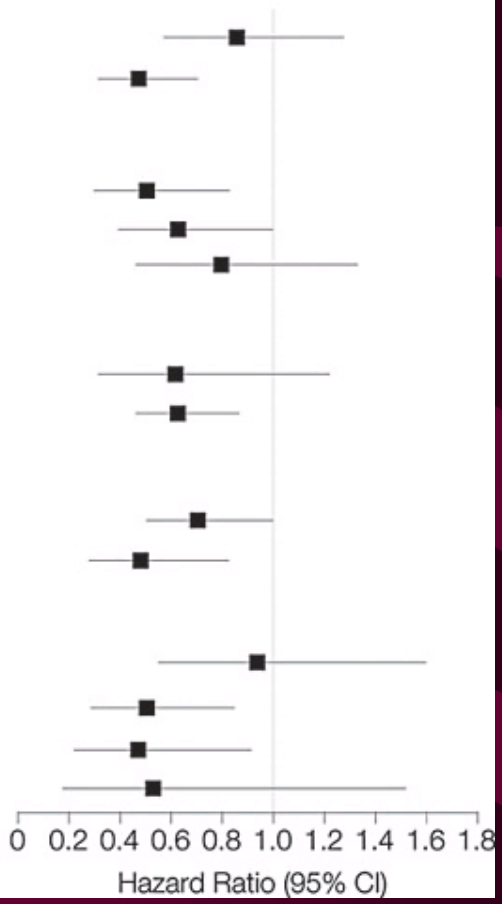


RRR (MI): 33% over 6 months

Cumulative Incidence of Study End Points Among Patients Treated With Eptifibatide or Placebo. For the composite end point of death or MI, HR, 0.63; 95% CI, 0.47-0.84; *P* =.002. For the composite end point of death, MI, or target vessel revisualization, HR, 0.75; 95% CI, 0.60-0.93; *P* =.008. For the end point of death, HR, 0.56; 95% CI, 0.24-1.34; *P* =.19. **JAMA 2001;285:2468-2473.**

Subgroup Analysis of the ESPRIT Trial

Subgroup	No. of Patients (%)	Rate of Death or MI (%)	
		Eptifibatide	Placebo
Age, y			
<65	1172 (57)	7.5	8.7
≥65	892 (43)	7.5	15.2
Weight, kg			
<76	571 (28)	8.1	15.1
76-89	723 (35)	7.7	12.1
≥90	770 (37)	6.7	8.4
Diabetes			
Present	419 (20)	6.3	10.2
Absent	645 (80)	7.7	11.8
Sex			
Male	1502 (73)	7.4	10.3
Female	562 (27)	7.5	14.6
Cardiac Events			
Stable Angina	794 (38)	6.9	7.3
ACS ≥2 d	664 (32)	6.1	11.7
ACS <2 d	279 (14)	9.5	18.6
ST-elevation MI <7 d	93 (5)	11.5	20.5



HR and 95% CI for risk of death/MI by Subgroup. ***JAMA 2001;285:2468-73.***

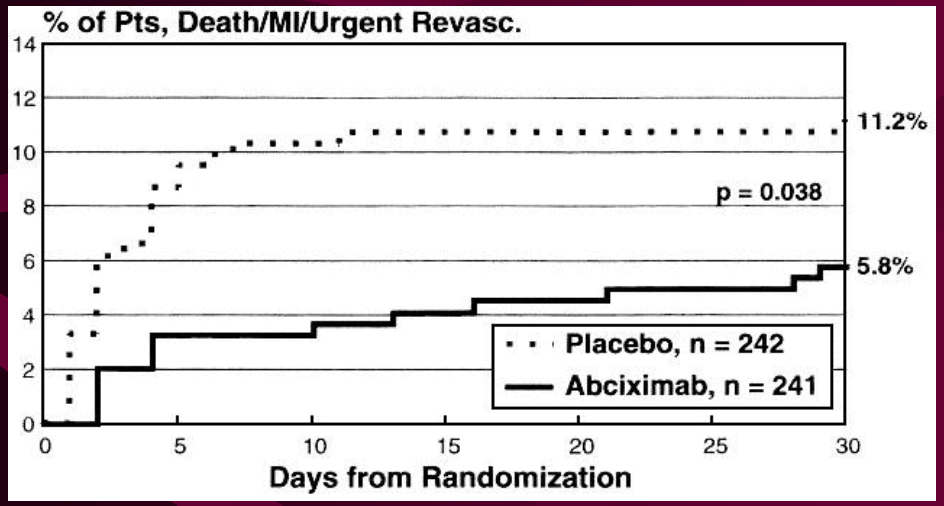
Implications of the ESPRIT Trial

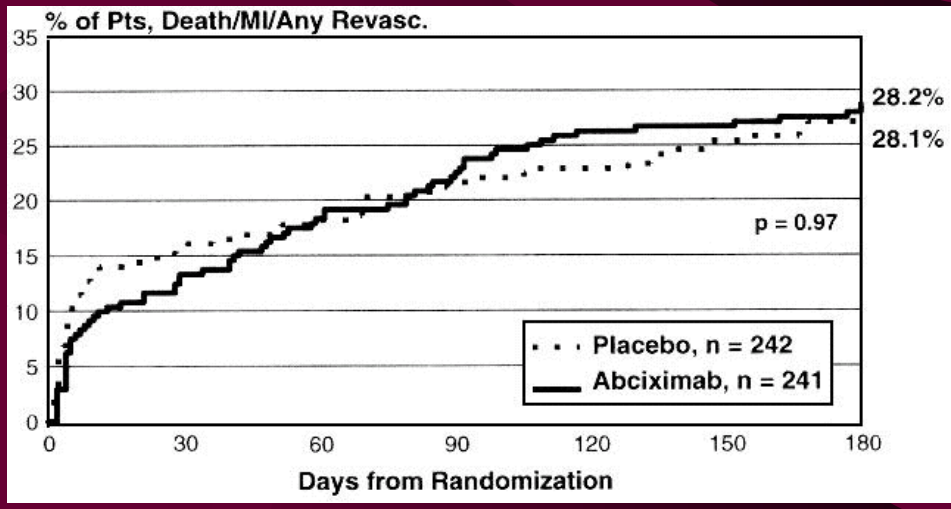
- Established a Role of eptifibatide during PCI and at the time of intervention
- Consistent reduction in all subgroups with the exception of SA group
- Inclusion criteria (? Higher risk)
- Stenting in 97% of patients
- Ticlid or Plavix only at the day of PTCA “at the discretion of the physician”, 97% of patients

GP IIb/IIIa Inhibitors during STEMI + PTCA: RAPPORT

483 STEMI patients
eligible for Primary PTCA or DCA
Stenting was discouraged

ASA+Heparin+Abciximab	ASA+Heparin+Placebo
n=241	n=242
ACT>300	ACT>300
60<PTT<85	60<PTT<85





Both 30 days' and 6 months' composite end point was driven from TVR. 20% stents (PL) versus 12% (AB), p=0.008. ***Circulation 1998;98:734-41.***

GP IIb/IIIa Inhibitors during STEMI + Stenting: ADMIRAL

300 patients with STEMI
ASA+Heparin
+PCI+ Ticlid (No load)
ACT>200 sec, PTT<2x control

- 149 Patients: Abciximab prior PCI
- 151 Patients: Placebo prior PCI

Primary Composite End Point (UVR driven)

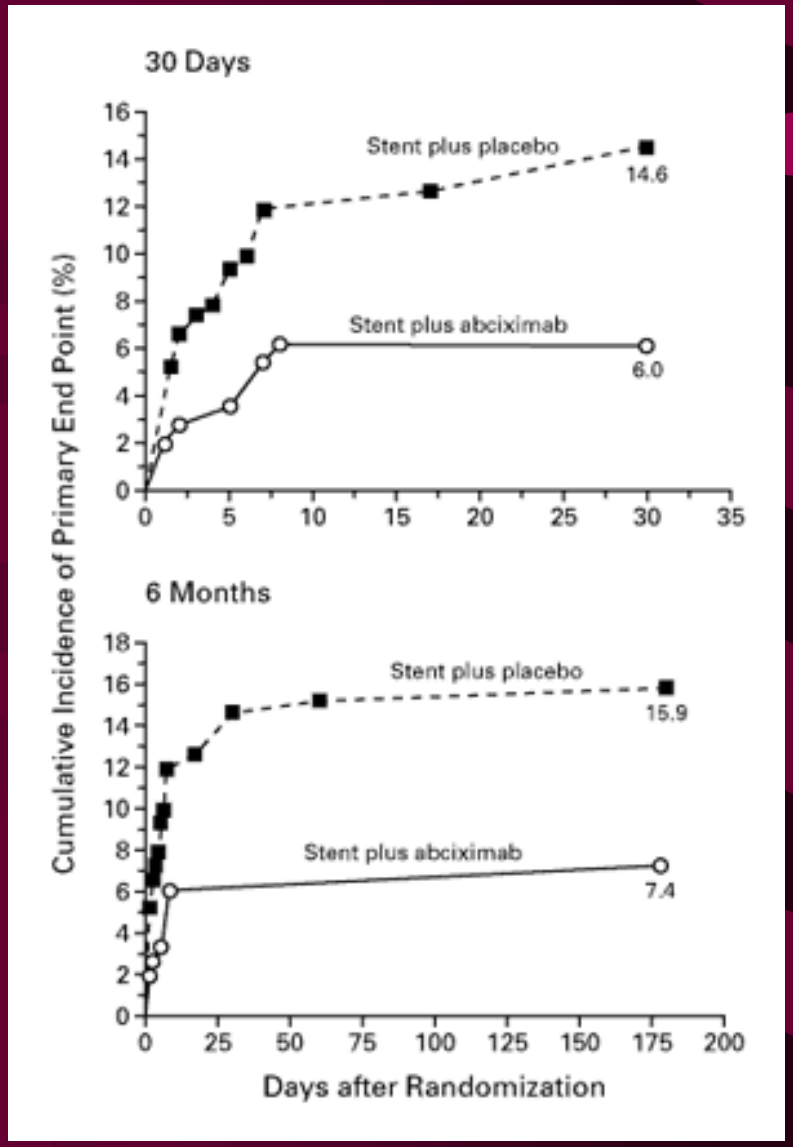
Death, Re-MI, UVR at 30 days

Key Secondary End Point (TVR driven)

Death, Re-MI, TVR (30 days/6 months)

Major bleeding

12.1% (AB) - 3.3% (PL), p=0.004



N Engl J Med 2001;344;1895-1903.

GP IIb/IIIa Inhibitors during STEMI: CADILAC

2082 patients with STEMI
ASA+Heparin+Plavix/Ticlid (load)
2.5-4.0 mm vessels

PTCA n=518	PTCA+Abciximab n=528	Stenting n=512	Stenting+Abciximab n=524

Outcome	PTCA (N=518)	PTCA plus Abciximab (N=528)	Stenting (N=512)	Stenting plus Abciximab (N=524)	P Value
At 6 months (cumulative)					
Death	4.5	2.5	3.0	4.2	0.23
Reinfarction	1.8	2.7	1.6	2.2	0.64
Disabling stroke	0.2	0.2	0.4	0.4	0.88
Revascularization of ischemic target vessel	15.7	13.8	8.3‖	5.2**	<0.001
Composite end point	20.0	16.5	11.5††	10.2‡‡	<0.001
Target-vessel revascularization for any reason	16.9	14.8	8.9‡‡	5.7**	<0.001

Hypothesis: Stenting was superior to PTCA and not inferior to PTCA+Abciximab with respect to composite end point. P values compare abciximab vs. non-abciximab groups.

N Engl J Med 2002;346:957-66.

Eptifibatide with PCI in STEMI

55 STEMI patients
Primary PCI
ASA+Heparin+Plavix (load)
+Eptifibatide (double bolus) x 24 hours

30 days' events
3.6% death
9.1% re-infarction
(all due to SAT)

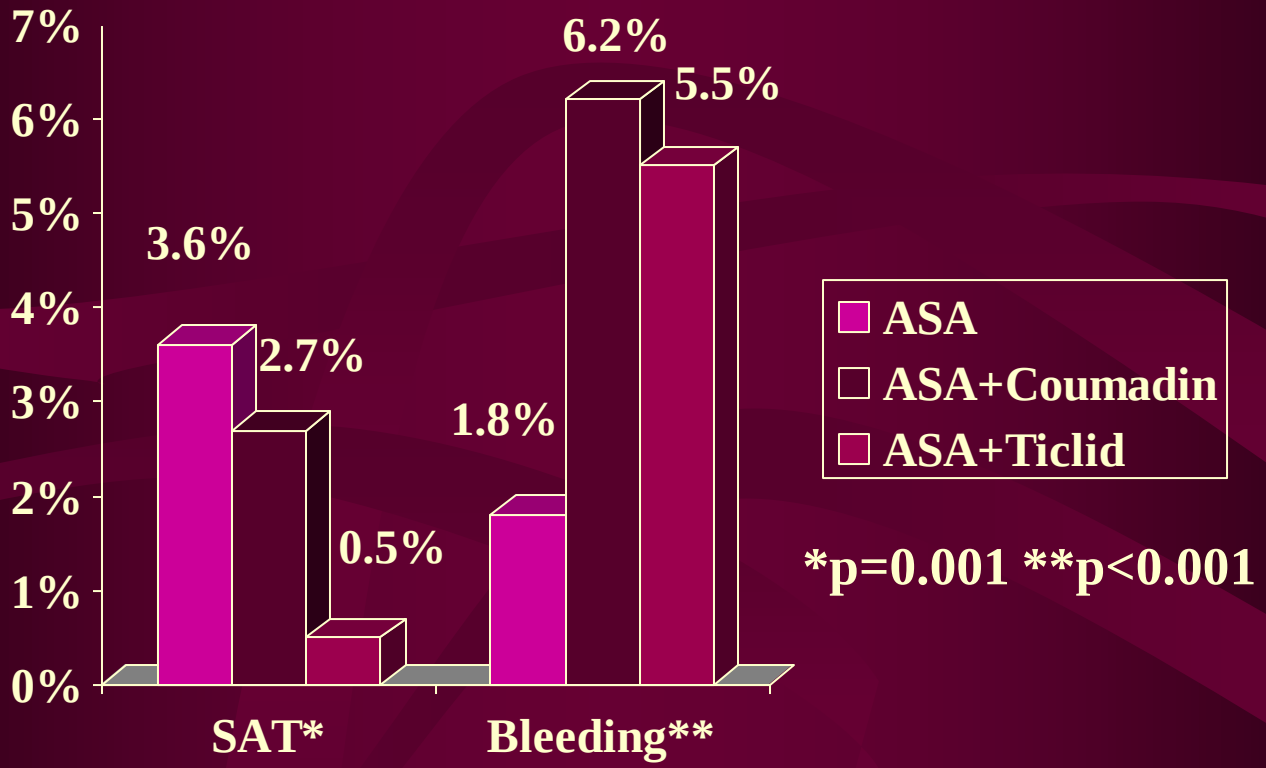
Angiographic F/U
Post Procedure TIMI 3: 93%
Pre-discharge TIMI 3: 86%
($p<0.05$)

Cathet Cardiovasc Intervent 2002;57:497-503.

Objectives

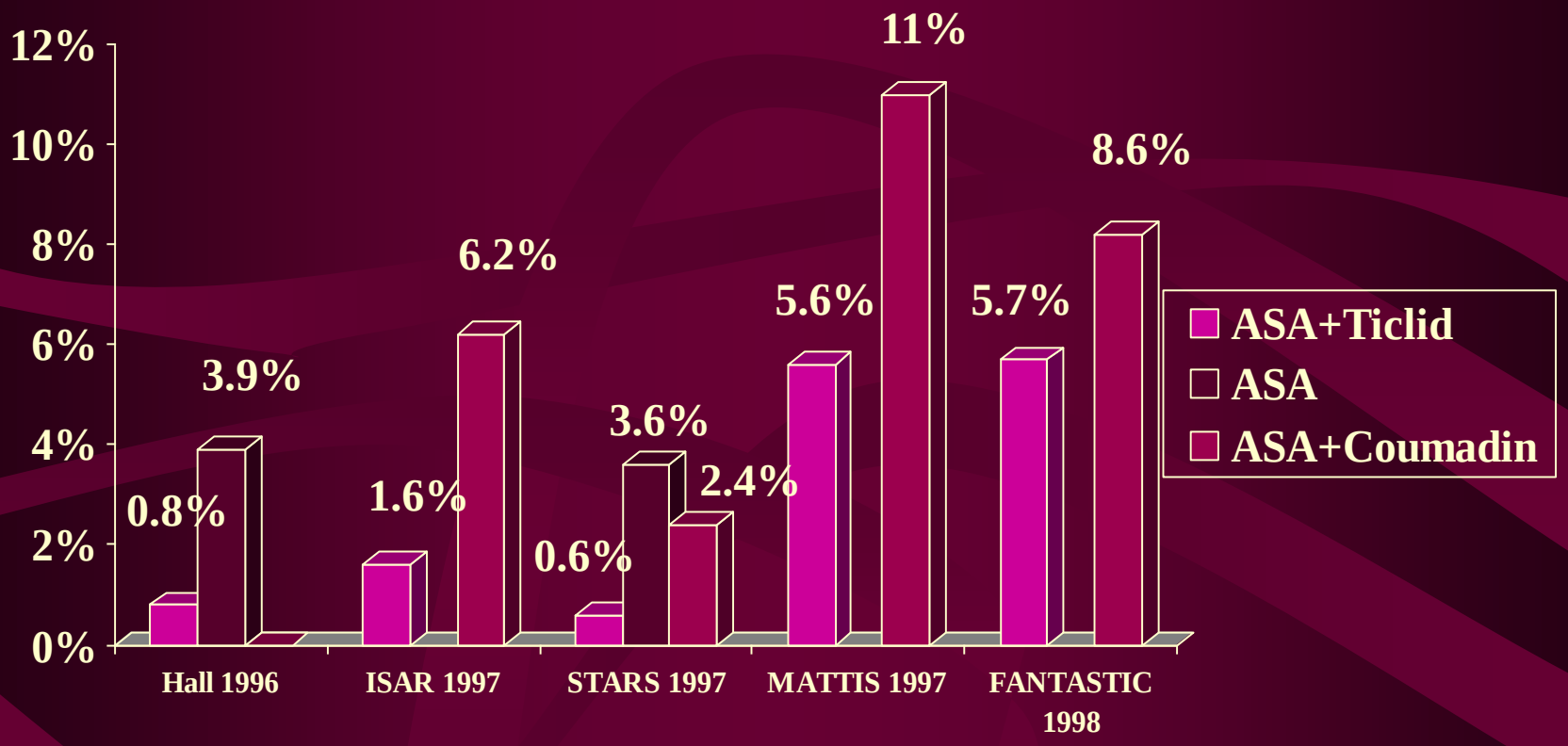
- Pharmacology of GP IIb/IIIa inhibitors and Monitoring of Platelet Inhibition
- Appropriate Use of GP IIb/IIIa inhibitors during PCI
- The Thienopyridines
- PCI Algorithm

ASA+Ticlopidine (No loading) in the setting of elective PCI with high-pressure inflation (n=1965)



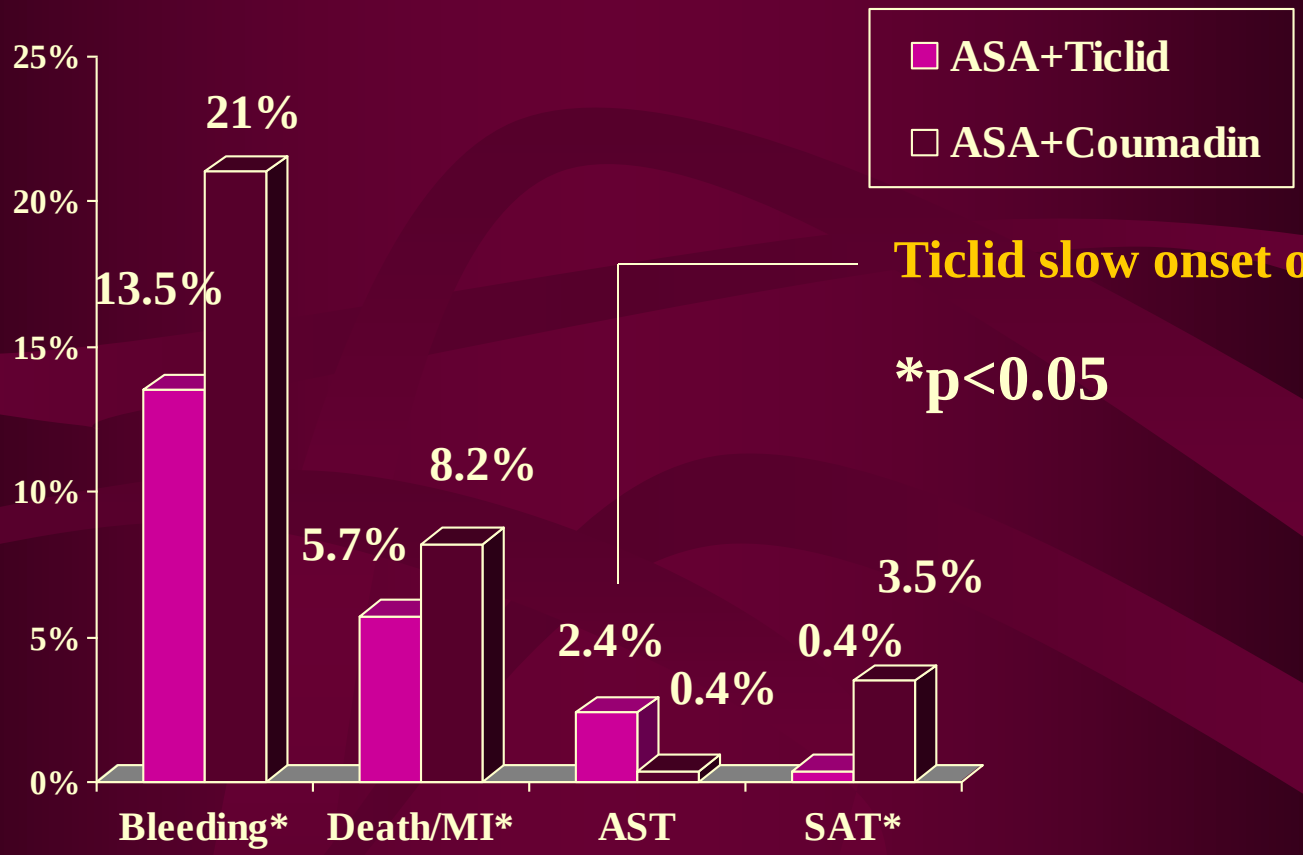
N Engl J Med 1998;339:1665-71.

Randomized Trials comparing ASA+Ticlopidine versus ASA+Coumadin or Coumadin alone



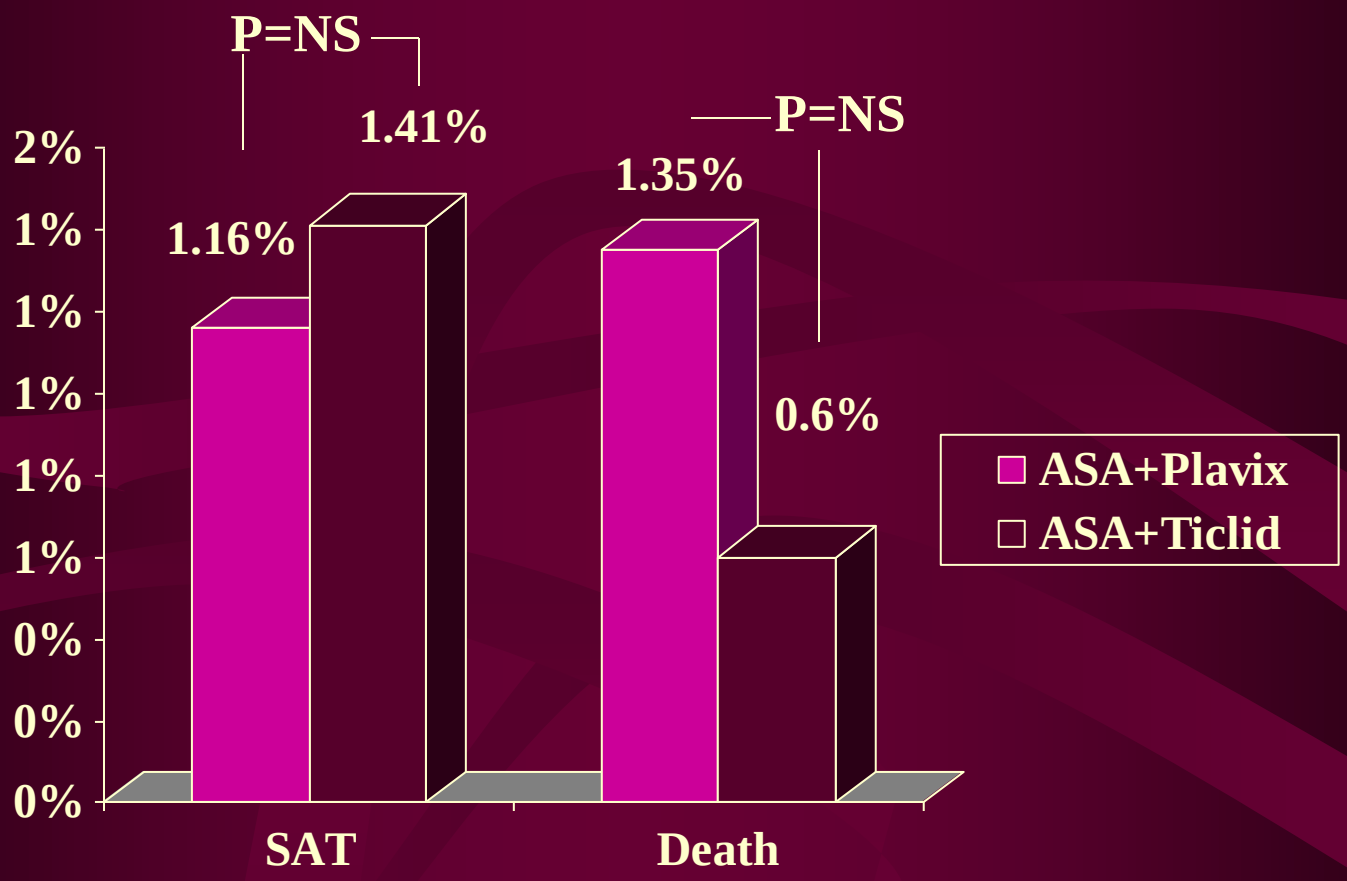
Cumulative Event Rates in 5 randomized Trials comparing three regimens post PCI.
J Interven Cardiol 2002;15:85-93.

ASA+Ticlopidine in Unplanned and Elective PCI (n=482): The FANTASTIC Trial: 6 weeks results



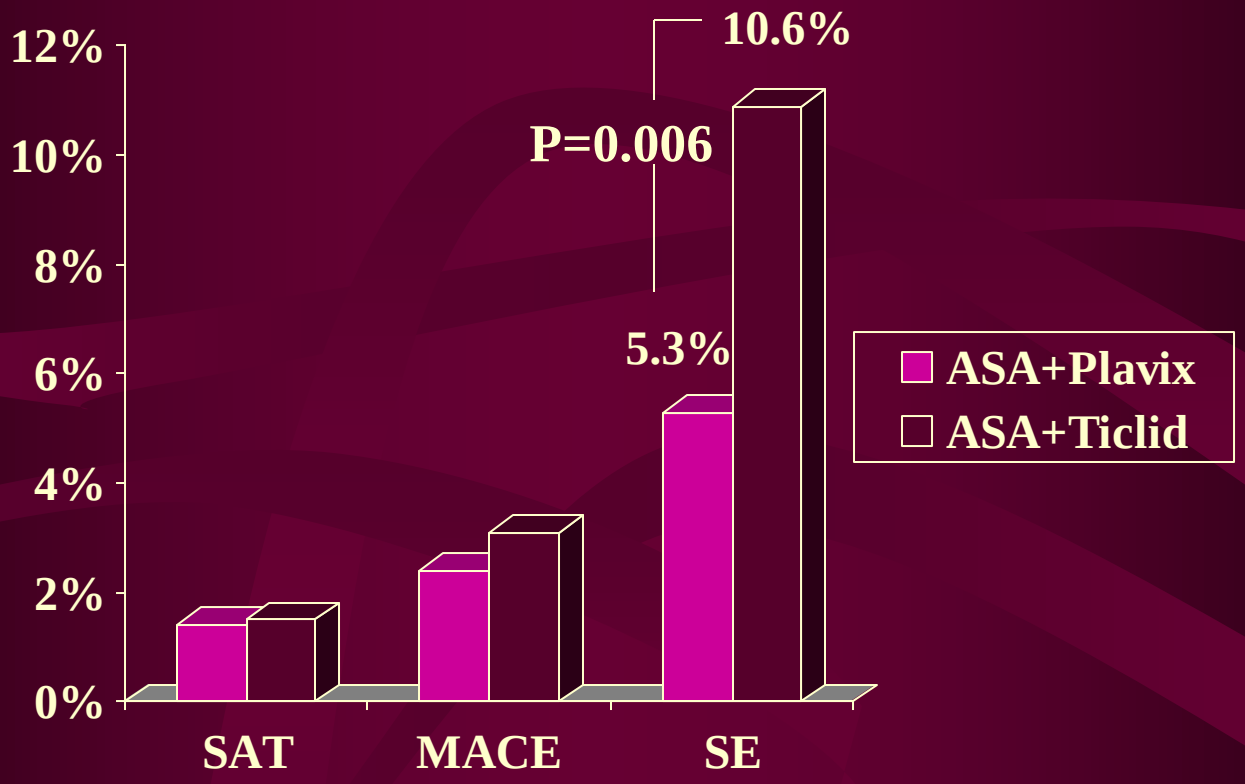
Circulation 1998;98:1597-1603.

Clopidogrel versus Ticlopidine in the setting of PCI



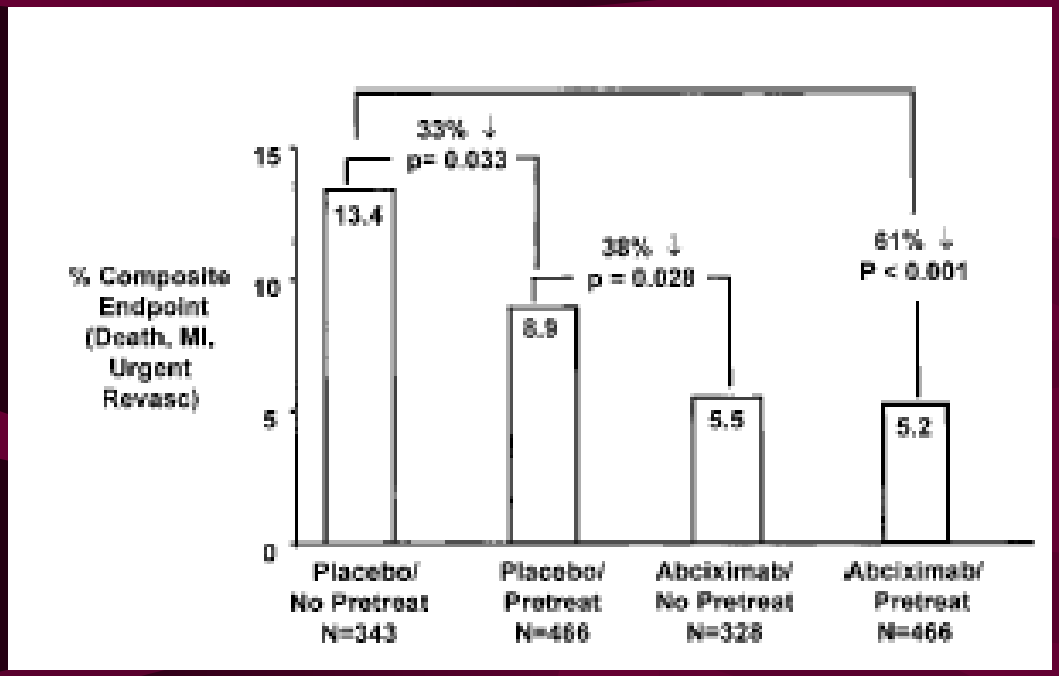
The TOPPS Study. Circulation 1999;100(Suppl. I):I:-379.

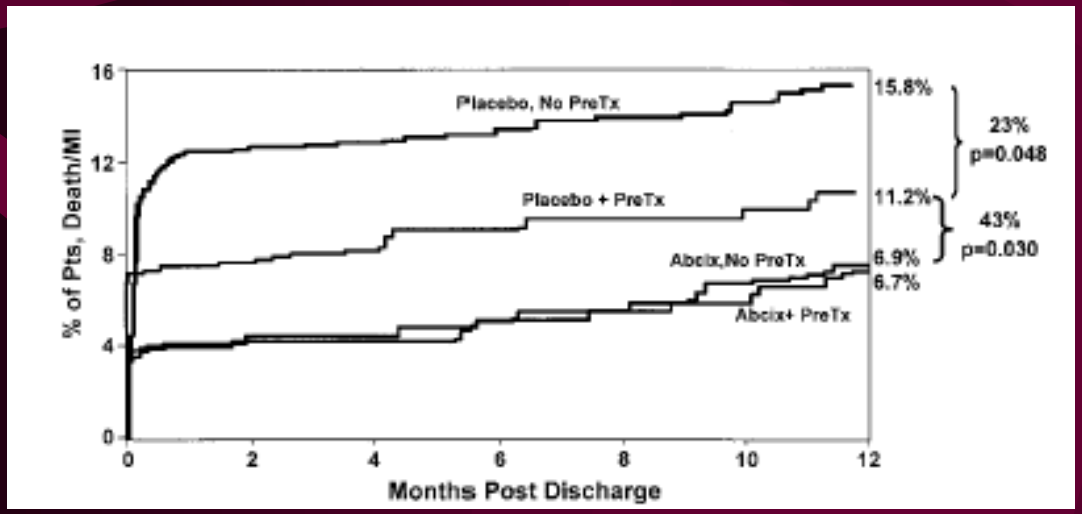
Clopidogrel versus Ticlopidine for the prevention of SAT and safety profile



Circulation 1999;99:2364-66.

Ticlopidine Pretreatment in the EPISTENT Trial

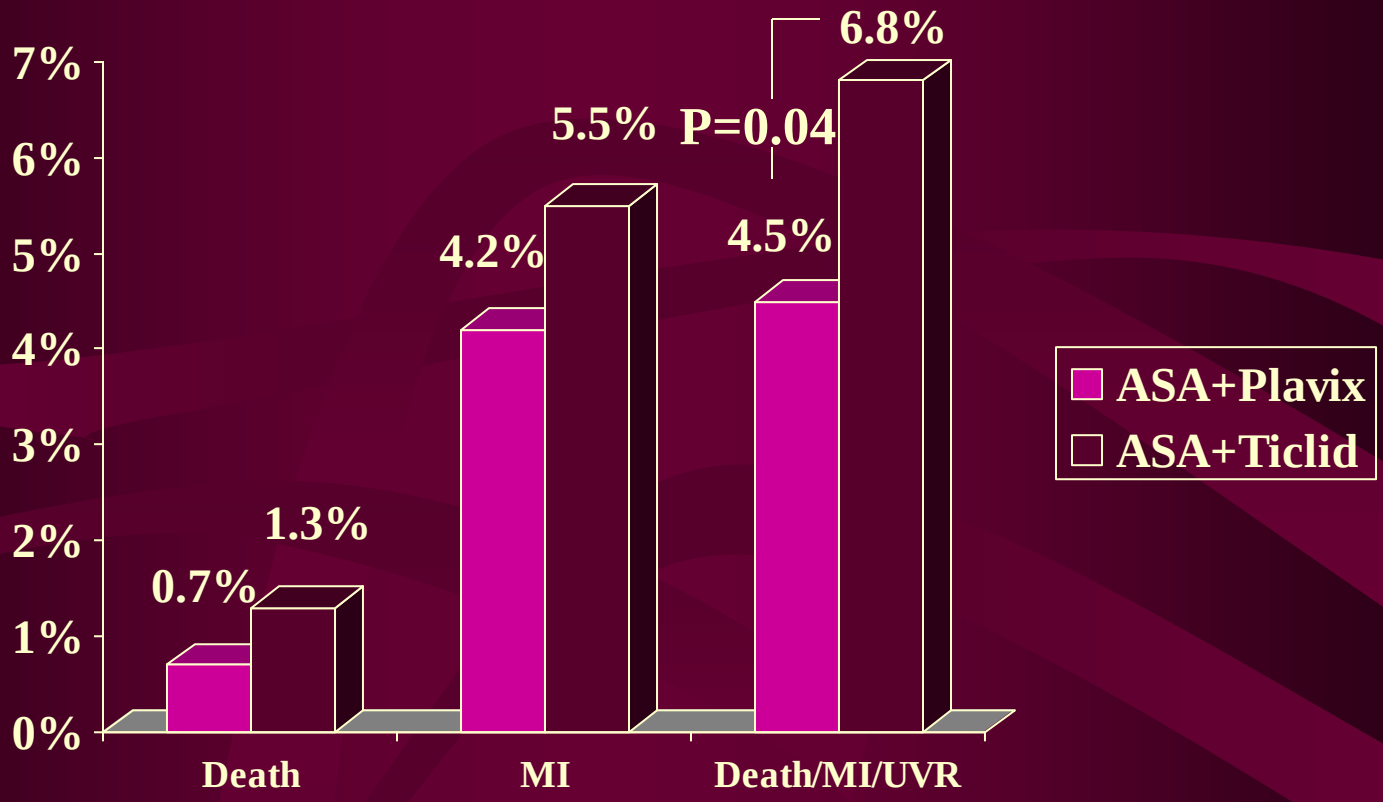




30-days and 1-year composite end point based on Ticlopidine pretreatment status.

Circulation 2001;103:1403-9.

High-Loading Dose of Clopidogrel during PCI with or without abciximab (60%)



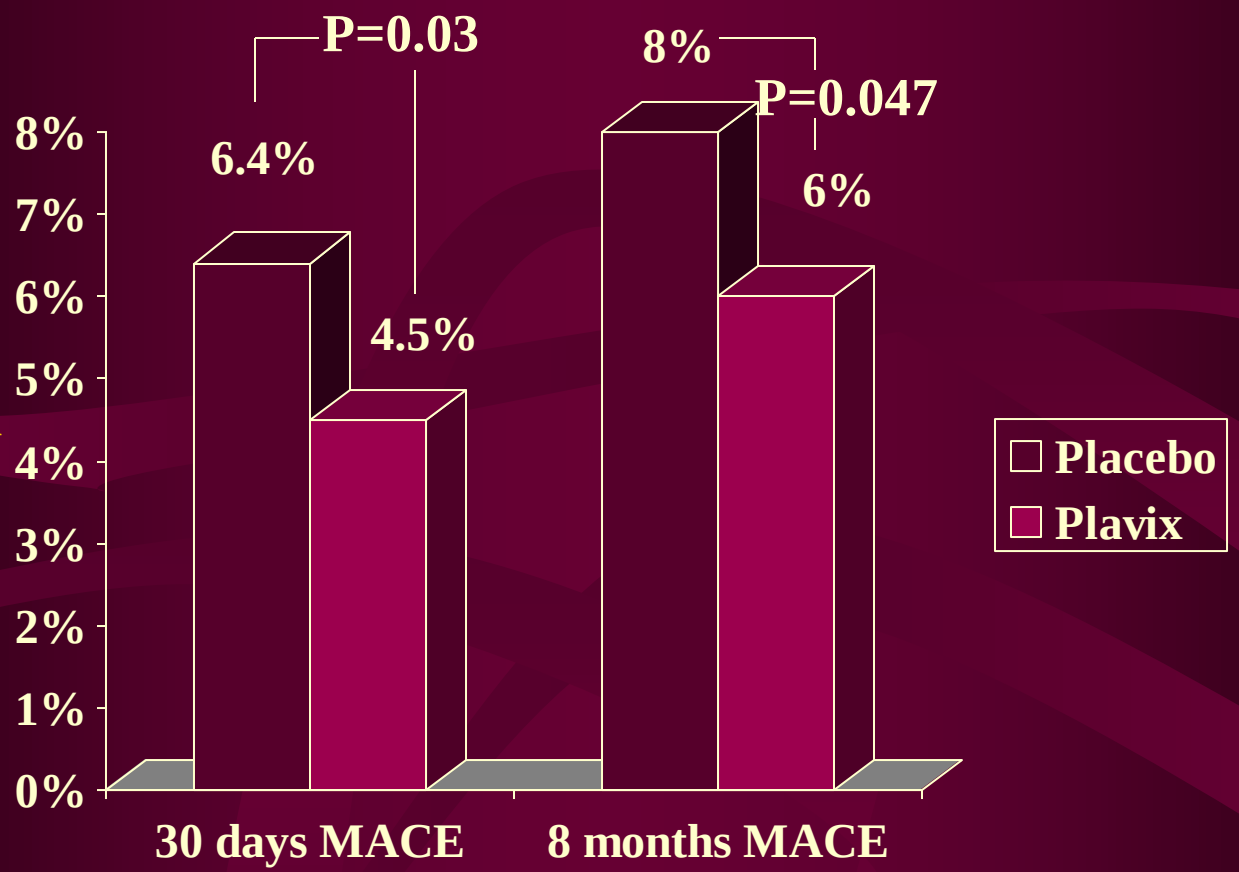
Clopidogrel: 600 mg load + 150 mg/d x 4 days + 75 mg/d x 4 weeks.
Ticlopidine: 500 mg load + 500 mg/d x 4 weeks.

Cathet Cardiovasc Intervent 2002;55:436-41.

The PCI-CURE Study

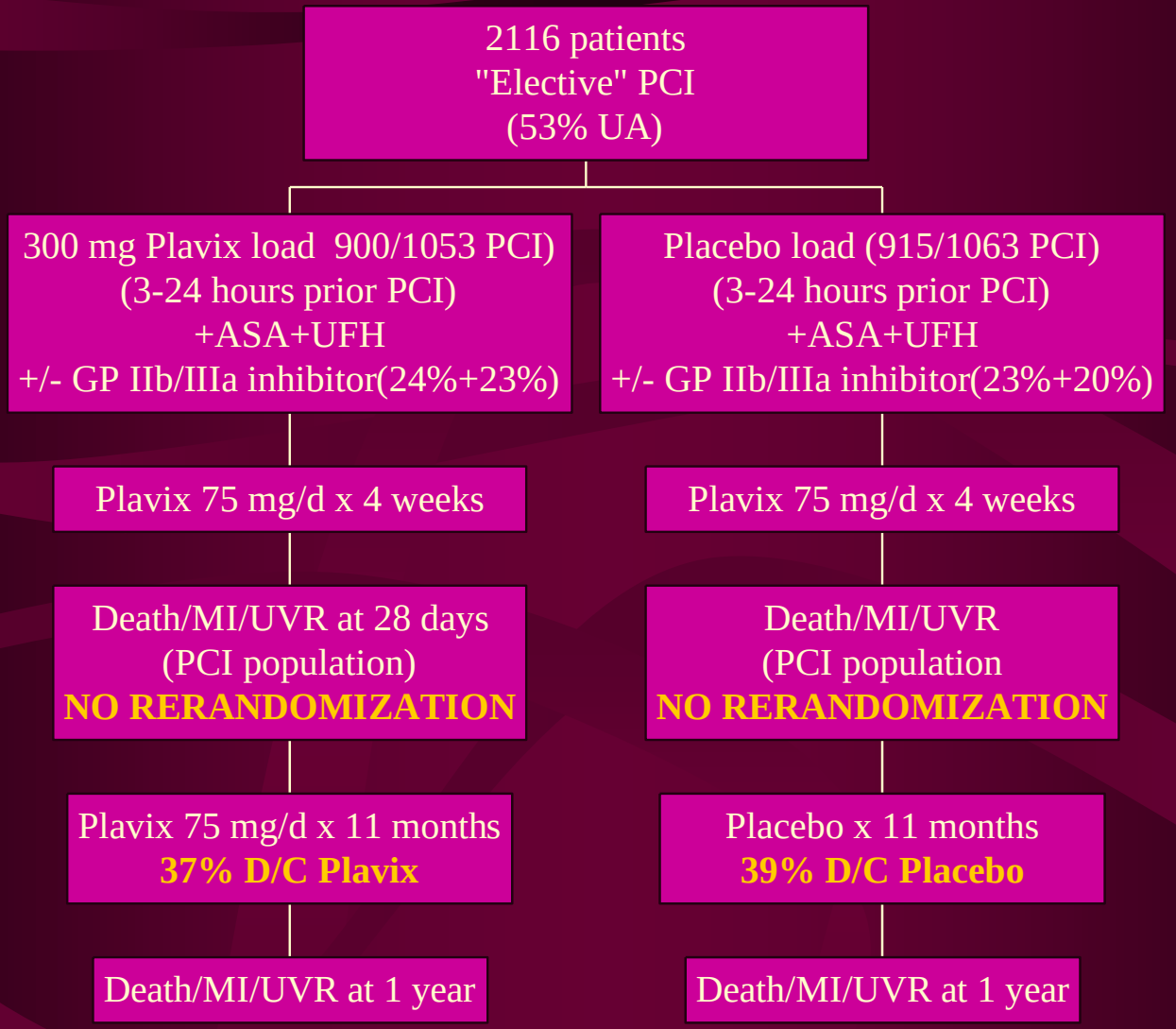
MACE:

Death/MI/UVR



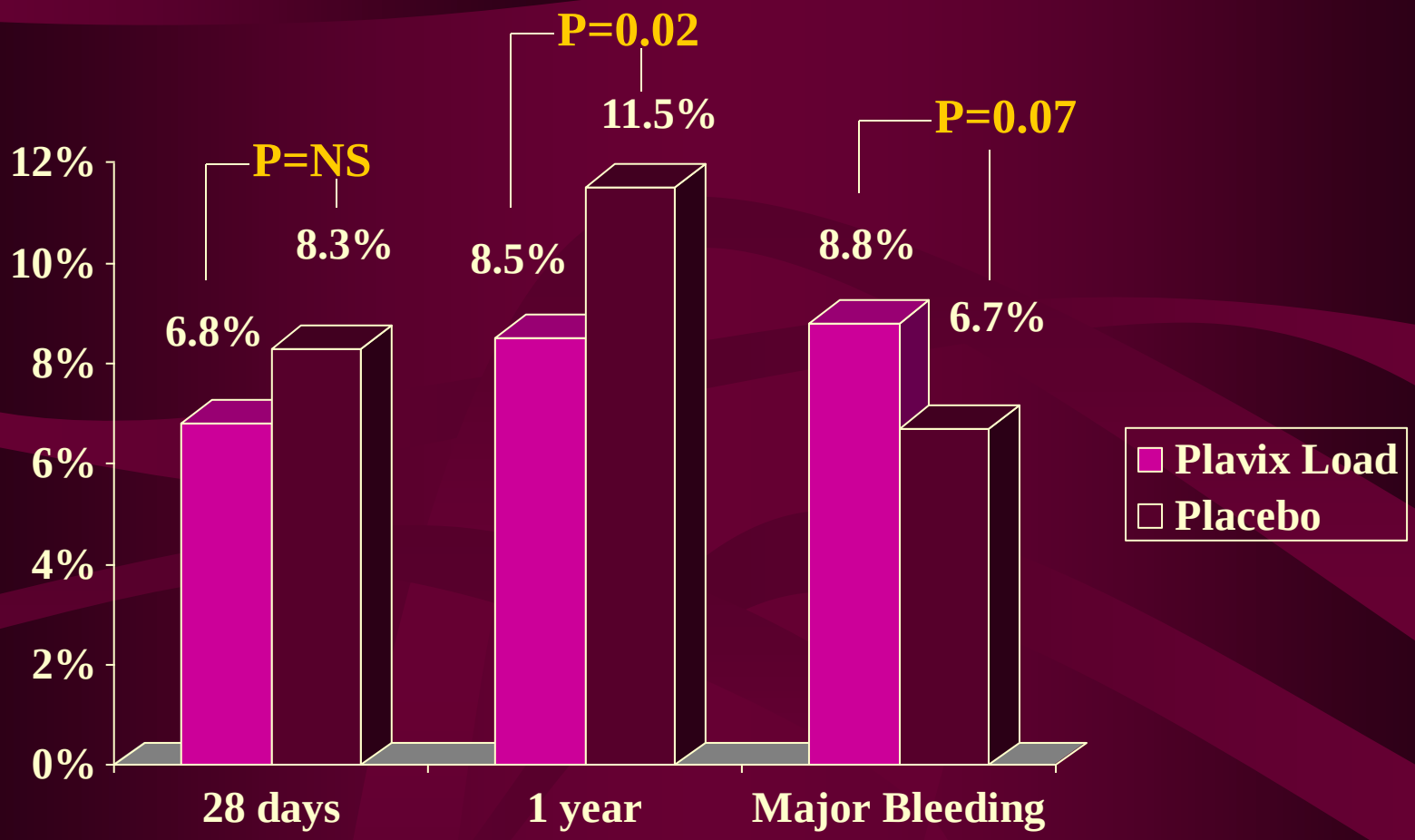
Lancet 2001;358:527-33.

The CREDO Trial: How much and for how long?



JAMA 2002;288:2411-2420.

CREDO Results

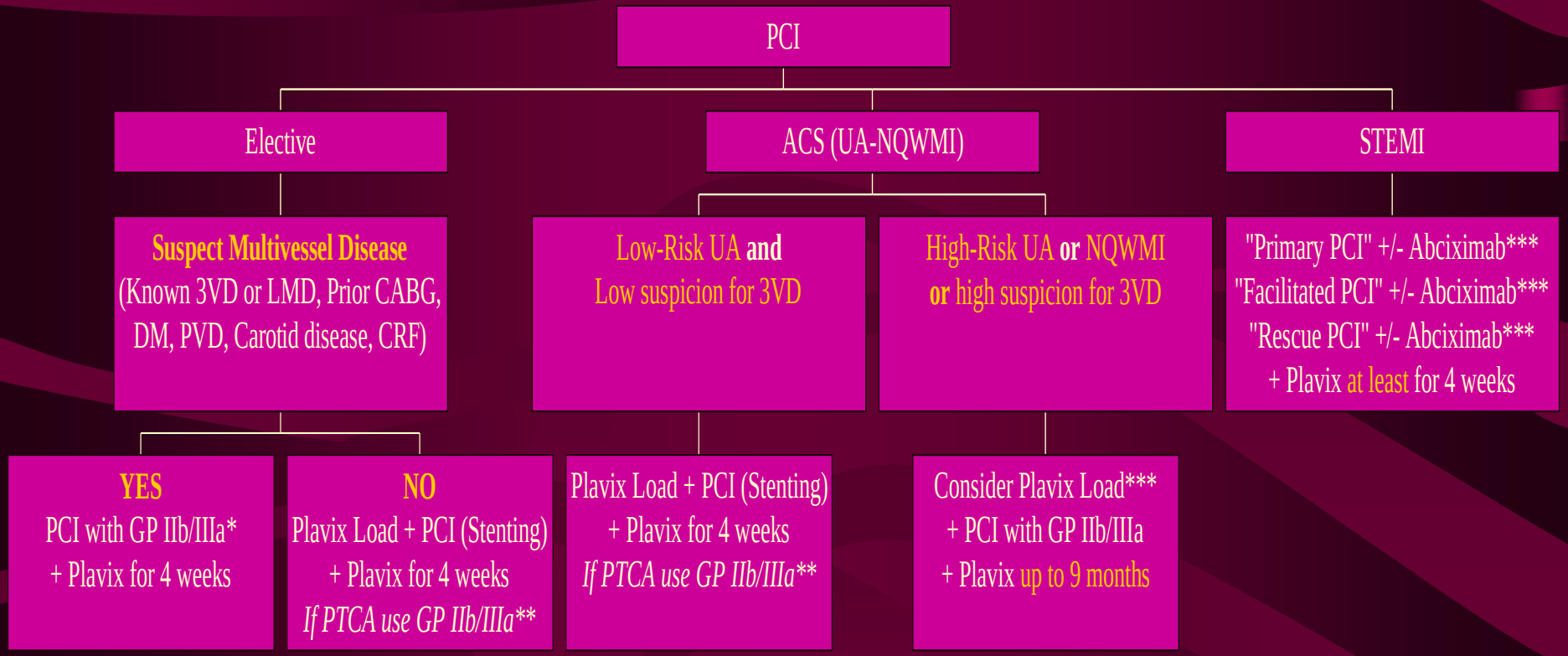


JAMA 2002;288:2411-2420.

Objectives

- Pharmacology of GP IIb/IIIa inhibitors and Monitoring of Platelet Inhibition
- Appropriate Use of GP IIb/IIIa inhibitors during PCI
- The Thienopyridines
- PCI Algorithm

Algorithm: Use of Antiplatelet therapy with PCI

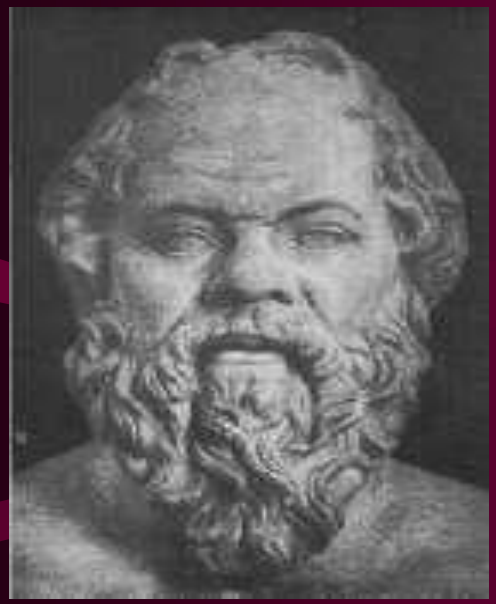


* Abciximab or Eptifibatide

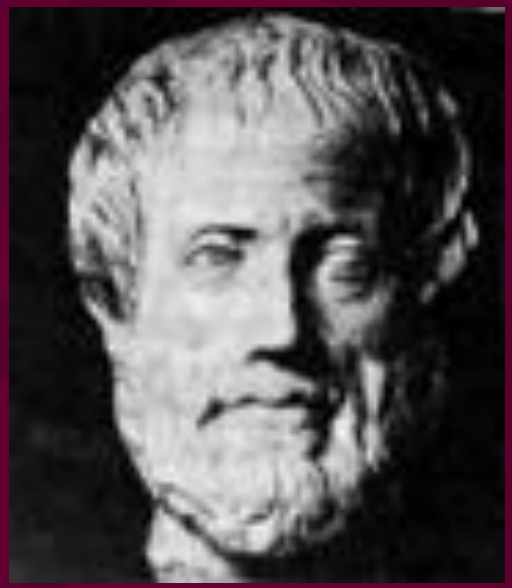
** Any GP IIb/IIIa (favors pretreatment with Tirofiban)

*** Safety Profile has not been established in large scale ACS-NSTEMI / Avoid Plavix load if high suspicion of multivessel disease / Individual bleeding risk and lesion characteristics to be assessed in both NSTEMI-STEMI

The struggle for evidence...



Socrates (469-399 BC)

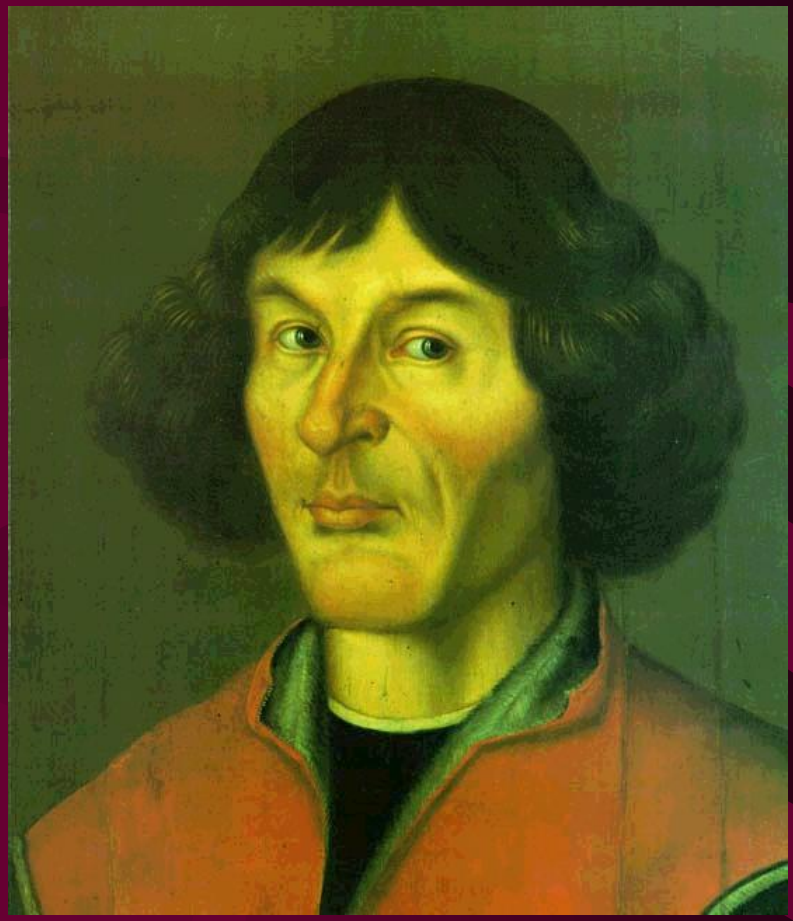


Aristotle (384-322 BC)

Plato (428-347 BC)

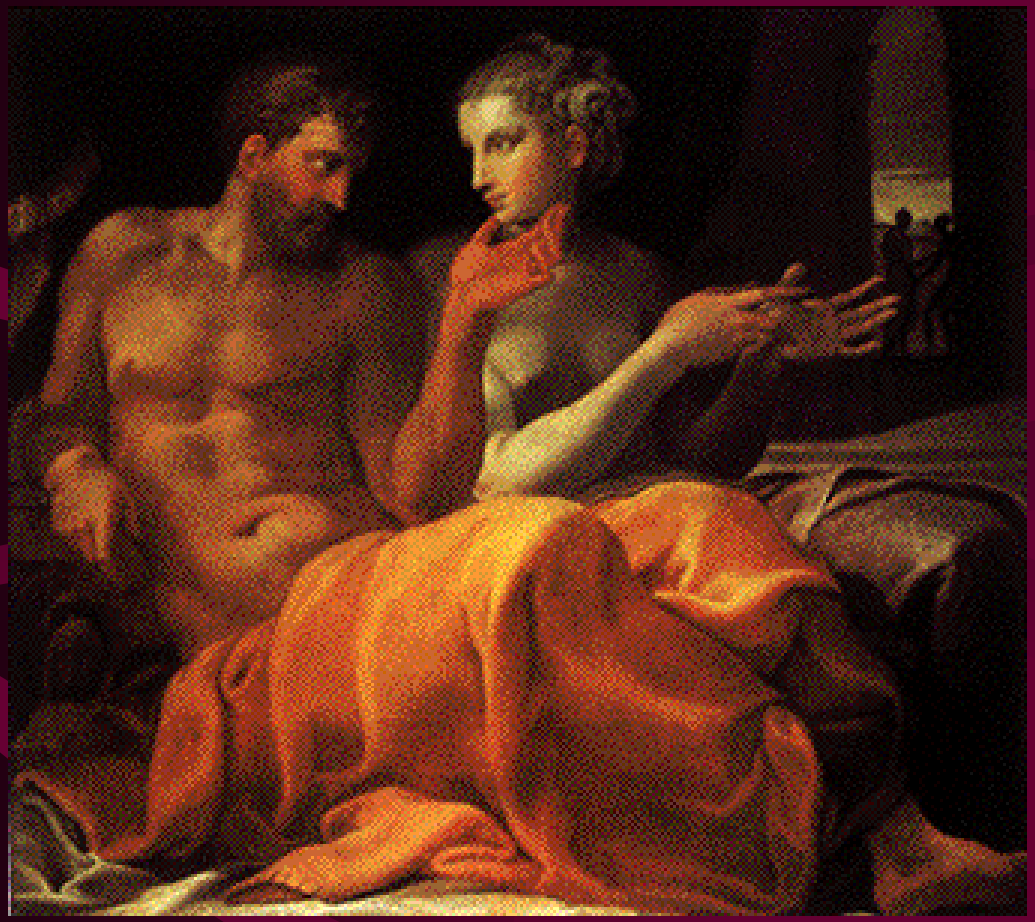
The persistence in evidence...

G. Galilei (1564-1642 AC)



N. Copernicus (1473-1543 AC)

The journey to evidence...



Odysseus and Penelope.

"When you sail for Ithaca
wish that your trip be long,
full of adventures,
full of knowledge..."

K. P. Kavafis (1863-1933)

Acknowledgements

Arietta

Katerina

Vassilis

Thank you so much…