Intravenous Antiplatelet Therapy in Coronary Artery Disease

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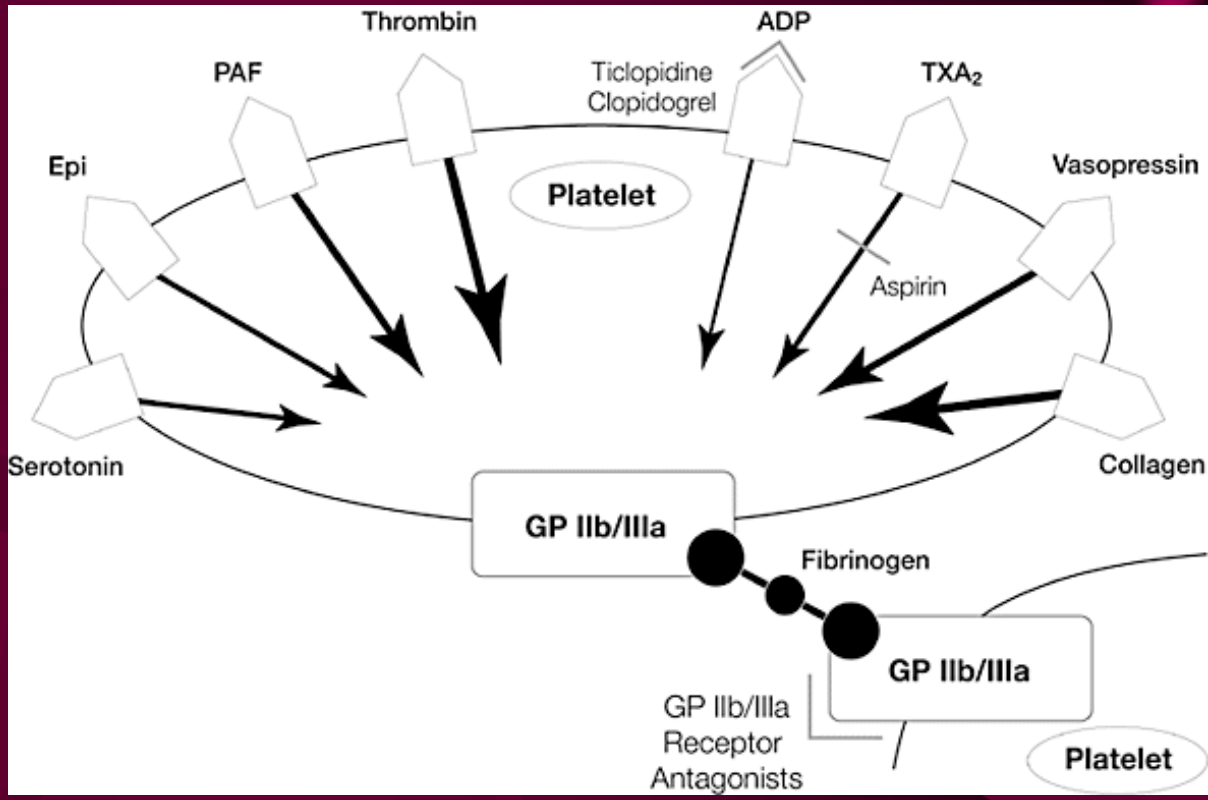
Objectives

- Platelet function and inhibition
- Current intravenous antiplatelet agents
  - Abciximab
  - Eptifibatide
  - Tirofiban
  - Cangrelor
- Key Notes

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**

Theurapeutic Targets

- ***Cyclooxygenase*** **1** (prevents TXA2) - Aspirin
- ***ADP Receptor P2Y12*** - Clopidogrel, Prasugrel, Ticagrelor, Cangrelor
- ***GP IIb-IIIa Antagonists***– abciximab, eptifibatide, tirofiban
- ***Thrombin receptor-Protease activated receptor 1 (PAR-1)*** (Inhibites thrombin-mediated platelet aggregation) - Vorapaxar, Atopaxar
- Novel agents e.g ***Ab targeting vWf***, ***GPIba receptor***

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GP IIb/IIIa Antagonists

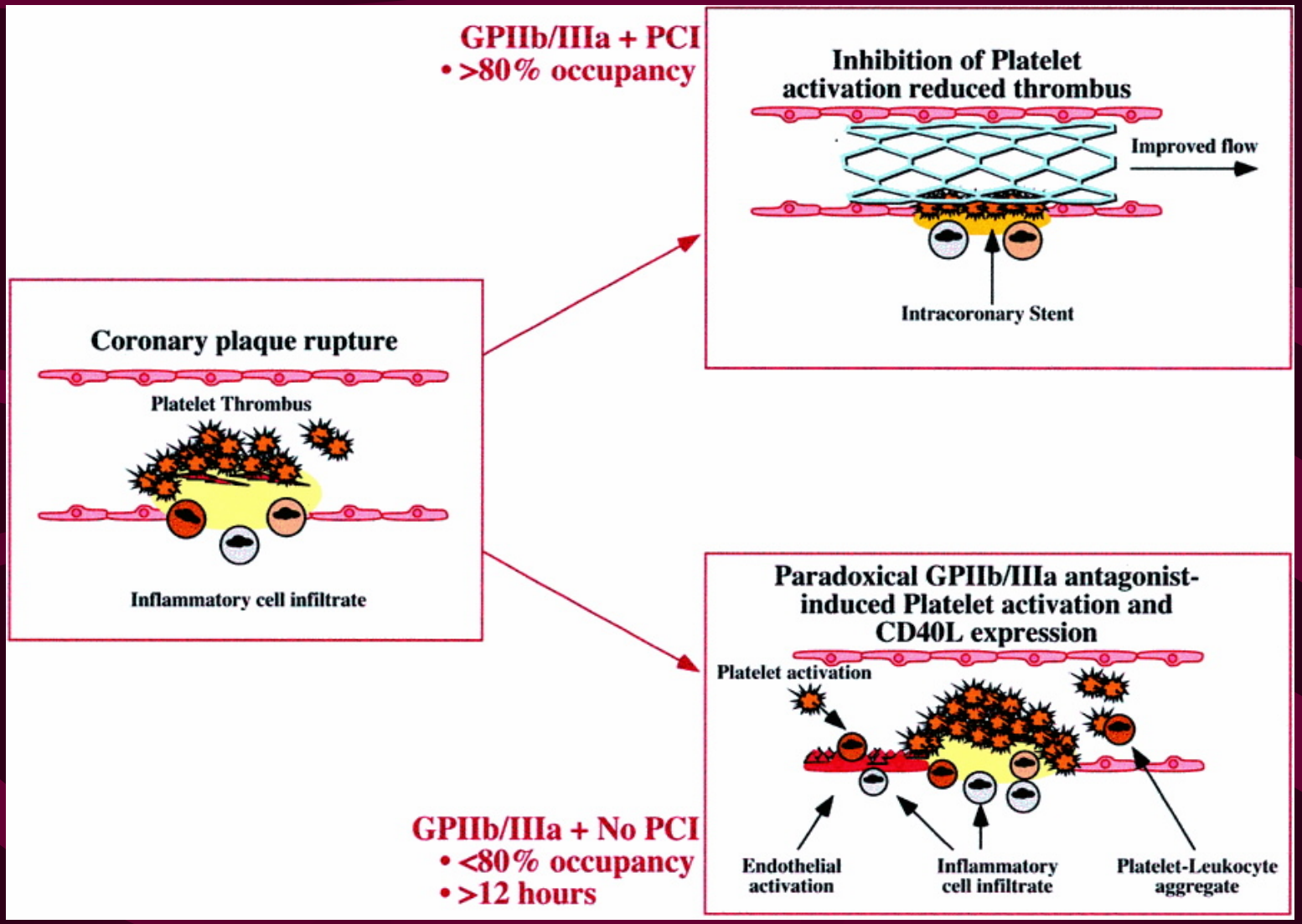
- Abciximab
  - Murine Monoclonal Antibody
  - Binds rapidly – dissociates slowly
  - Not IIb/IIIa integrin-specific (Mac-1, Vitronectin)
  - Inhibits Thrombin generation
  - 6% anti-abciximab antibodies

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

Platelet Aggregation Inhibition Essays

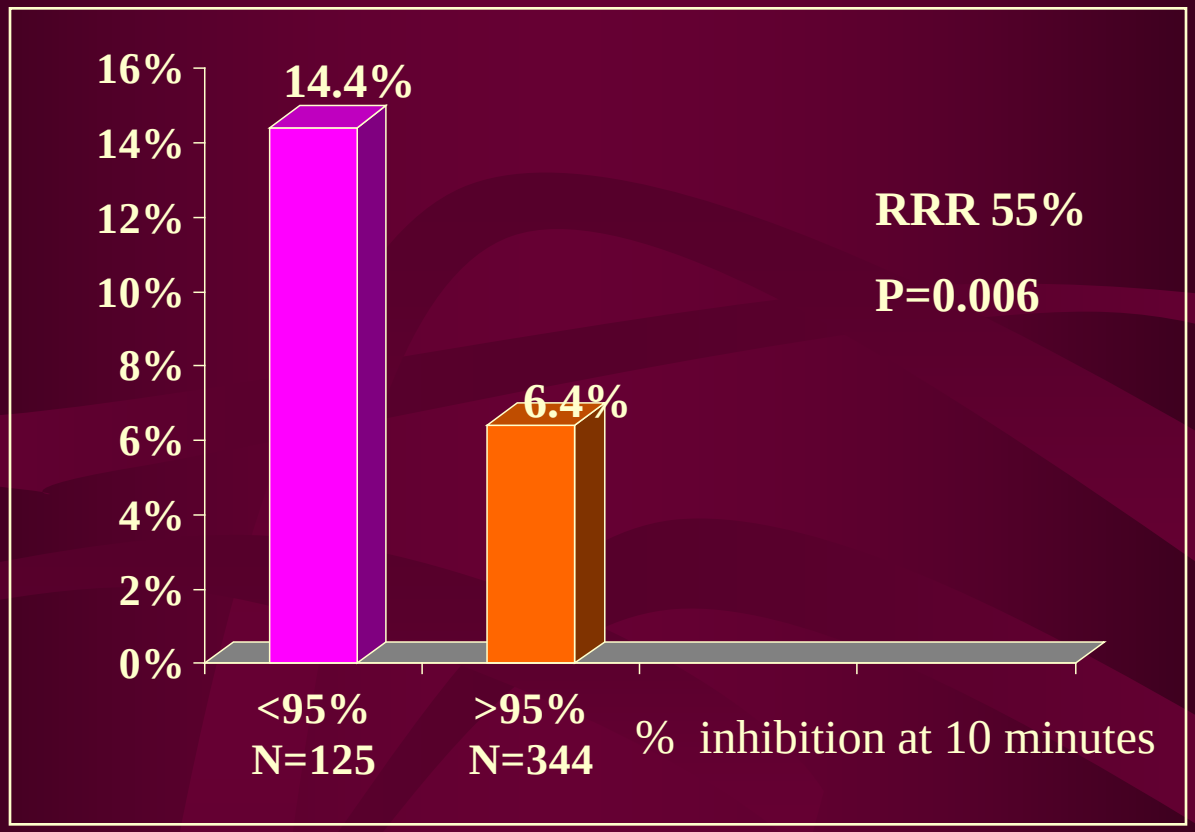
- **Light Transmission Aggregometry (LTA)**
  - **Time consuming**
  - **Linear relationship**
  - **Anticoagulants (Sodium citrate, PPACK, UFH, EDTA)**
  - **Platelet agonists (ADP, thrombin)**
  - **Tirofiban (3.4-5 μM ADP) vs. abciximab/eptifibatide (20 μM)**
  - **>80%: surrogate inhibition**
- Rapid 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



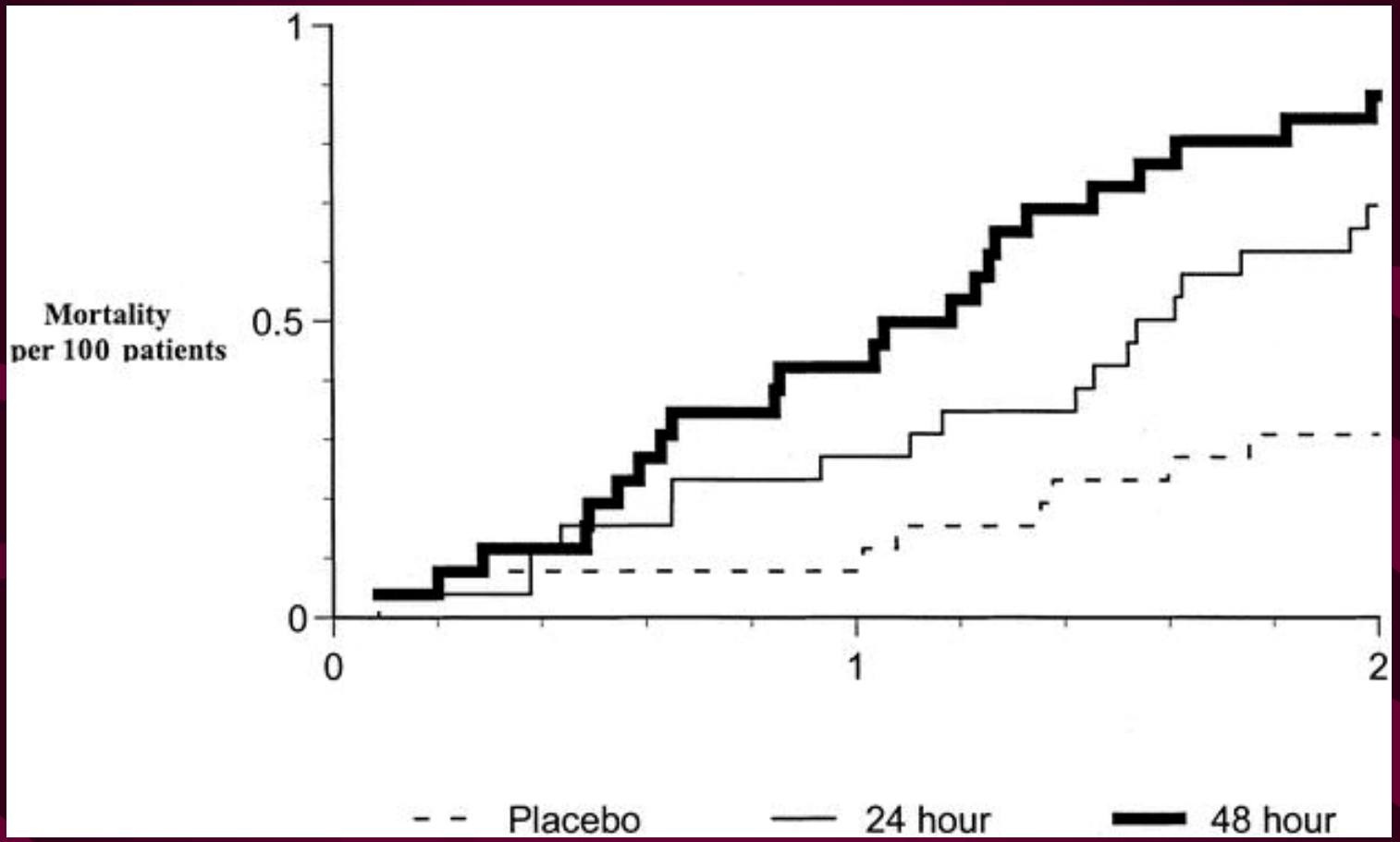
Quinn et al. *Circulation 2002;106:379-85.*

MACE Versus Platelet Inhibition by RPFA



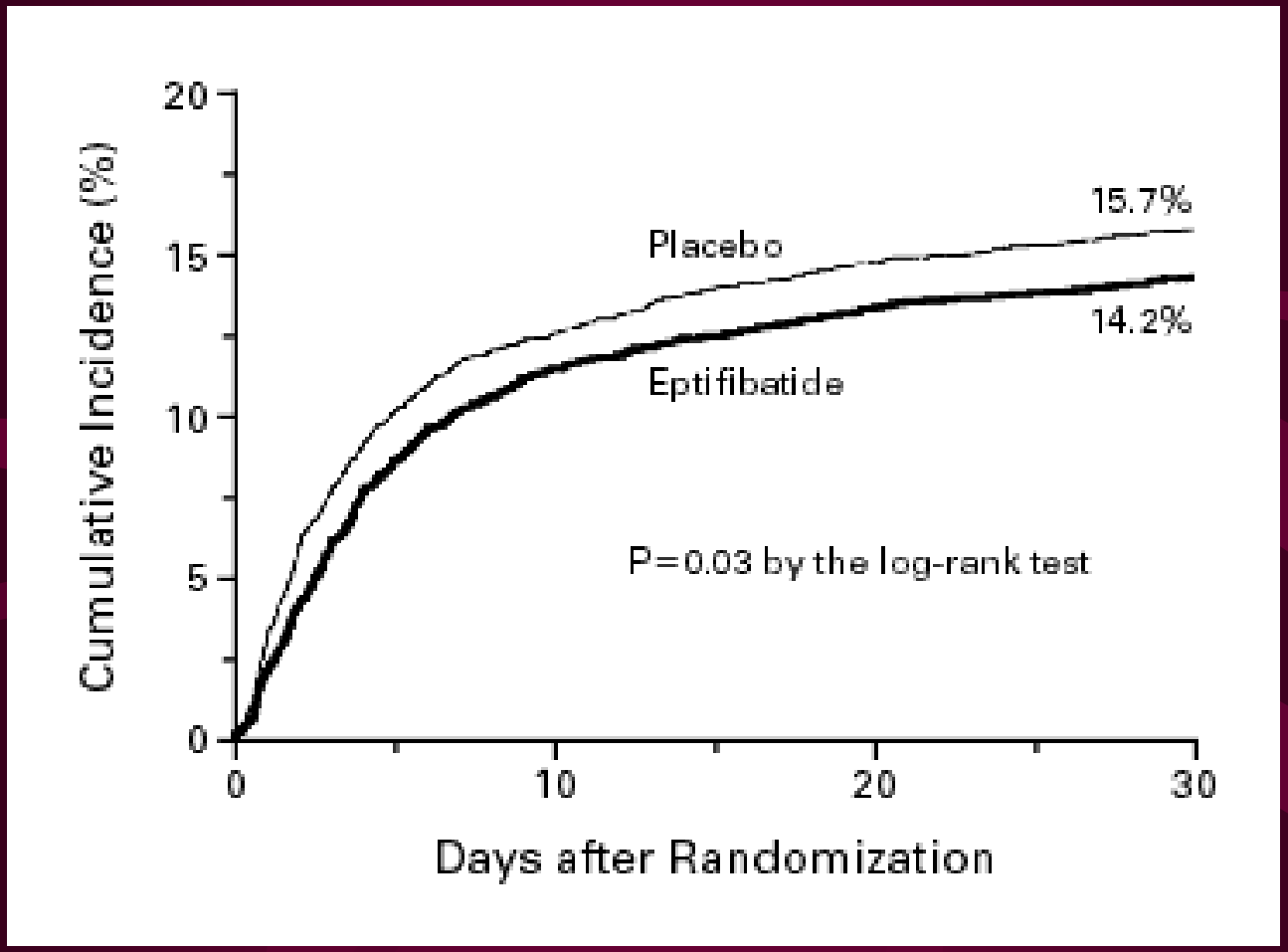
The GOLD Trial. ***Circulation 2001;103:2572-78.***

Clinical Implications: GUSTO IV-ACS



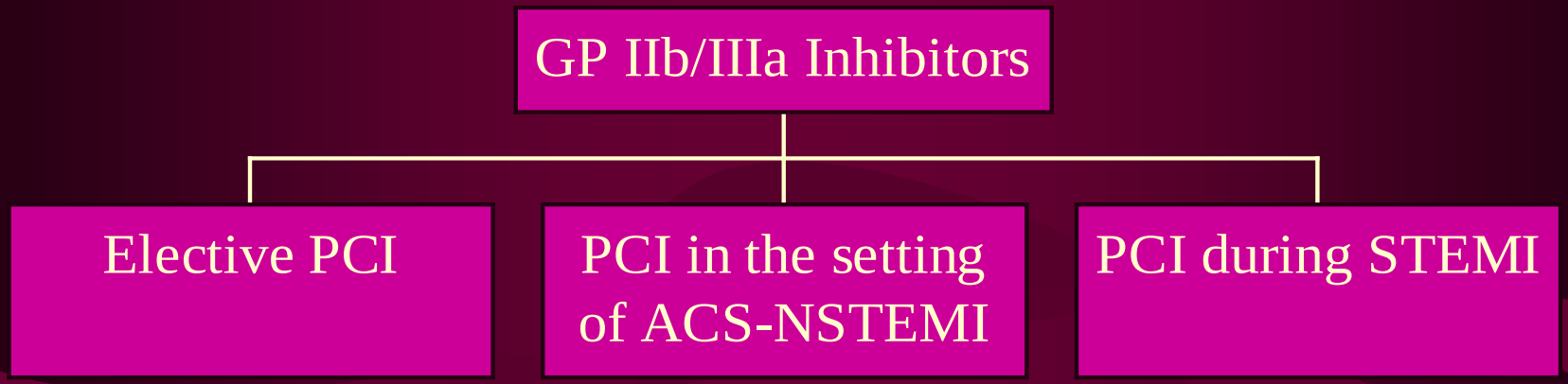
Increased mortality in the 24-hr (p=0.048) and 48-hr (p=0.007) abciximab groups. The curves separate early an continue to separate after 24 hrs. **Circulation 2002;106:379-85.**

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.**

Initial Trials with GP IIb/IIIa Inhibitors during PCI



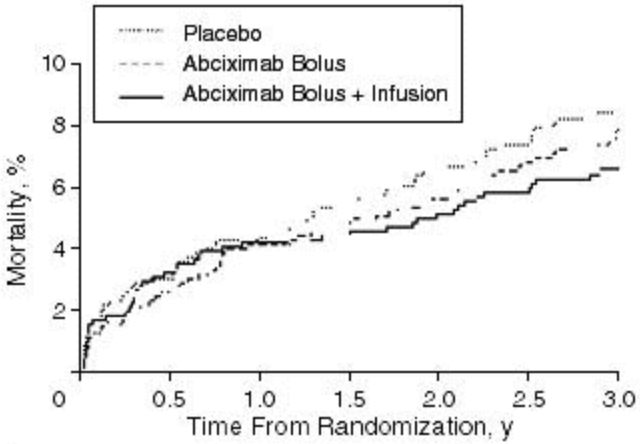
EPILOG* (Low Risk UA)
EPISTENT (40% SA)
ERASER
Kini et al (HSRA)
Tamburino et al
IMPACT
IMPACT-II* (42% ACS)
ESPRIT (12% ACS)
Harrington et al
Kereiakis et al

EPIC* (high-risk PCI)
EPISTENT (37% UA)
CAPTURE
Simoons et al
ISAR-2
IMPACT-II* (42% ACS)
RESTORE

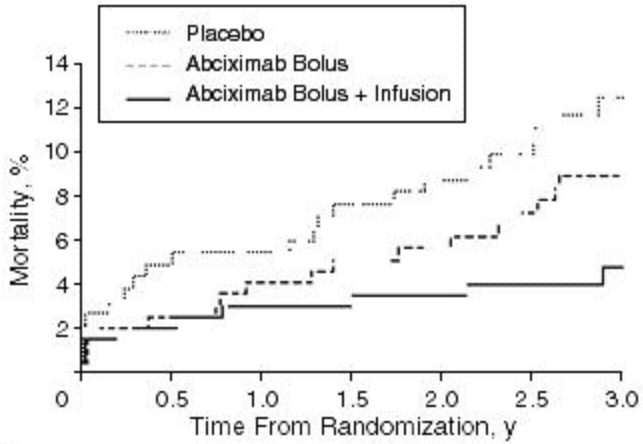
RAPPORT
ADMIRAL
CADILLAC
Petronio et al (Rescue PTCA)

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

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

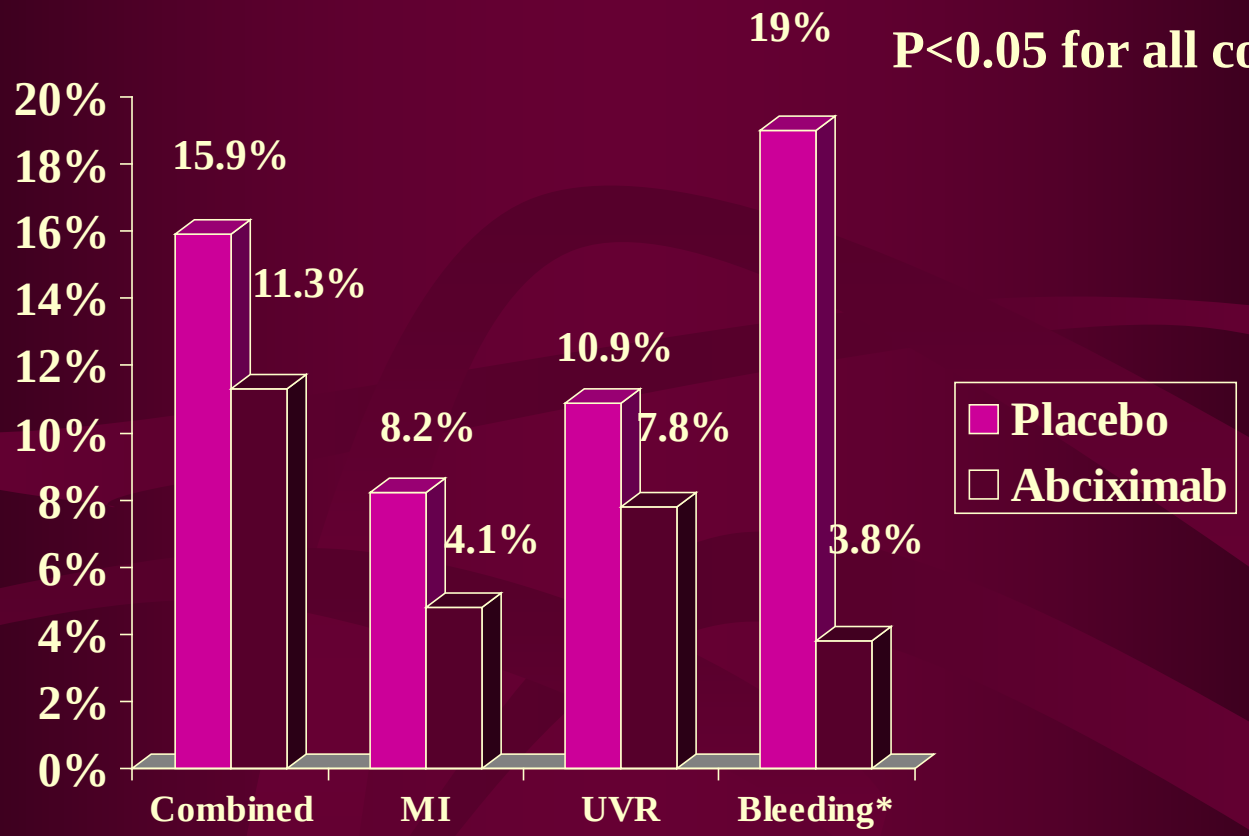


Completed Follow-up							
Placebo	179	179	178	178	178	170	101
Bolus	188	188	188	188	187	180	98
Bolus + Infusion	188	188	188	187	187	180	99

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).

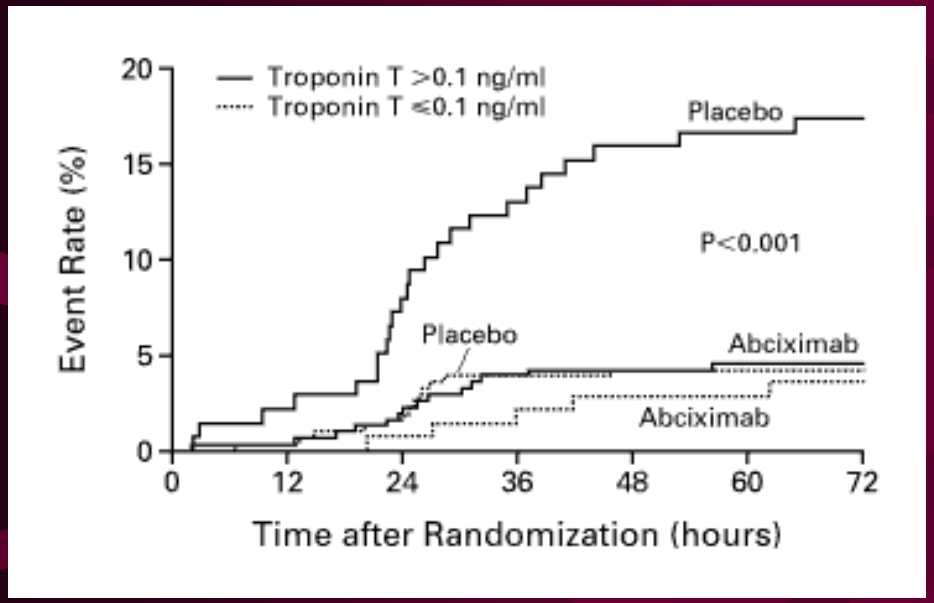
JAMA 1997;278:479-84.

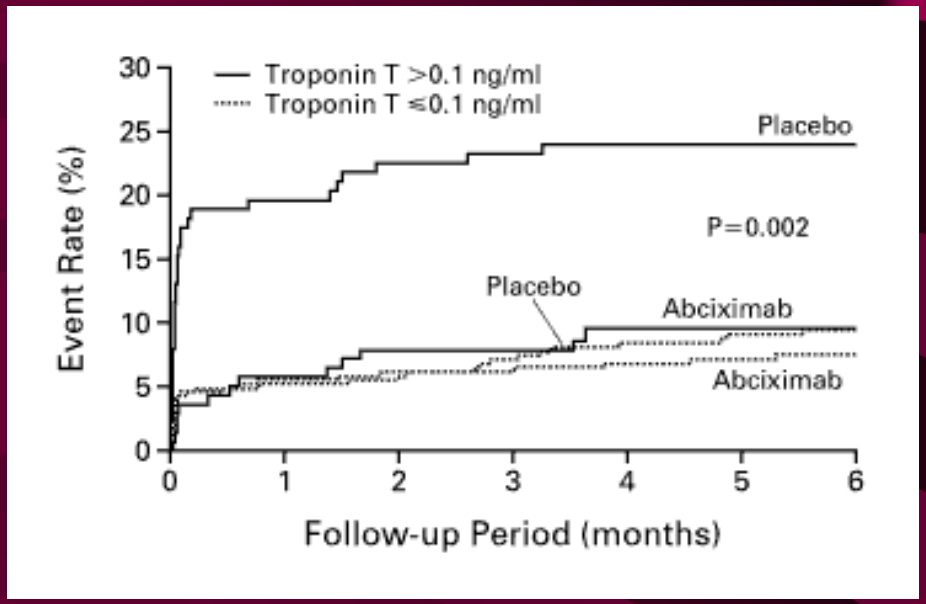
CAPTURE 30-days Results



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

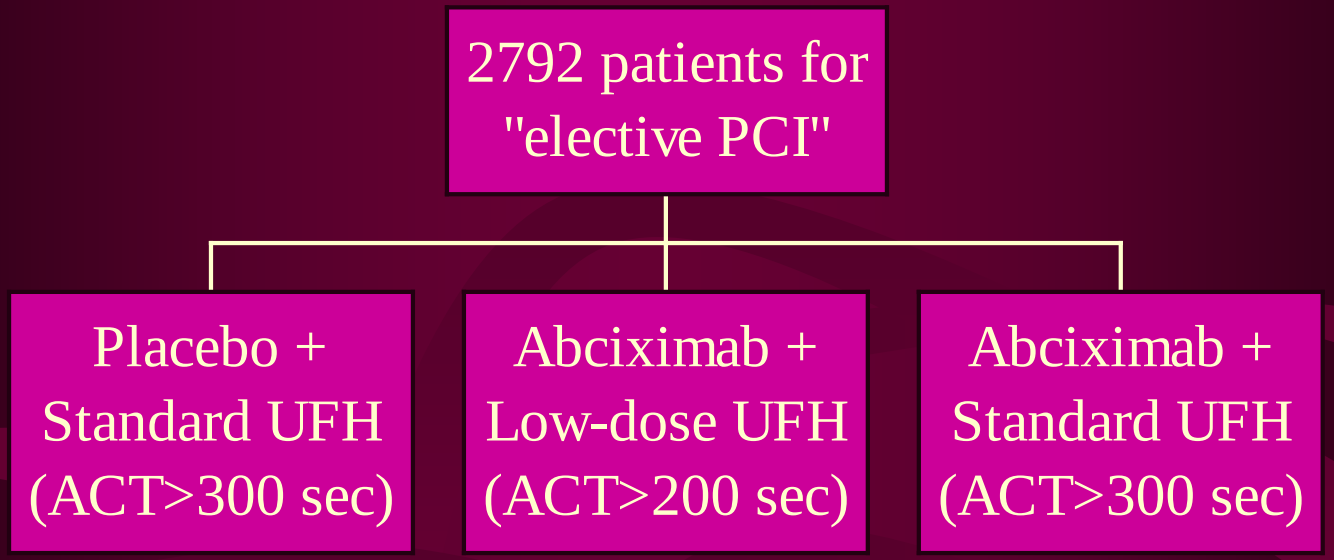




Cardiac Events (death + MI) in the Initial 72 Hours (Left) and during the 6 Months of Follow-up (Right) among Patients with Serum Troponin T Levels above and those with Levels below the Diagnostic Cutoff Point.

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

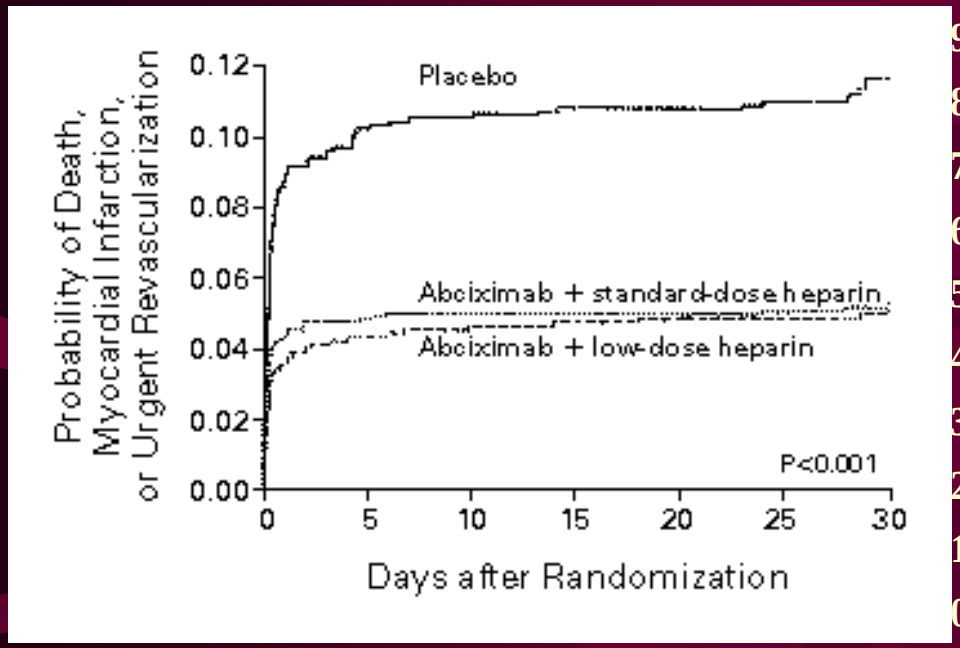
GP IIb/IIIa Inhibitors during Elective PCI: EPILOG

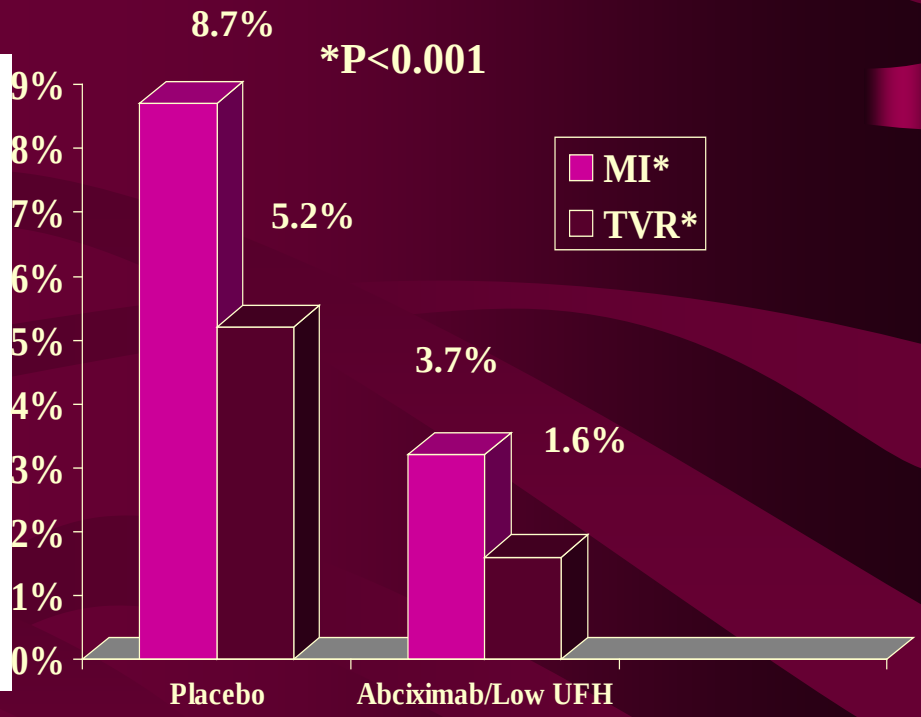


- Patients with UA or ECG changes within the last 24 hours were excluded
- ASA 325 mg, Standard versus Low-dose heparin
- Primary Efficacy End point: Death, Non fatal MI, severe ischemia (TVR) at 30 days
- No Plavix or Ticlid
- Minimal % of stenting

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.***

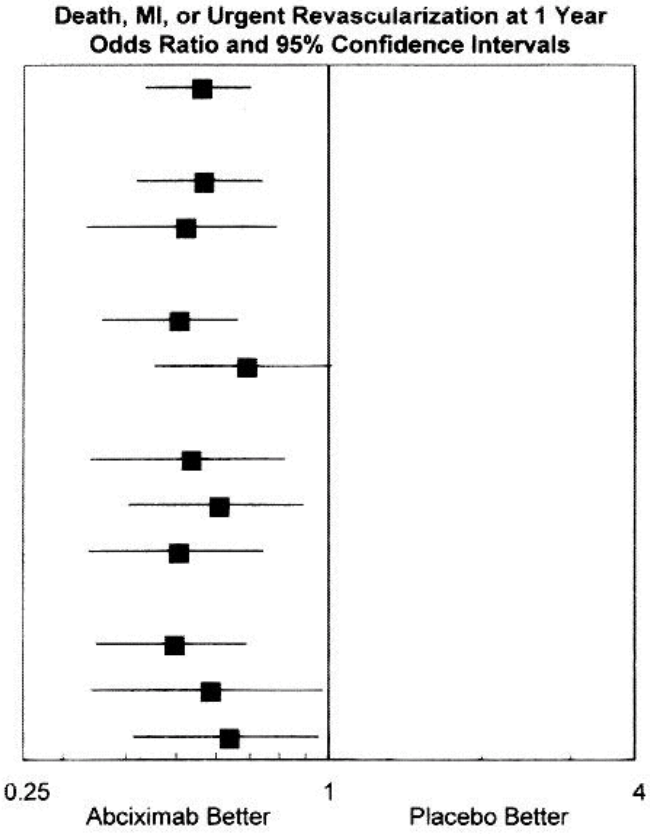
EPILOG 1-year Results: The higher the risk the greater the benefit of Abciximab during PCI

Results

Efficacy Analysis at 1 Year

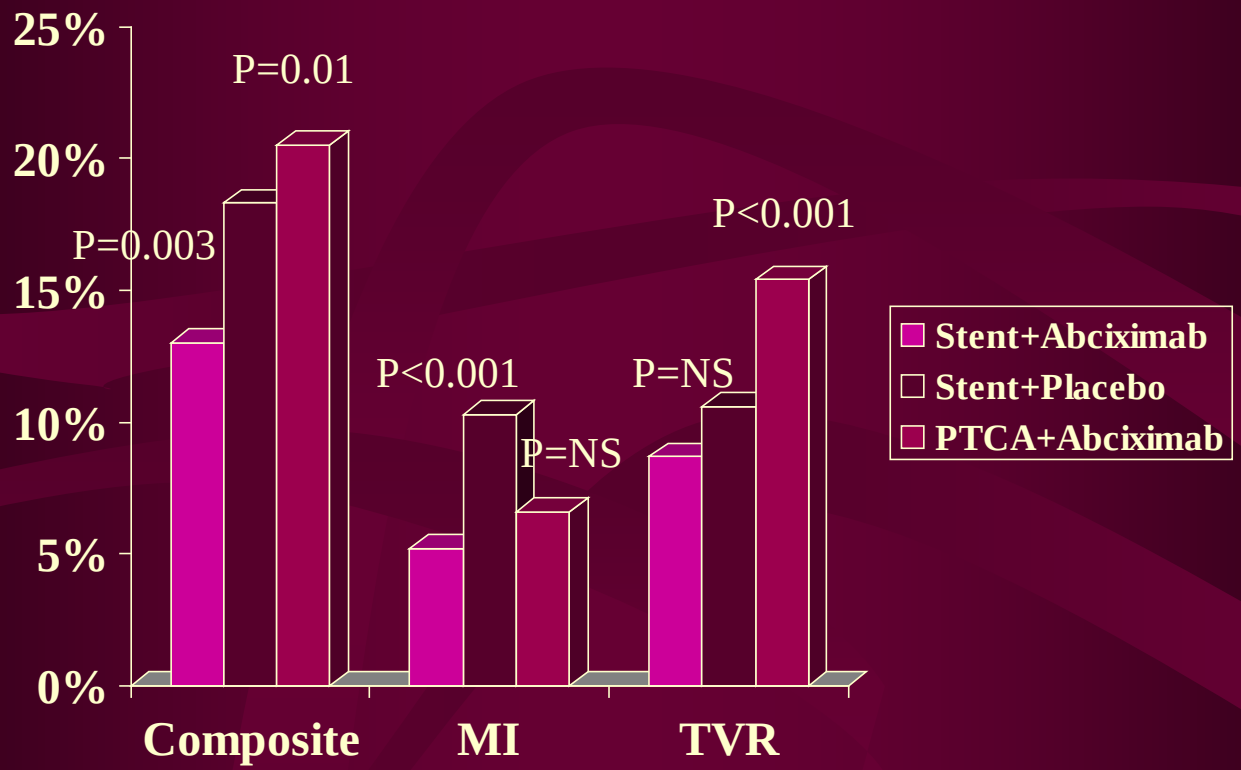
The incidence of the primary composite end point of death, myocardial infarction, or urgent revascularization (the

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)



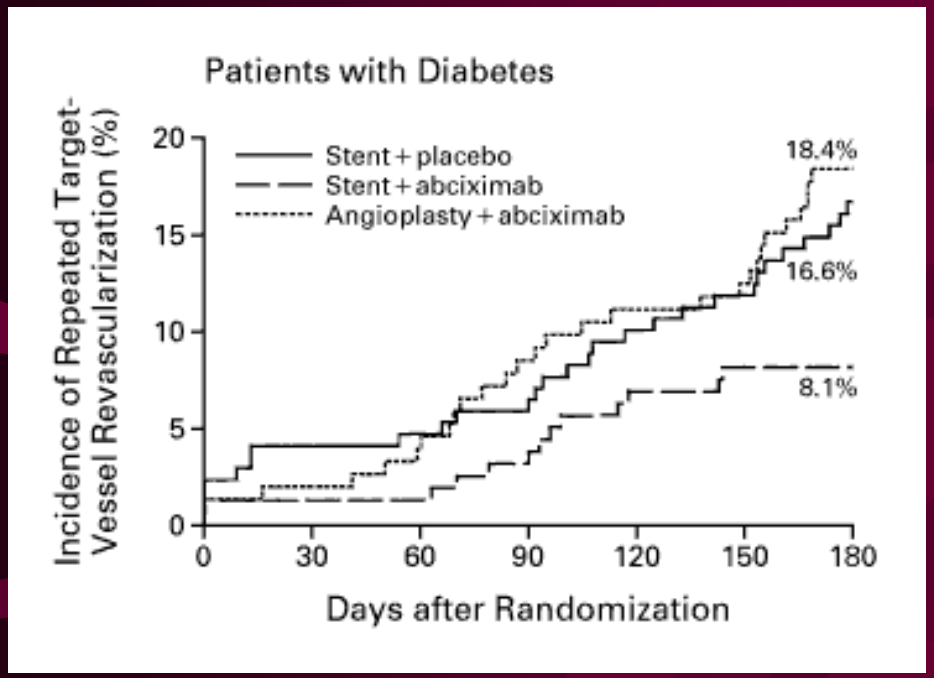
Circulation 1999;99:1951-8.

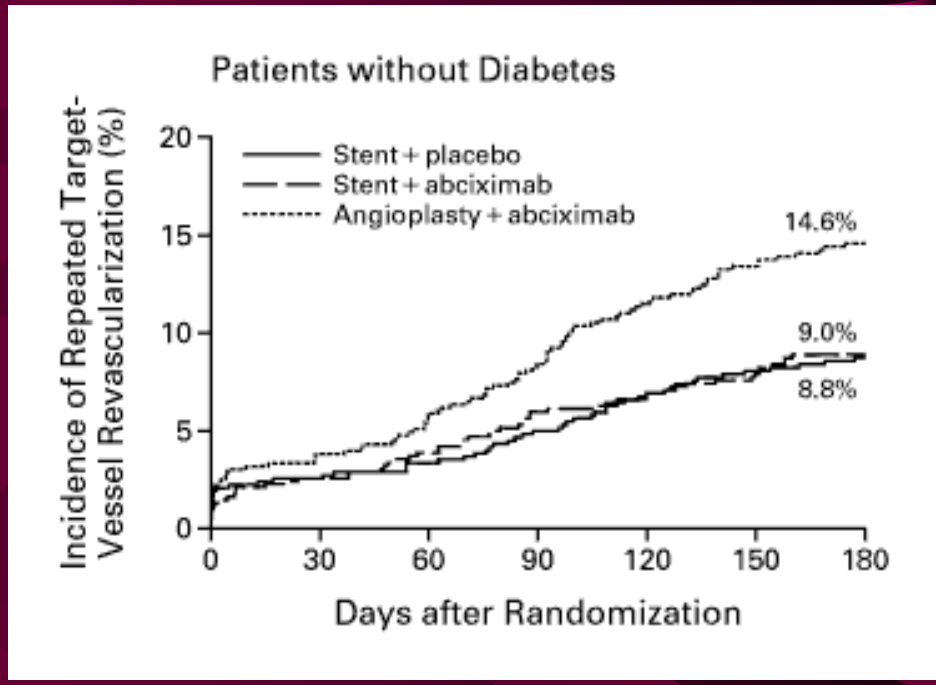
EPISTENT 6 months



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

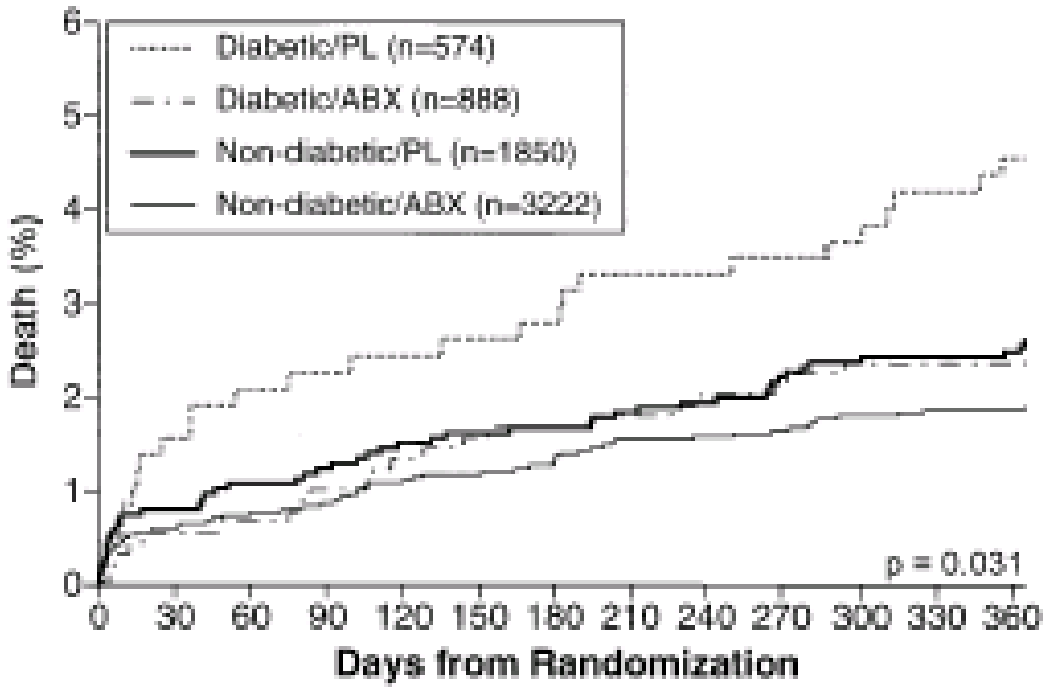
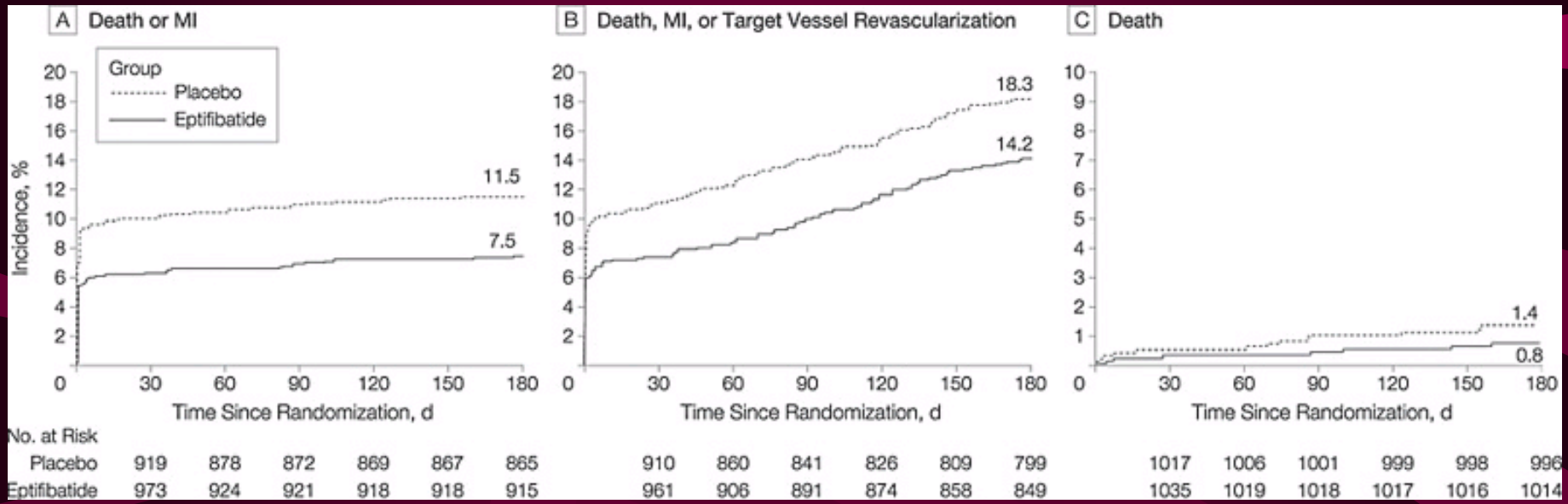


Figure 3. The Kaplan-Meier curves are shown for one-year mortality in diabetics and nondiabetics randomized to either placebo (PL) or abciximab (ABX).

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

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

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



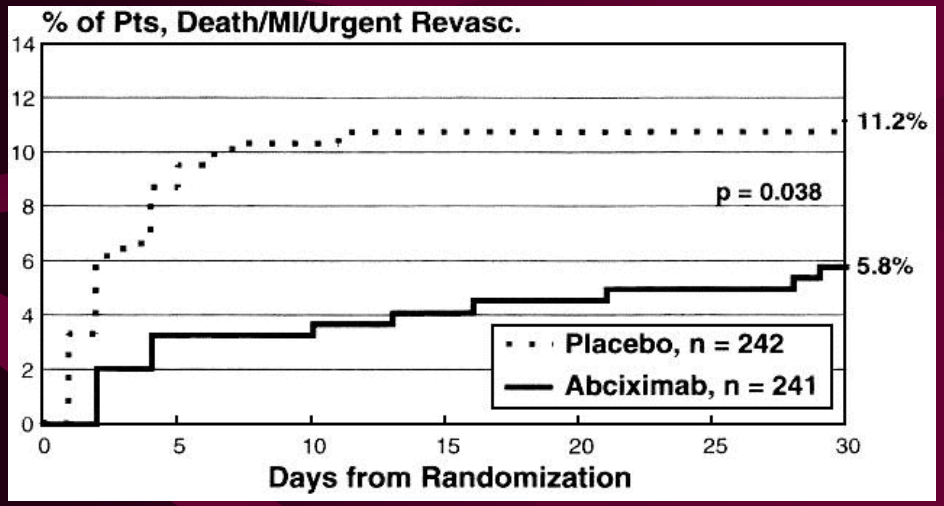
RRR (MI): 33% over 6 months

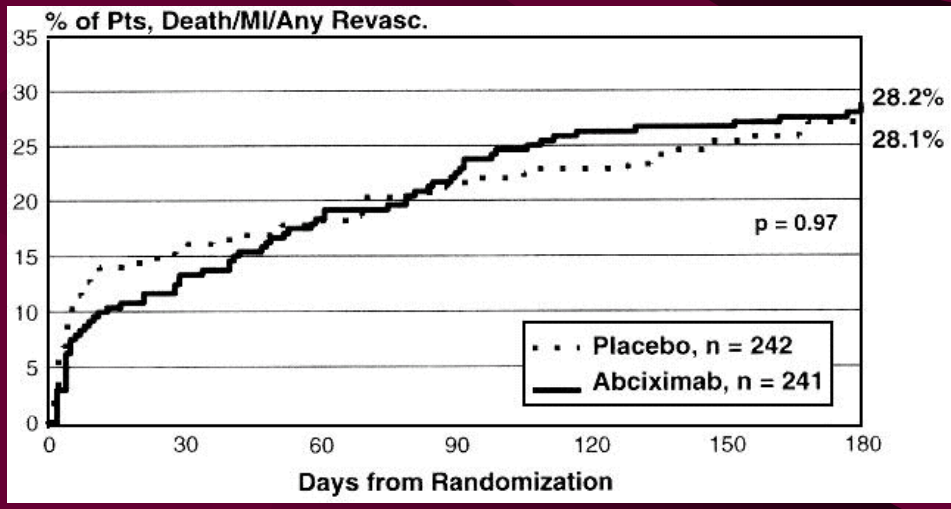
Cumulative Incidence of Study End Points Among Patients Treated With Eptifibatide or Placebo. For the composite end point of death or MI, HR, 0.63; 95% CI, 0.47-0.84; *P* =.002. For the composite end point of death, MI, or target vessel revisualization, HR, 0.75; 95% CI, 0.60-0.93; *P* =.008. For the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

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





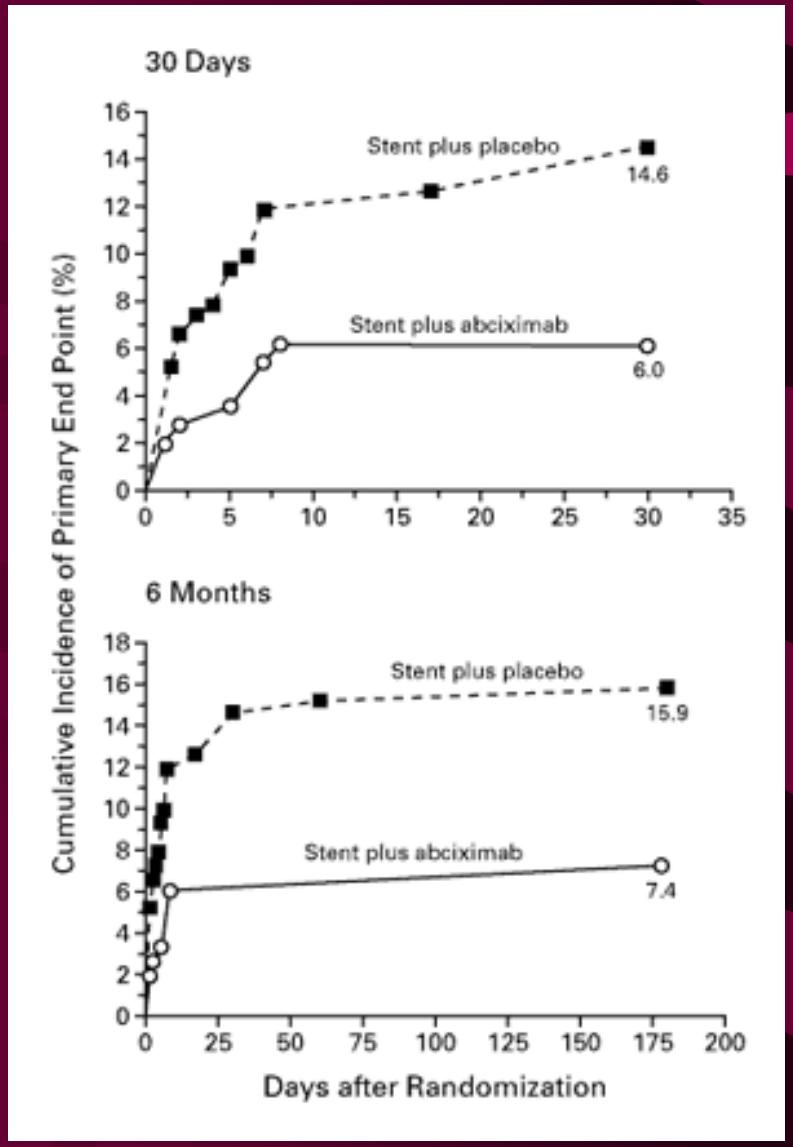
Both 30 days' and 6 months' composite end point was driven from TVR. 20% stents (PL) versus 12% (AB), p=0.008. ***Circulation 1998;98:734-41.***

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

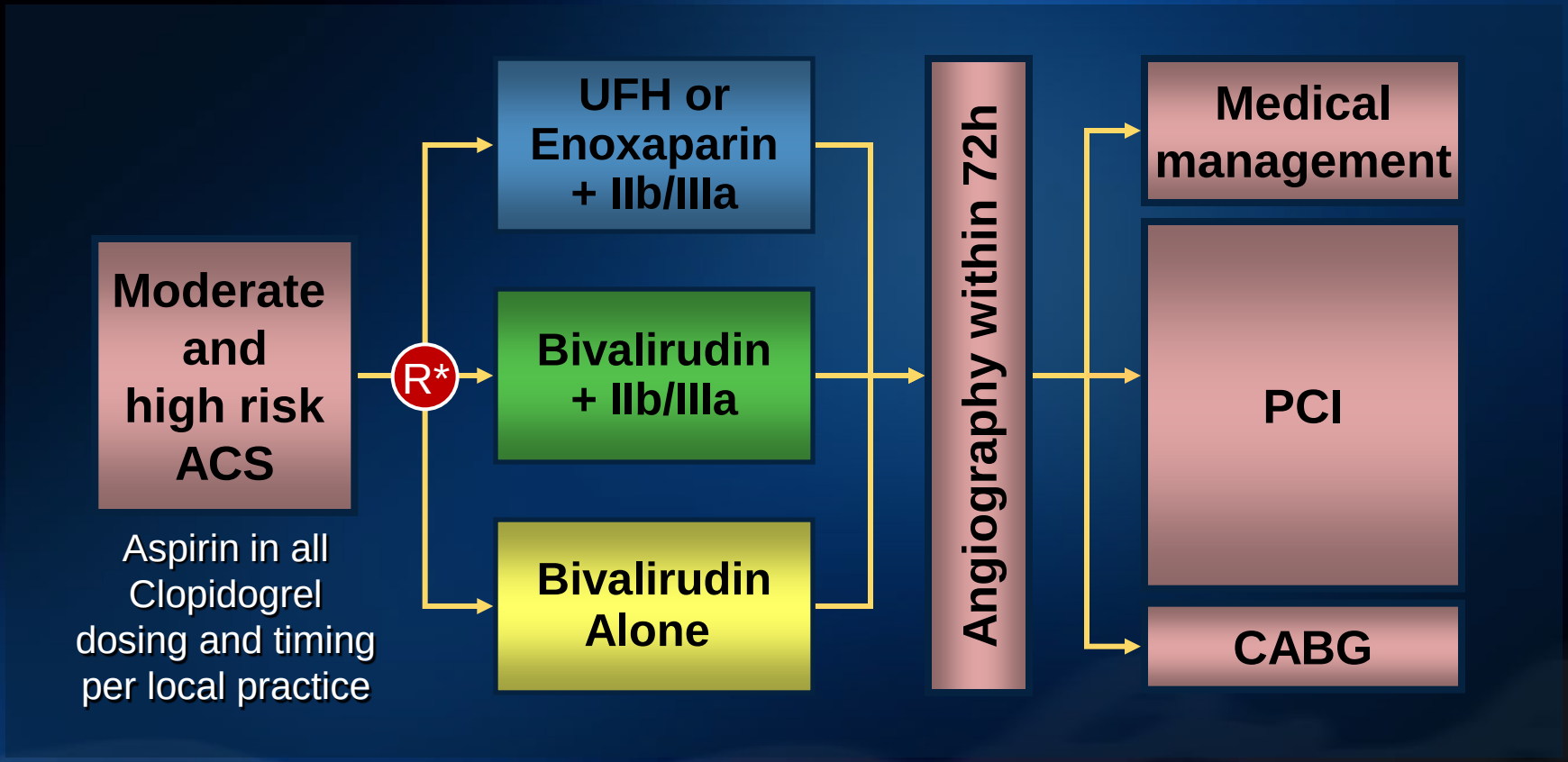
Outcome	PTCA (N=518)	PTCA plus Abciximab (N=528)	Stenting (N=512)	Stenting plus Abciximab (N=524)	P Value
At 6 months (cumulative)					
Death	4.5	2.5	3.0	4.2	0.23
Reinfarction	1.8	2.7	1.6	2.2	0.64
Disabling stroke	0.2	0.2	0.4	0.4	0.88
Revascularization of ischemic target vessel	15.7	13.8	8.3‖	5.2**	<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.

ACUITY Study (ACC, March 2006)

Moderate and high risk unstable angina or NSTEMI undergoing an invasive strategy (N = 13,819)



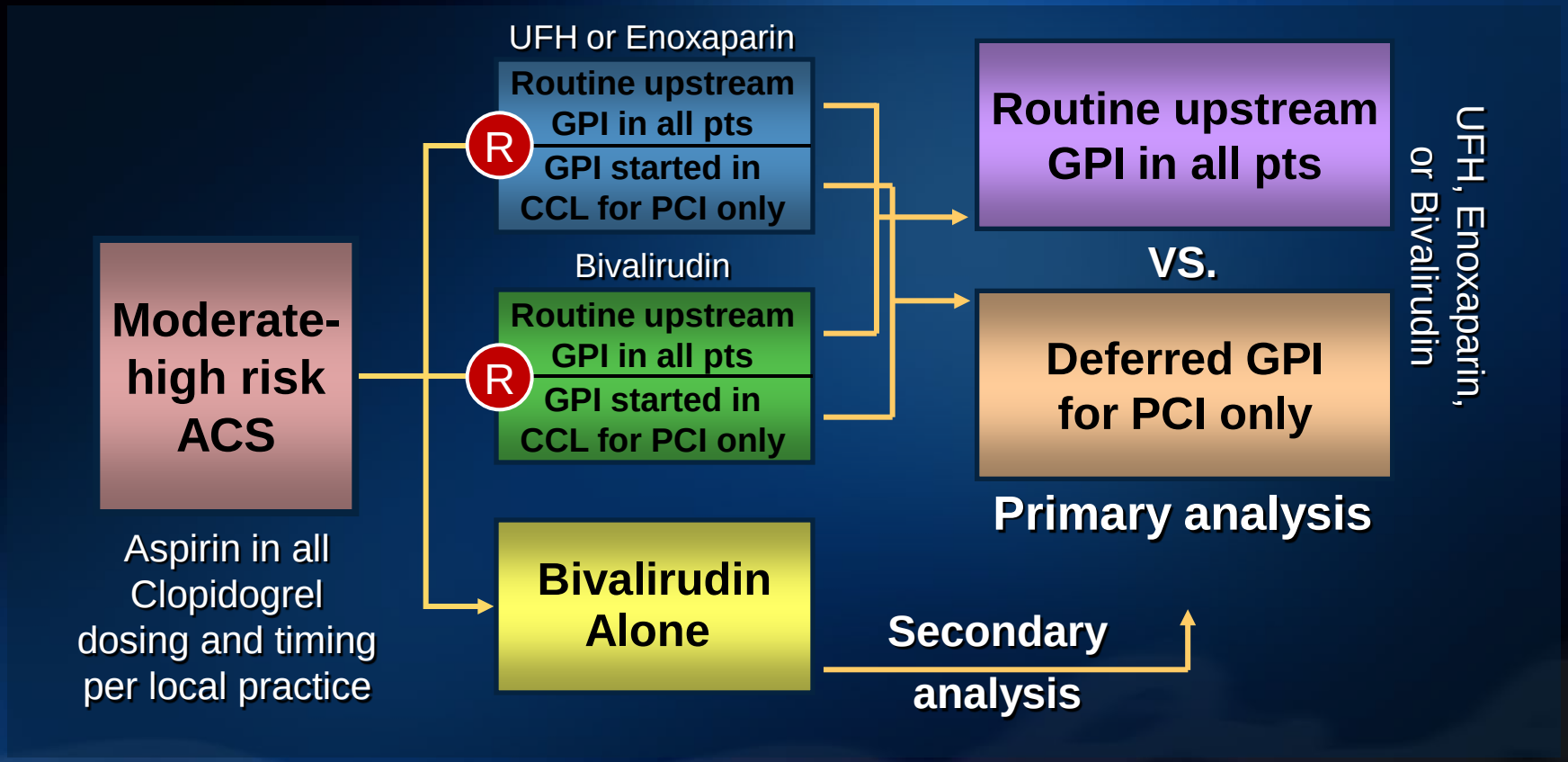
*Stratified by pre-angiography thienopyridine use or administration

ACUITY Design. Stone GW et al. AHJ 2004;148:764–75

ACUITY

Study Design – Second Randomization

Moderate-high risk unstable angina or NSTEMI undergoing an invasive strategy (N = 13,800)



Summary Conclusions

ACUITY Timing Trial

	Routine upstream GPI in all pts	Deferred GPI for PCI only	
Net Composite Outcome	11.7%	11.7%	P_{NI} <0.0001
Ischemic Composite	7.1%	7.9%	P_{NI} = 0.044* P_{Sup} = 0.13
Major Bleeding	6.1%	4.9%	P_{Sup} = 0.009

*RR [95%CI] = 1.12 [0.97-1.29]

ACUITY

EARLY ACS Study Design

2 of 3 high-risk criteria:
1. Age ≥ 60 years
2. + CKMB or TnT/I
3. ST ↓ or transient ST ↑

(Or age 50-59, h/o CVD and + CKMB or TnT/I)

High-risk NSTE ACS
n = 10,500

Routine, early eptifibatide
(180/2/180)

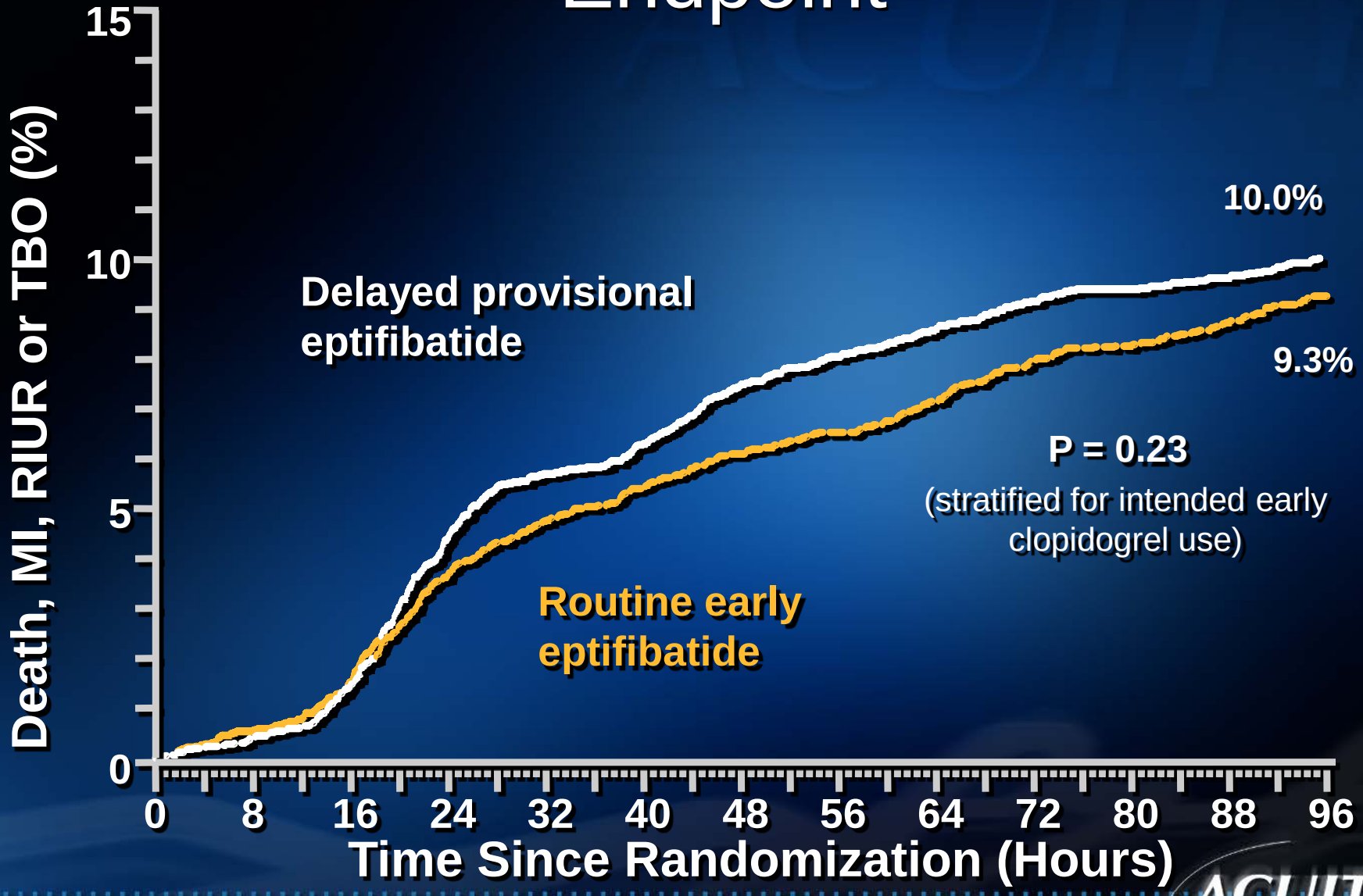
Placebo / delayed provisional eptifibatide pre-PCI

Randomize within 12 hours of presentation

Invasive strategy: 12 to 96 hours after randomization

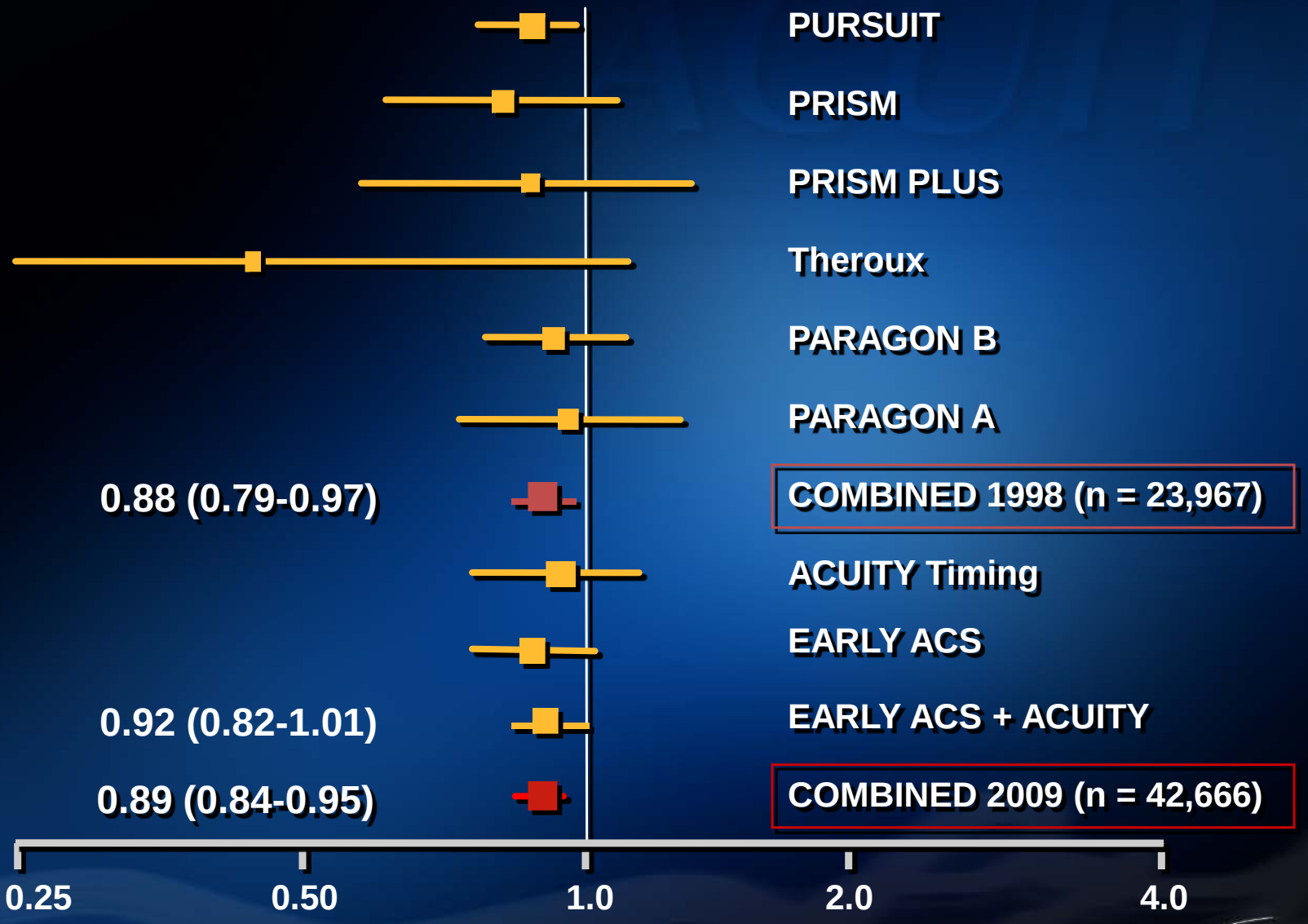
Safety Endpoints at 120 hrs: Bleeding (GUSTO and TIMI scales), Transfusions, Stroke, Non-hemorrhagic SAEs

Kaplan-Meier Curves for Primary Endpoint



ACUITY

Small Molecule GP IIb/IIIa Inhibition in NSTE ACS



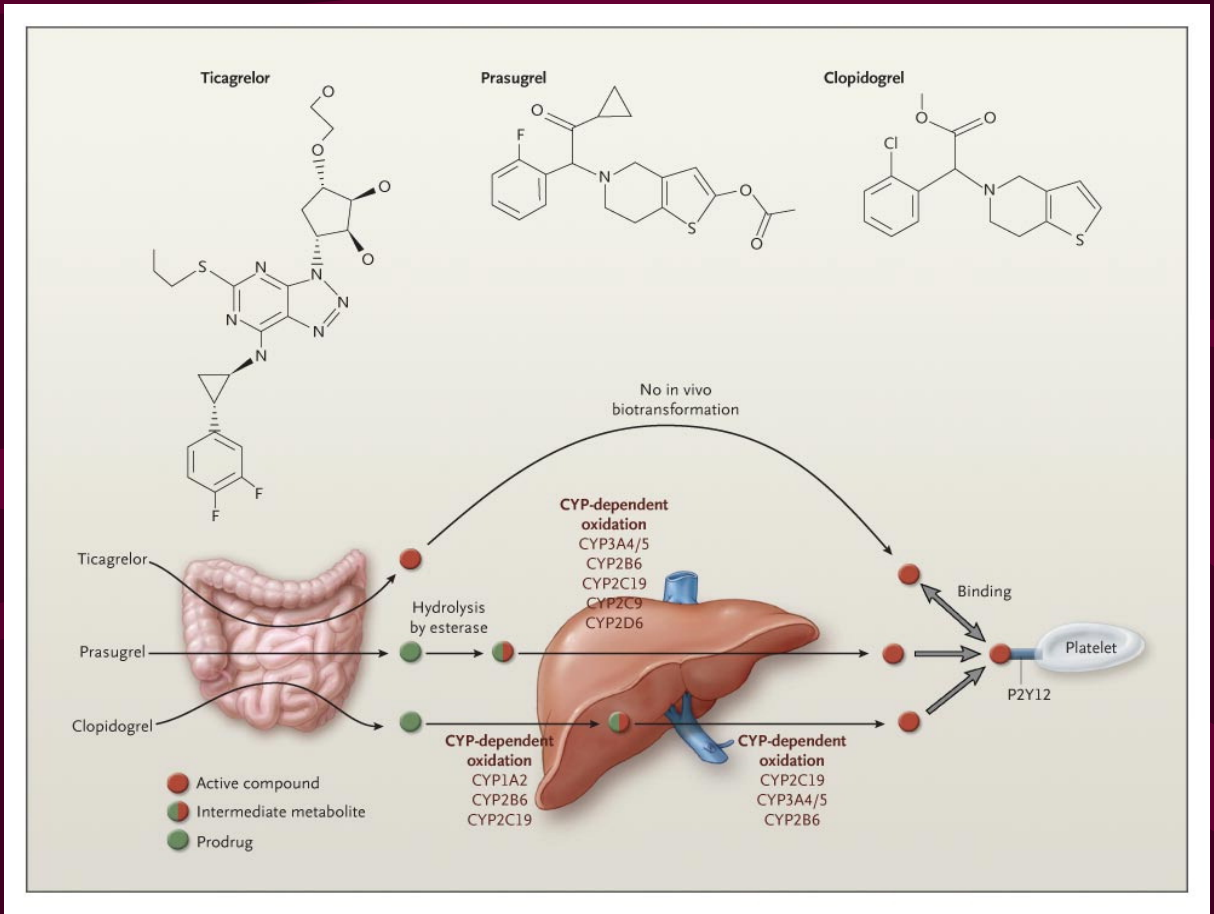
Current Status of GPIIbIIIa antagonists

- Newer oral agents (prasugrel, ticagrelor) with more rapid and reversible action
- Aggressive interventional treatment of ACS
- STEMI: No Class I (ESC, ACC)-Bailout Rx if no reflow, thrombus or thrombotic complication (IIa)-Routine or upstream use in high risk transfer patients (IIb)-Not recommended if PCI is not intended (III)
- NSTEMI: In high risk patients, not adequately Rx with oral agents Class I (ACC), otherwise IIb.

Objectives

- Platelet function and inhibition
- Current intravenous antiplatelet agents
  - Abciximab
  - Eptifibatide
  - Tirofiban
  - Cangrelor
- Key Notes

Biotransformation and Mode of Action of Clopidogrel, Prasugrel, and Ticagrelor: P2Y12 Receptor



Cangrelor: IV P2Y12 Antagonist-No conversion to active metabolite, ½ life 2.9-5.5 min-onset within 2 min-offset 60 min after infusion cessation-dose dependent action

Schömig A. N Engl J Med 2009;361:1108-1111.

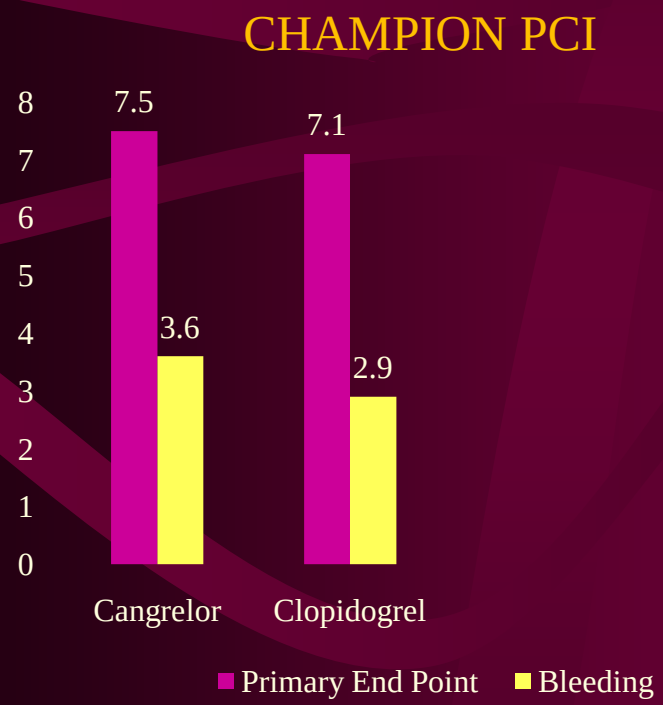
The NEW ENGLAND JOURNAL of MEDICINE

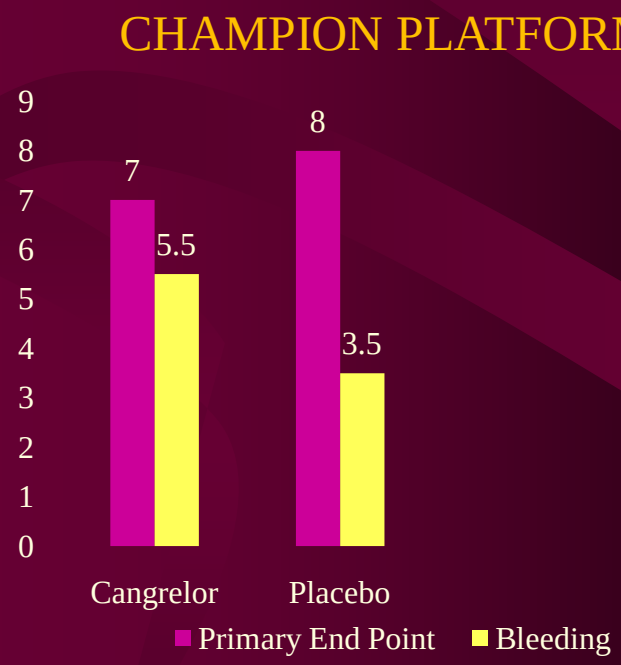
Cangrelor

- Greater inhibition than clopidogrel
- Phase II dose ranging study 4 mcg/kgr produce 100% platelet inhibition within 15 min, similar to abciximab
- Simultaneous administration of cangrelor and clopidogrel prevents clopidogrel from inhibiting P2Y12 receptor – to maintain inhibition after cangrelor, clopidogrel must be administered after cessation of cangrelor

CHAMPION PCI-CHAMPION PLATFORM

- Phase III studies to test Cangrelor vs Clopidogrel during PCI-Early termination (8882 Pts) due to low likelihood to achieve superiority in the primary end point
- No difference in the combined endpoint, but mainly driven by a raise in CPK MB-Troponin
- Pooled data from both suggest some benefit of cangrelor over clopidogrel





CHAMPION-PHOENIX (IV Cangrelor vs Oral Clopidogrel for the Management of Periprocedural PCI Complications)

R Harrington (Stanford University, CA)
American College of Cardiology 2013 Scientific Sessions

- A randomized, parallel-assignment, double-blind trial comparing IV **cangrelor** to oral **clopidogrel** standard of care therapy in subjects who require PCI
- Population and treatment:

  11 145 patients undergoing urgent or elective PCI were randomized to receive cangrelor in a bolus plus infusion or a 600-mg or 300-mg loading dose of clopidogrel. Patients had been slated for PCI for stable CAD, STEMI, or NSTEMI. Cangrelor was given as 30 µg/kg followed by an infusion of 4 µg/kg/min for at least two hours.
- Primary outcome measures:

  A composite incidence of all-cause mortality, MI, ischemia-driven revascularization, and stent thrombosis [48 hours]

  Secondary outcome measures: Incidence of stent thrombosis [48 hours]

CHAMPION-PHOENIX: Results (efficacy)

- Cangrelor's benefit of a 22% drop in a composite efficacy end point was driven by reductions in MI and stent thrombosis and was not associated with an increase in bleeding complications as they were prospectively defined.

Efficacy outcomes at 48 hours after randomization, cangrelor vs clopidogrel

End points	HR (95% CI)	p
Primary efficacy end point*	0.78 (0.66-0.93)	0.005
Stent thrombosis	0.62 (0.43-0.90)	0.01
MI	0.80 (0.67-0.97)	0.02

*All-cause mortality, MI, ischemia-driven revascularization, stent thrombosis

CHAMPION-PHOENIX: Bleeding

- Whether cangrelor has an effect on bleeding risk depends on how bleeding is defined.
- Defined according to the **GUSTO** criteria used for the primary safety end point, bleeding didn't differ significantly between the two treatment arms.
- But with the **ACUITY** criteria, which are more sensitive measures of bleeding, there was more bleeding with cangrelor than with clopidogrel.

Bleeding complications by different bleeding criteria, cangrelor vs clopidogrel

Bleeding complication	HR (95% CI)	p
GUSTO criteria*		
Severe non-CABG bleeding	1.50 (0.53-4.22)	0.44
Severe or moderate bleeding	1.63 (0.92-2.90)	0.09
TIMI criteria		
Major bleeding	1.00 (0.29-3.45)	> 0.999
Minor bleeding	3.00 (0.81-11.10)	0.08
ACUITY criteria		
Major bleeding	1.72 (1.39-2.13)	< 0.001
Minor bleeding	1.42 (1.26-1.61)	< 0.001

*Primary safety end point

CHAMPION PHOENIX

- Intravenous cangrelor reduces risk of ischemic events due to potent platelet inhibition, rapid onset and offset and there is no need for pretreatment with other antiplatelet agents
- Tested only against clopidogrel
- Transition strategies to clopidogrel (after), prasugrel (after) and ticagrelor (pre) makes Rx more complicated
- Once coronary anatomy is known both PCI and CABG can be performed without delay

Objectives

- Platelet function and inhibition
- Current intravenous antiplatelet agents
  - Abciximab
  - Eptifibatide
  - Tirofiban
  - Cangrelor
- Key Notes

Is there still a role for IV antiplatelet agents in ACS

- YES!
- Advantages of IV route
- GPIIbIIIa Inhibitors still needed during PCI (provisionally) in patients with high thrombotic risk, low bleeding risk and those without effective DAPT (2 hr onset of ticagrelor, prasugrel)
- Cangrelor is the only P2Y12 IV antagonist with favorable results currently approved in patients undergoing PCI who have not been pretreated with an oral P2Y12 receptor inhibitor and not receiving a GPIIbIIIa inhibitor