Update on Antithrombotics
Adjunctive Antithrombotics Therapy in STEMI patients

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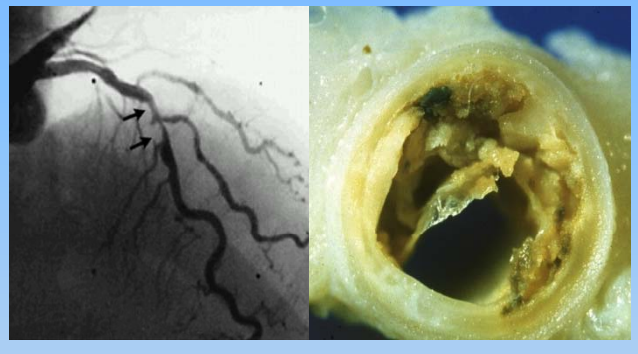
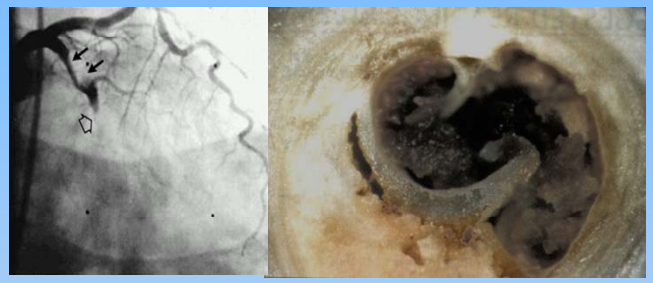
Goal of Adjunctive Antithrombotics in Acute Phase of AMI

1. *To stabilize the ruptured plaque*





2. *To facilitate safe definitive revascularization (PCI or CABG)*

Current Anti-thrombotics in Acute Phase of AMI

Anti Thrombotic Activity

Bleeding

Safety

Thrombosis

Days

Sum of ATA

Anti-thrombin:UFH,enox

Dual oral anti-platelet

provisional

upstreamGPI

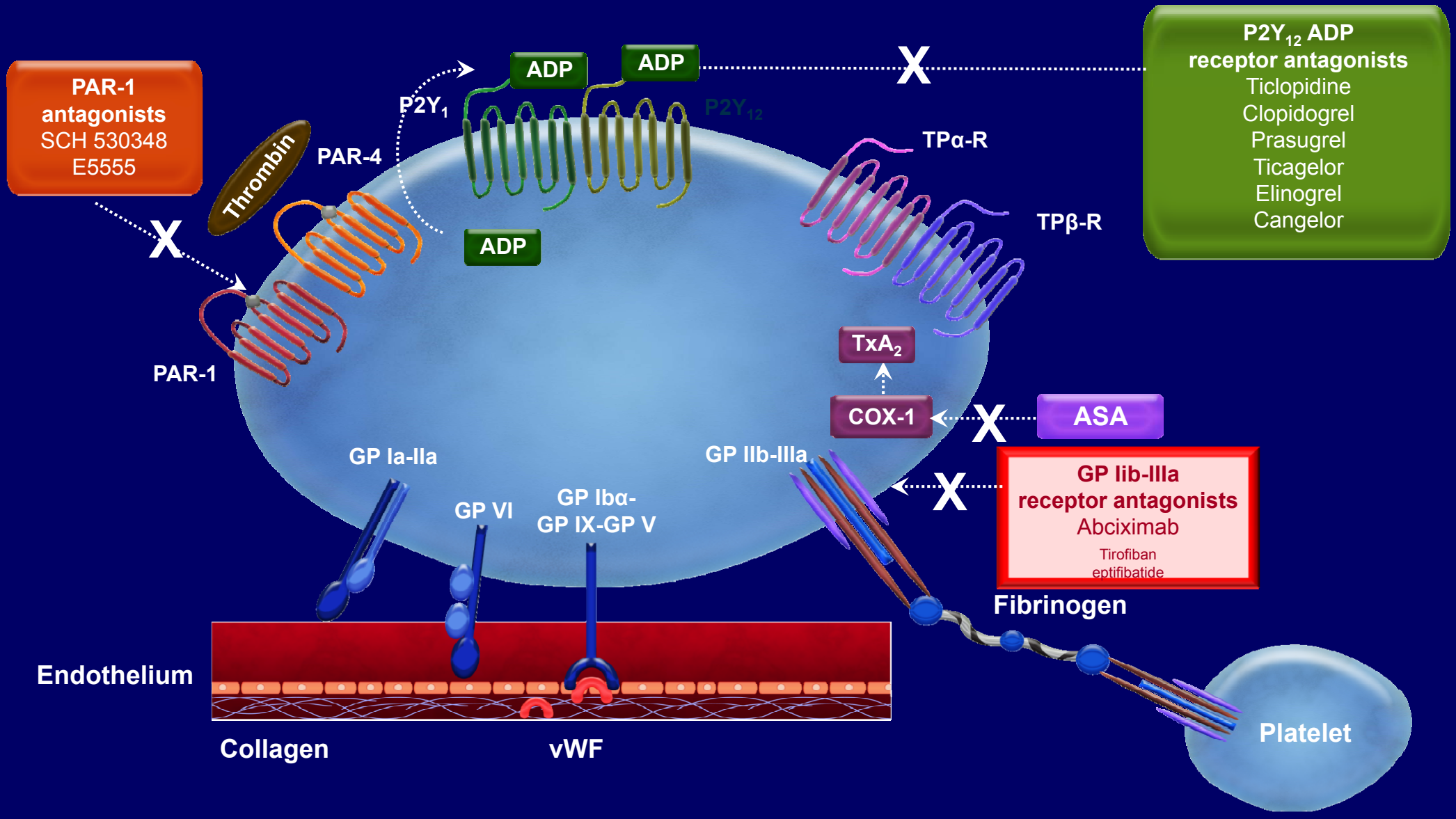
Ideal Antithrombotics

- ✓ Rapid onset, possible to abolish
- ✓ Dose dependent, predictable
- ✓ No interaction with other drug
- ✓ No side effect

Bleeding Risk — **Ischemic Risk**

Clinical Trials → **Best AT**

Platelet Agonists and Antiplatelet Agents



Issues of GPI in STEMI

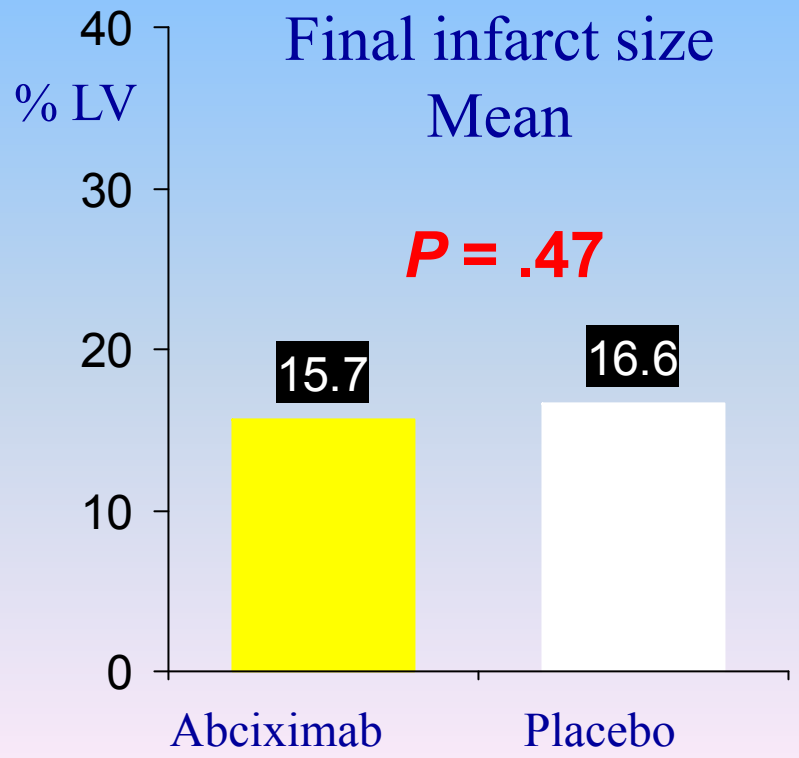
- ✓ Effectiveness on contemporary dual anti-platelet therapy
  - ✓**BRAVE-3, ON-TIME 2, HORIZONS-AMI**
- ✓Which is better? Abciximab, tirofiban, eptifibatide
  - ✓ **MULTISTRATEGY, HORIZONS-AMI**
- ✓Administration timing
  - ✓ **FINESSE**

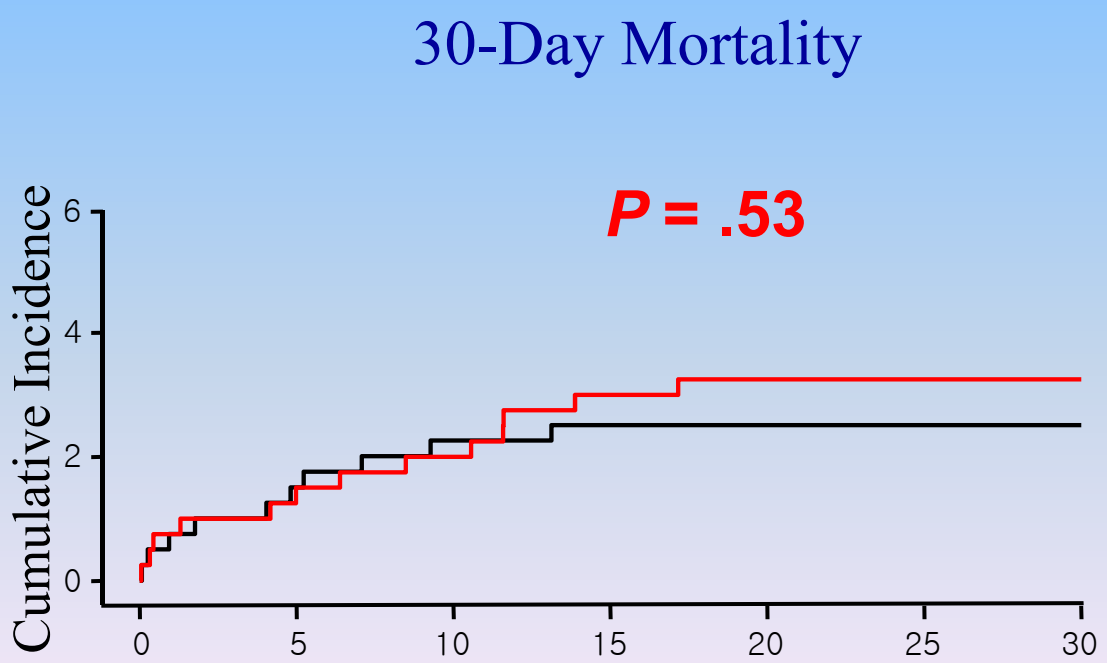
BRAVE-3 Trial: STEMI

Bavarian Reperfusion AlternatiVes Evaluation-3 Trial

Clopidogrel 600 mg oral
Aspirin 500 mg i.v. or oral
Unfractionated Heparin 5000 IE

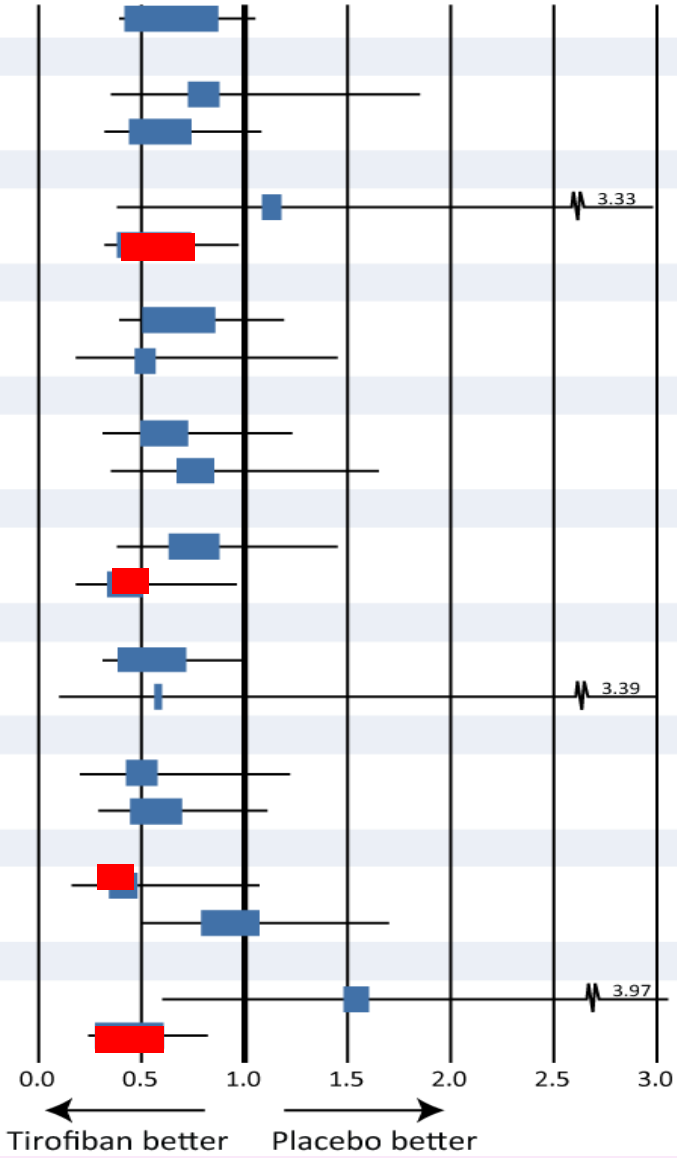
→ Abciximab (n=401) Vs.
Placebo (n=399)





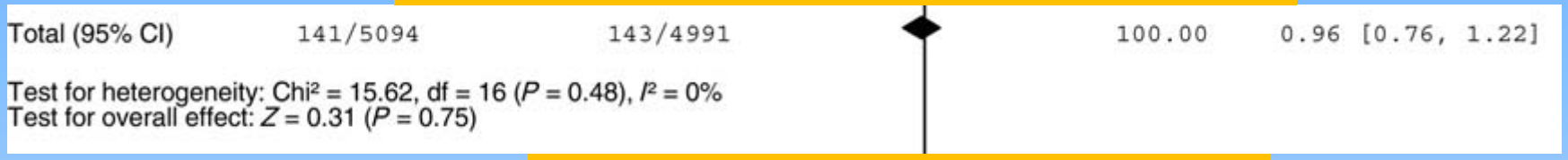
ON-TIME 2 Trial: STEMI

	Tirofiban	Placebo	Death within One Year Risk Ratio, 95% Confidence Interval	p-value
	no./total no.			
All patients	25/670	38/656	0.64 (0.39 - 1.05)	0.078
Sex				
Female	9/154	12/164	0.80 (0.35 - 1.84)	0.597
Male	16/516	26/492	0.59 (0.32 - 1.08)	0.083
Age(years)				
<= 61.6	7/337	6/327	1.13 (0.38 - 3.33)	0.822
> 61.6	18/333	32/329	0.56 (0.32 - 0.97)	0.035
Diabetes				
No	20/595	29/585	0.68 (0.39 - 1.18)	0.169
Yes	5/75	9/69	0.51 (0.18 - 1.45)	0.197
Location				
Anterior MI	12/253	20/259	0.61 (0.31 - 1.23)	0.164
Non anterior MI	11/343	14/331	0.76 (0.35 - 1.65)	0.483
Killip > 1				
No	15/587	19/554	0.75 (0.38 - 1.45)	0.385
Yes	6/69	18/87	0.42 (0.18 - 0.96)	0.039
Timi flow grade before PCI				
0-2	16/473	30/491	0.55 (0.31 - 0.99)	0.047
3	2/134	3/116	0.58 (0.10 - 3.39)	0.665
Time start study drug to balloon inflation/angiography				
<= 55	7/331	14/331	0.50 (0.20 - 1.22)	0.121
> 55	13/326	22/314	0.57 (0.29 - 1.11)	0.093
Time symptom onset to diagnosis				
<= 75	6/340	13/303	0.41 (0.16 - 1.07)	0.059
> 75	18/315	21/340	0.93 (0.50 - 1.70)	0.803
Primary PCI				
No	11/93	6/78	1.54 (0.60 - 3.97)	0.368
Yes	14/577	32/578	0.44 (0.24 - 0.81)	0.007

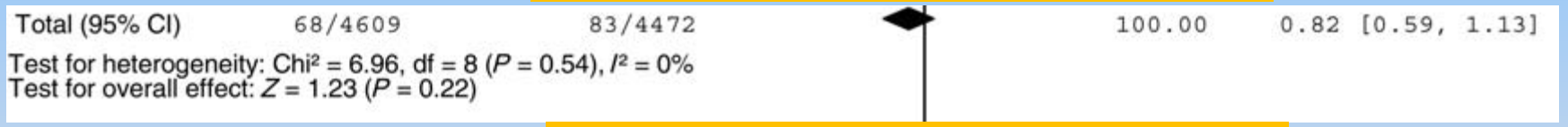


GPI among STEMI with Primary PCI
Meta analysis

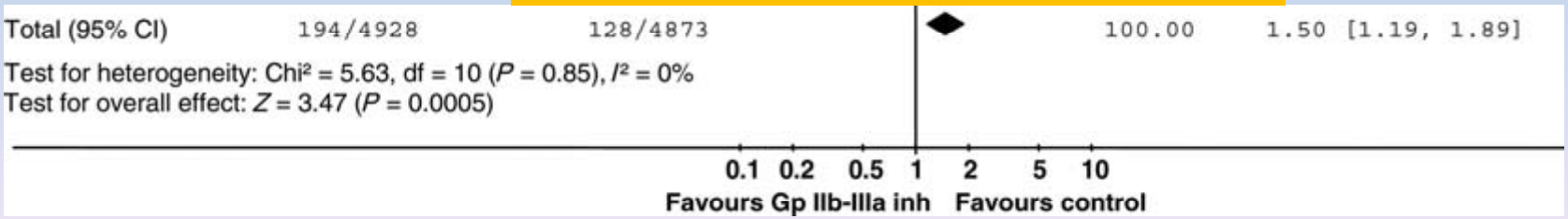
30 day mortality



Reinfarction



Major bleeding



De Luca G, European Heart Journal (2009) 30, 2705–2713

Issues of GPI in STEMI

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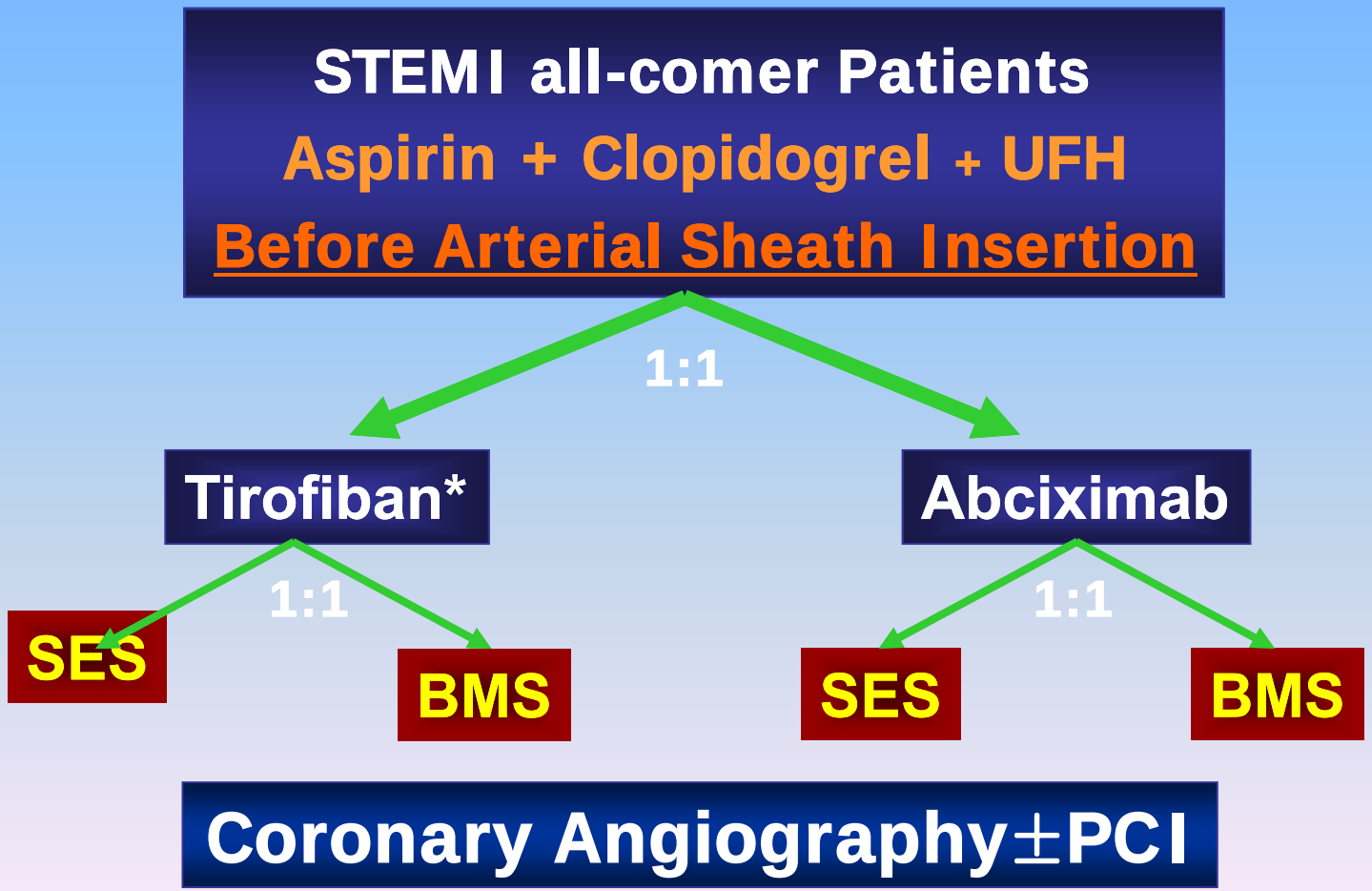
  - **NO effect or uncertain**
- ✓Which is better? Abciximab, tirofiban, eptifibatide
  - ✓ MULTISTRATEGY, HORIZONS-AMI
- ✓Administration timing
  - ✓ FINESSE

MULTISTATEGY Trial: STEMI

Multicentre Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study



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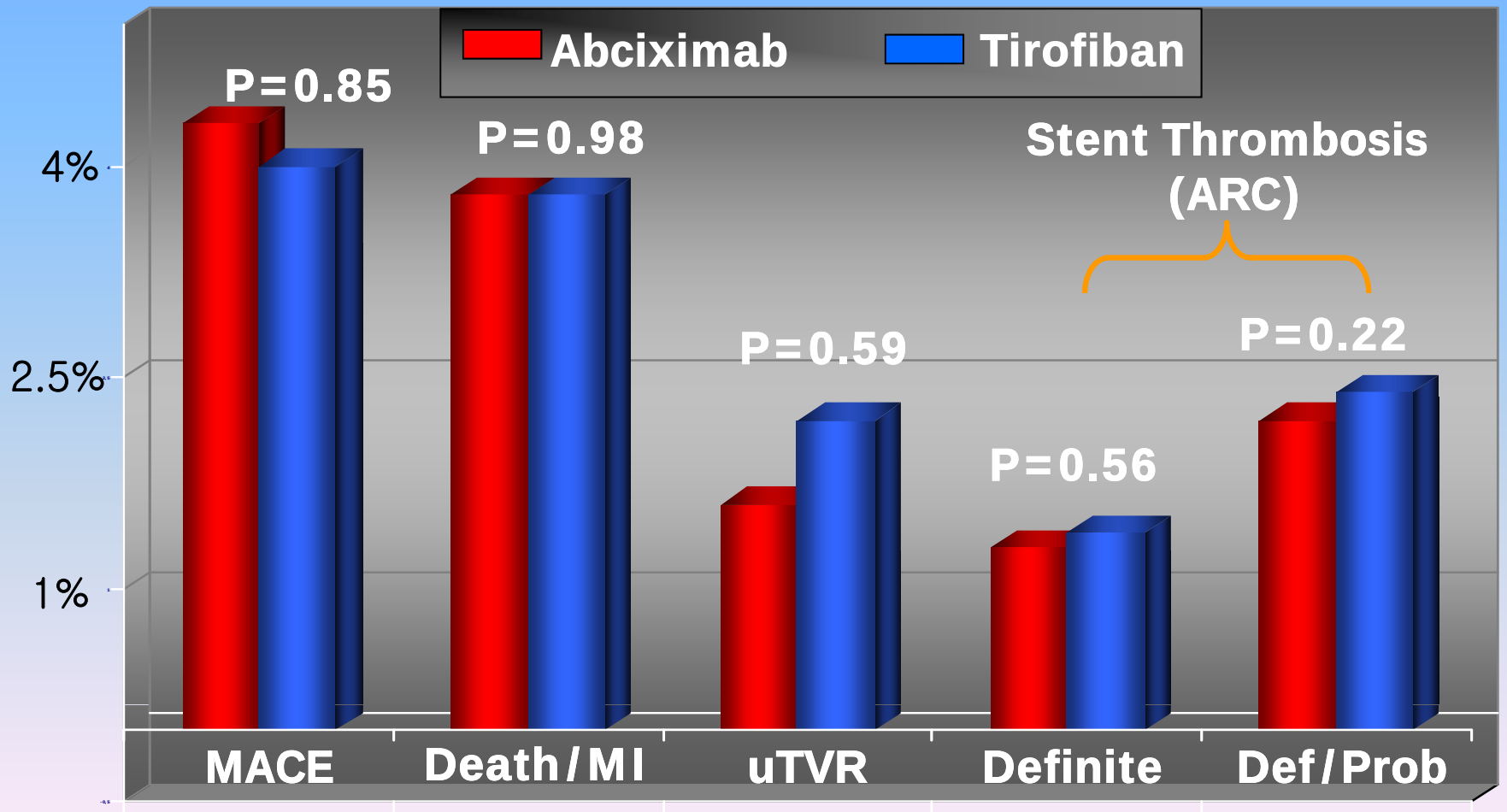

30 day Efficacy

MULTISTATEGY Trial: STEMI

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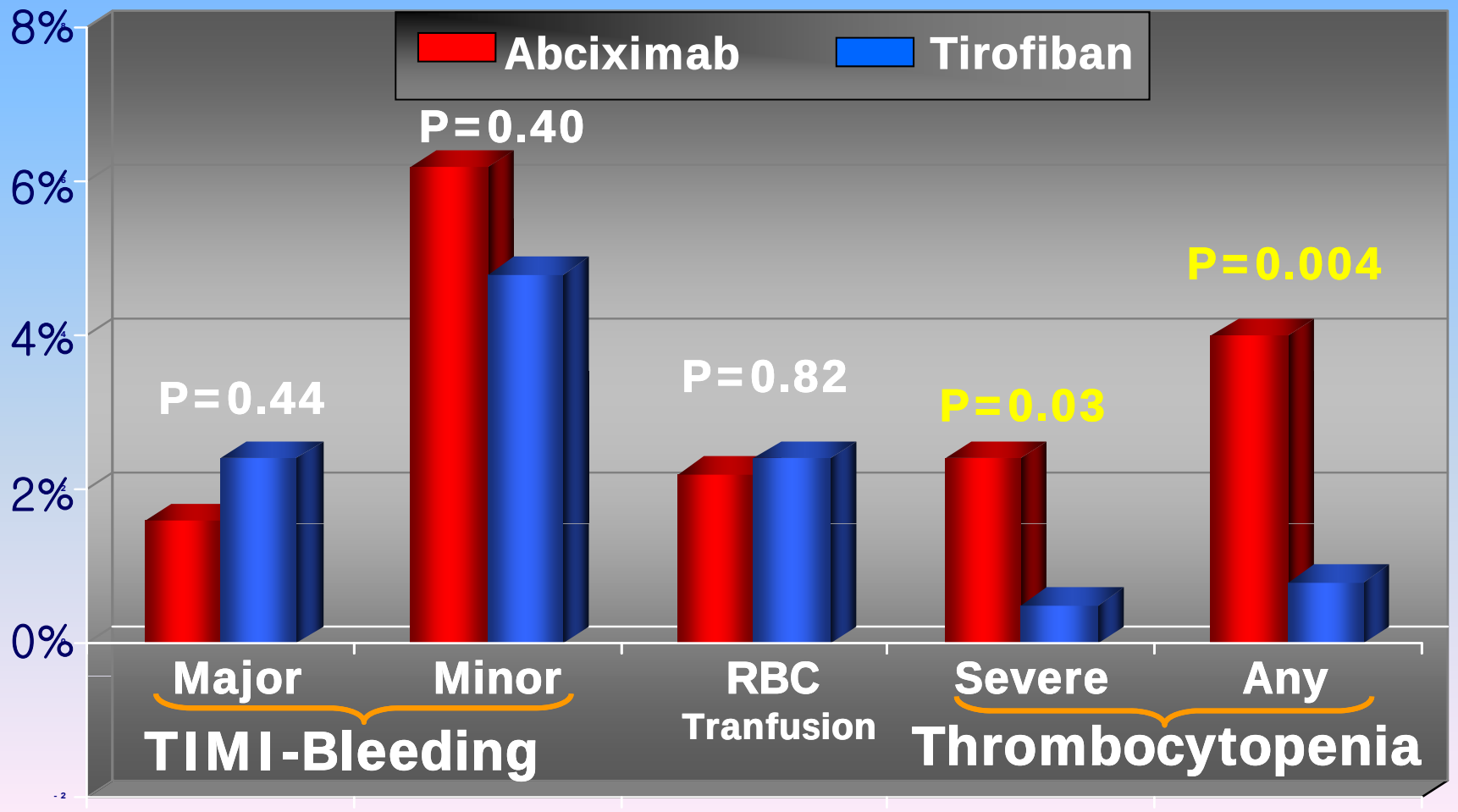

30 day safety

Issues of GPI in STEMI

- ✓ Effectiveness on contemporary dual anti-platelet therapy
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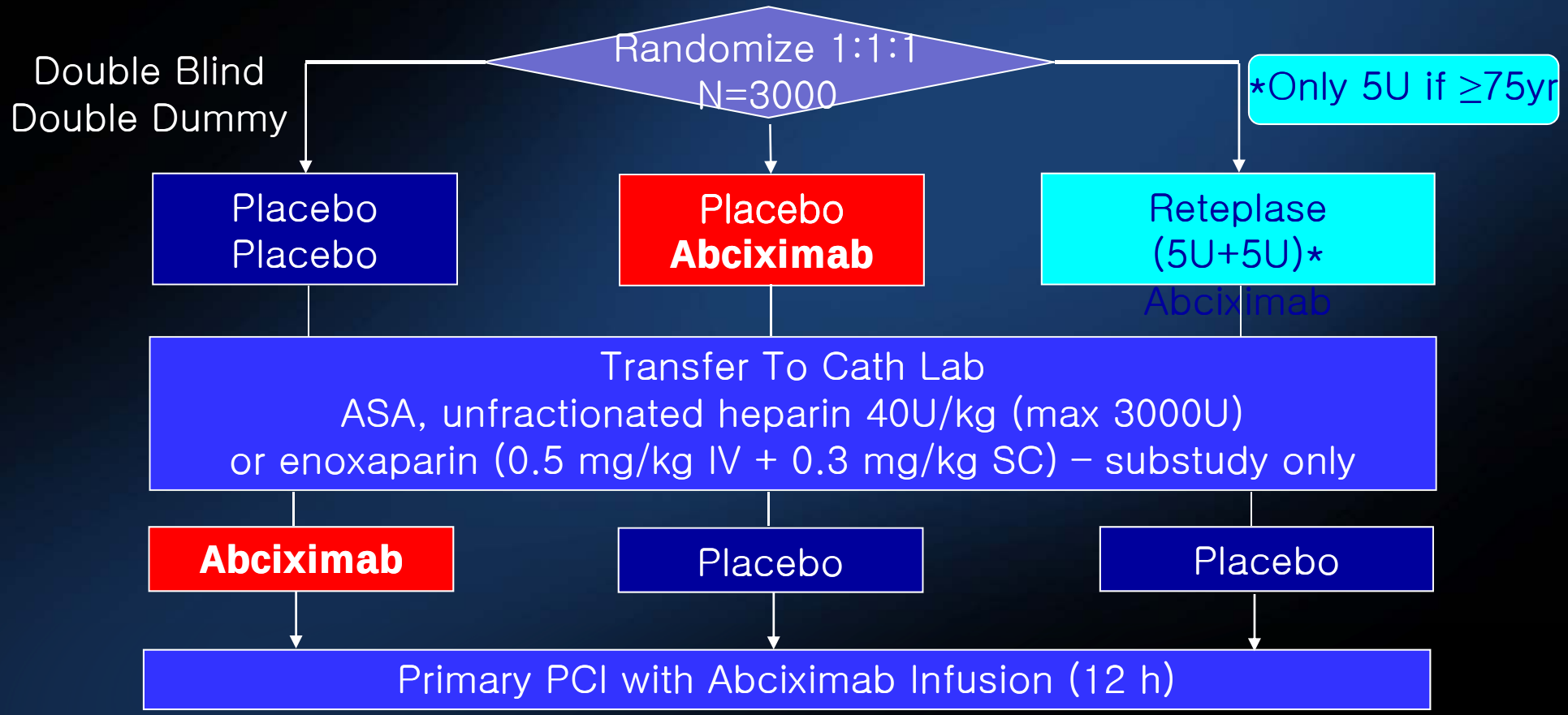
  - **NO difference, abciximab: thrmobocytopenia**
- ✓Administration timing
  - ✓ **FINESSE**

FINESSE Trial: STEMI

Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events



FINESSE Results:

Endpoint	Primary PCI (%)	Abciximab-facilitated (%)	Combination (abciximab/ reteplase)-facilitated (%)	Combination-facilitated vs primary PCI (P)	Combination-facilitated vs abciximab-facilitated (P)
Primary end point *	10.7	10.5	9.8	NS	NS
All-cause mortality	4.5	5.5	5.2	NS	NS
TIMI major bleeding	2.6	4.1	4.8	0.025	NS
TIMI minor bleeding	4.3	6.0	9.7	<0.001	0.006

* All cause mortality; rehospitalization or ED treatment for CHF; resuscitated ventricular fibrillation occurring > 48 hours after randomization; cardiogenic shock ED=emergency department

Ellis S. European Society of Cardiology Congress 2007; September 3, 2007; Vienna, Austria

Issues of GPI in STEMI

- ✓ Effectiveness on contemporary dual anti-platelet therapy
  - **NO effect or uncertain**
- ✓Which is better? Abciximab, tirofiban, eptifibatide
  - **NO difference, abciximab: thrmobocytopenia**
- ✓Administration timing
  - **At the time of PCI, less bleeding**

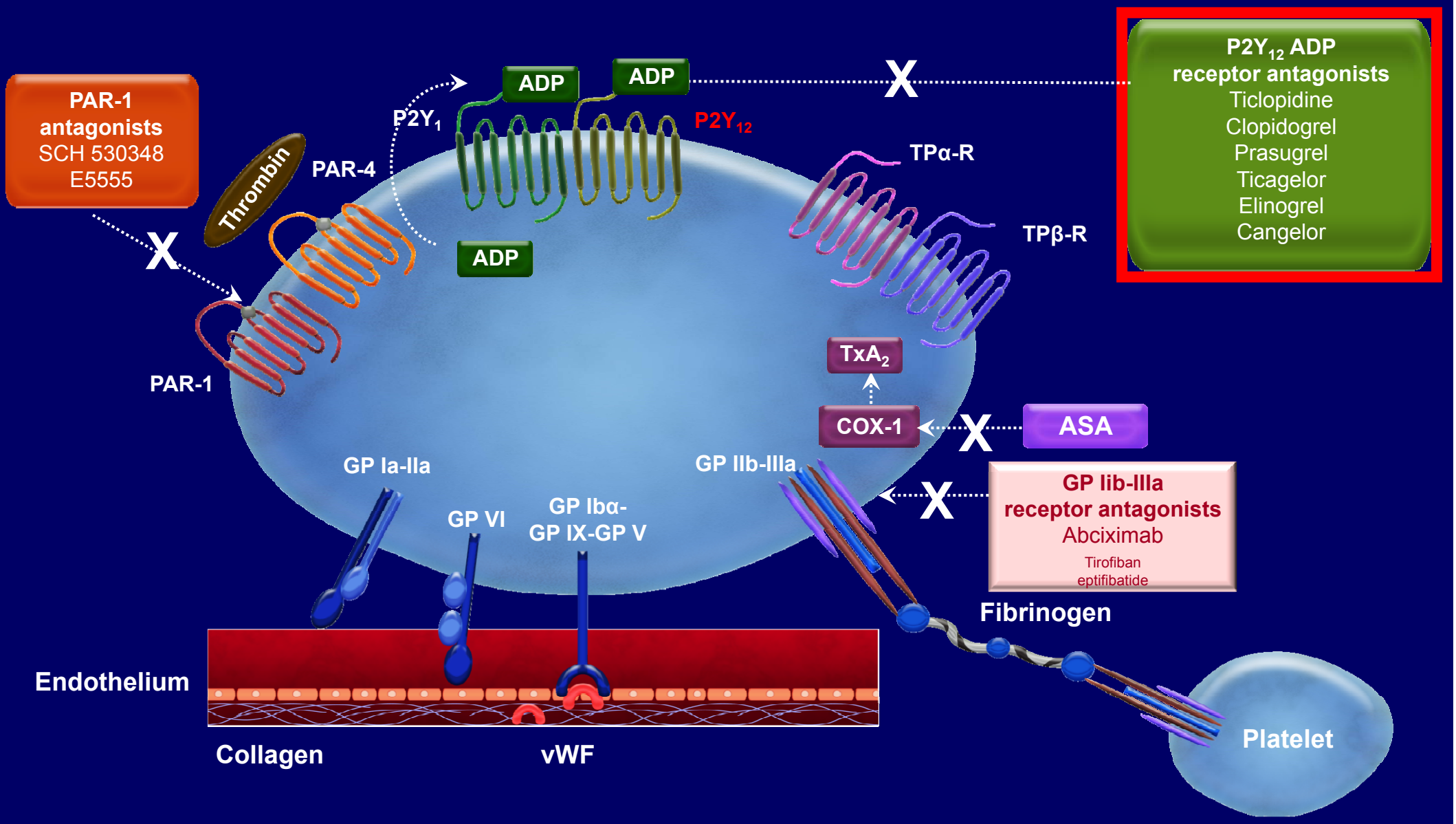
Recommendations for the Use of Glycoprotein IIb/IIIa Receptor Antagonists

2009 Joint STEMI/PCI focused update recommendation

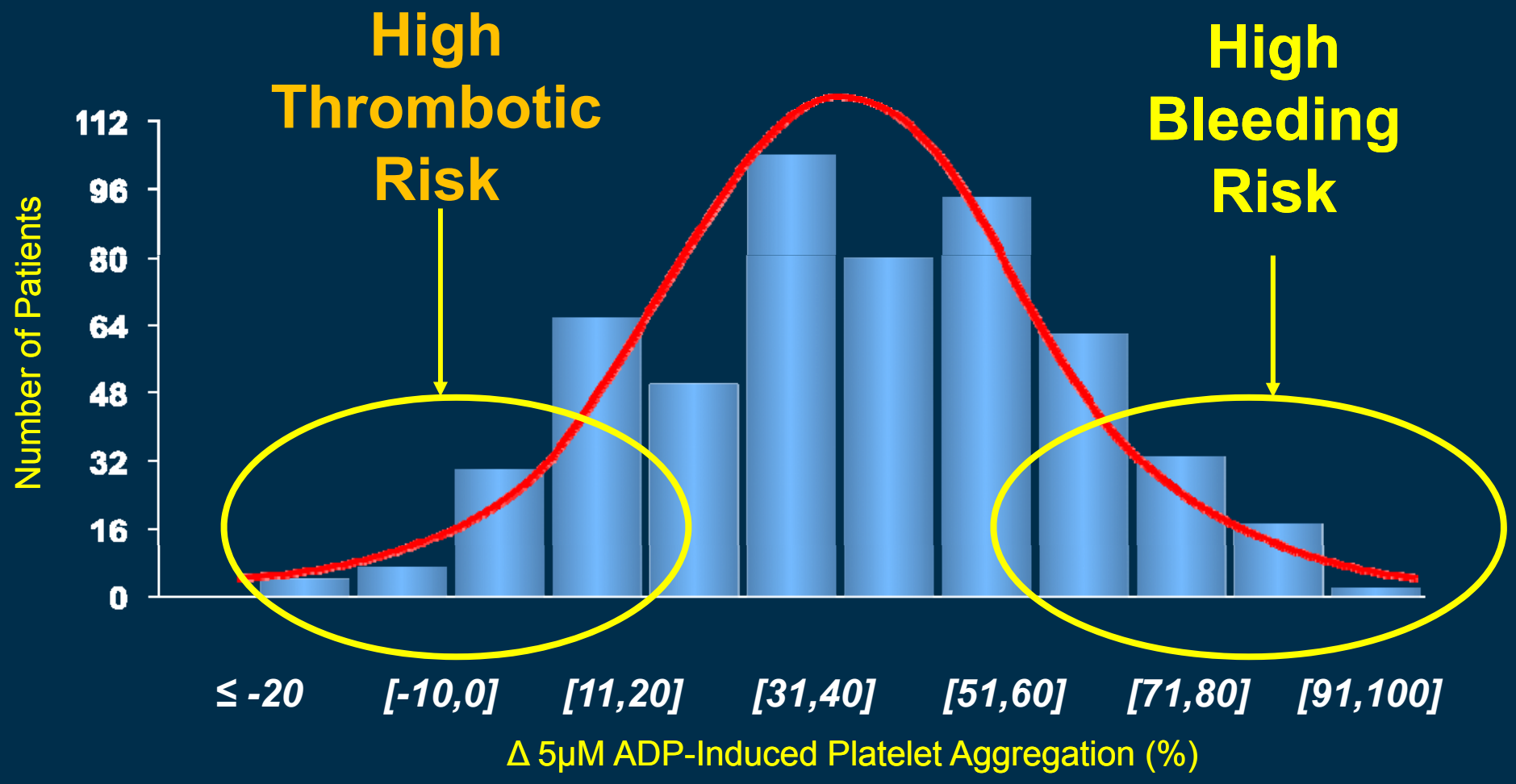
- **Class IIa: It is reasonable to start treatment with GPI at the time of primary PCI in selected patients with STEMI.**

- **Class IIb: The usefulness of GPI (as part of a preparatory pharmacological strategy) is uncertain (Class IIb, B)**

Platelet Agonists and Antiplatelet Agents

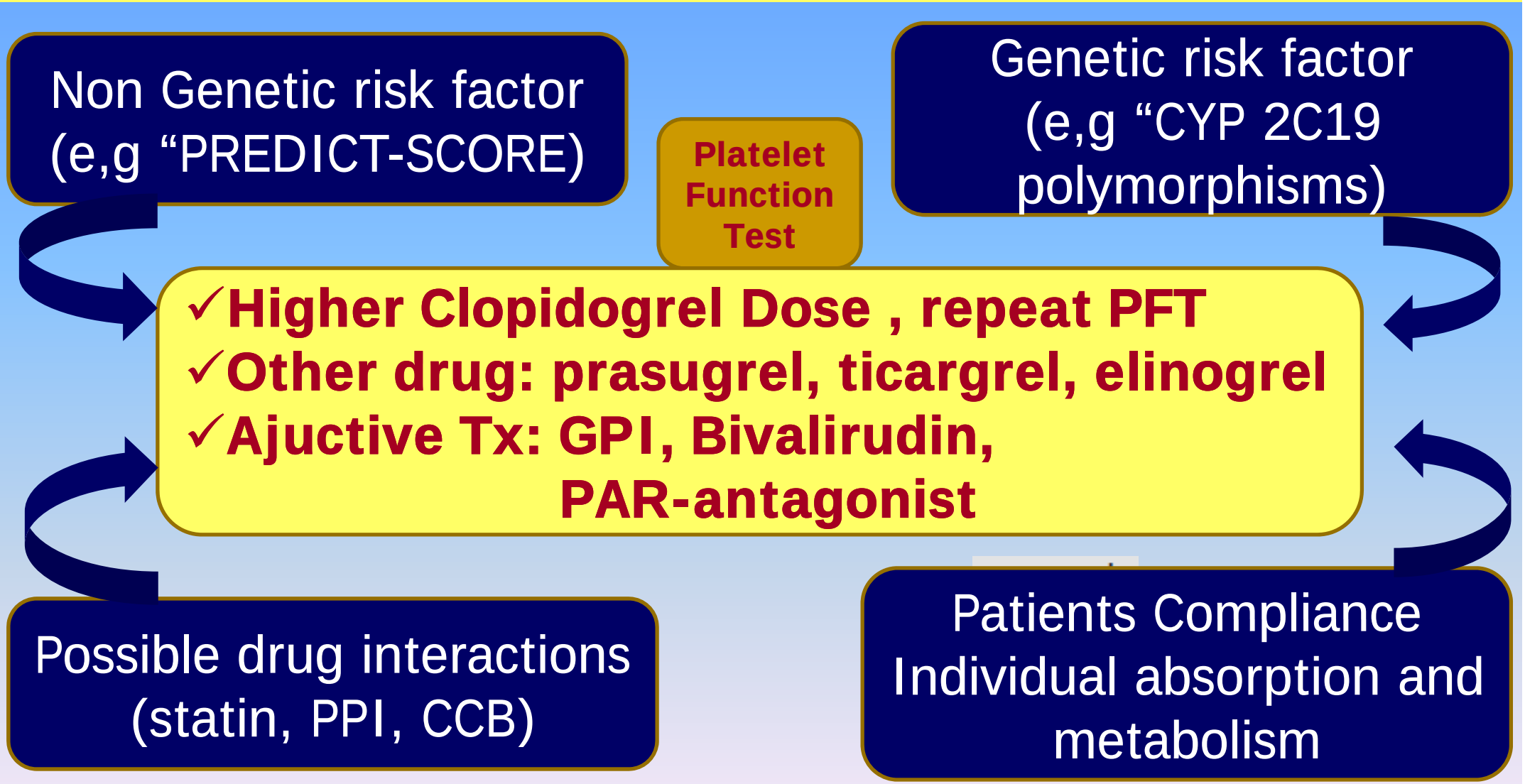


IPA Responses to Clopidogrel



Adapted from: Serebruany V et al. J Am Coll Cardiol. 2005.

Contributing factors for Clopidogrel Resistance

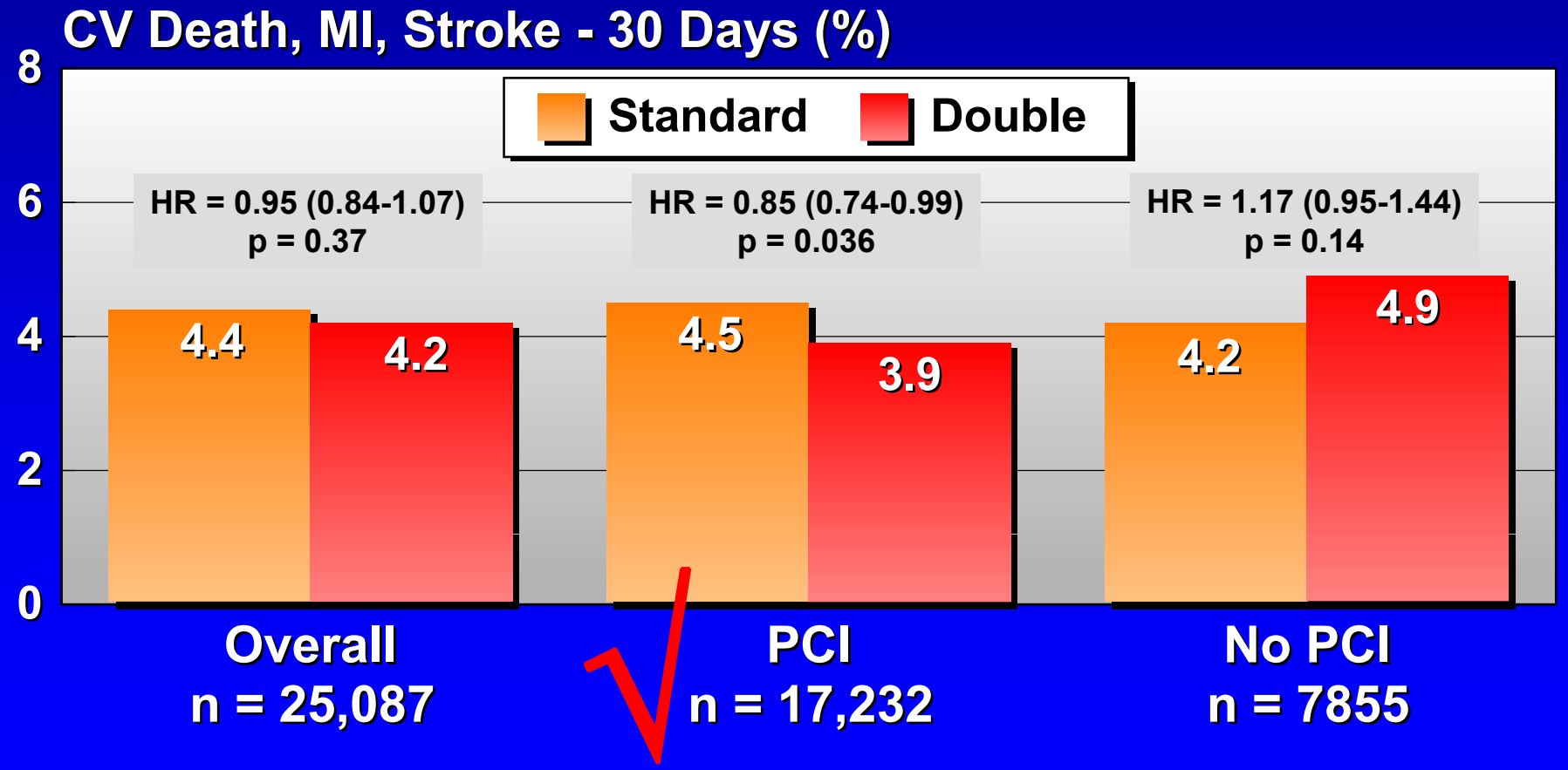


Zurn CS, Thromb Haemost 2010; 103: 496–506

Higher Dose: CURRENT – OASIS 7 Trial

Double-Dose vs Standard-Dose Clopidogrel in ACS

Clopidogrel: 600 mg load, 150 mg/d x 7d, then 75 mg/d – vs – 300 mg load, 75 mg/d



Mehta A. ESC 2009 Presentation

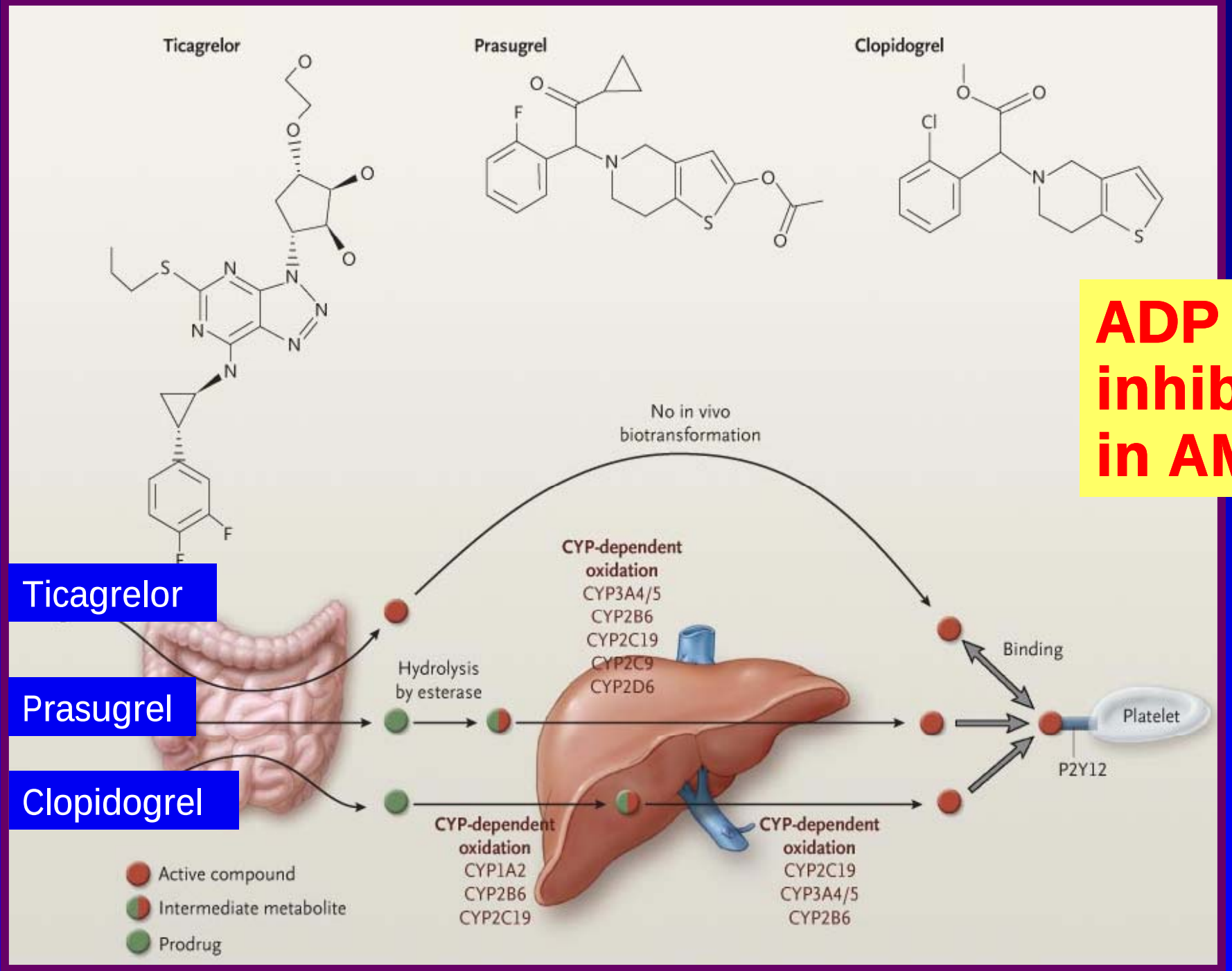
Higher Dose: CURRENT – OASIS 7 Trial

Clopidogrel Dose Comparison

% of patients	Clopidogrel Dose 300 / 75 N = 12,579	Clopidogrel Dose 600 / 150 / 75 N = 12,508	HR (95% CI)	P
Stent Thrombosis	2.3	1.6	0.71 (0.57-0.89)	0.002
Definite (angiographic)	1.2	0.7	0.58 (0.42-0.79)	0.001
TIMI Major Bleed	0.95	1.04	1.09 (0.85-1.40)	0.50
CURRENT Major Bleed	2.0	2.5	1.25 (1.05-1.47)	0.01
CURRENT Severe Bleed	1.5	1.9	1.23 (1.02-1.49)	0.03
Fatal Bleed	0.11	0.13	1.15 (0.56-2.35)	0.71
ICH	0.05	0.03	0.67 (0.19-2.37)	0.53
RBC Tx >= 2 U	1.76	2.21	1.26 (1.06-1.51)	0.01

Mehta A. ESC 2009 Presentation

ADP inhibitors in AMI

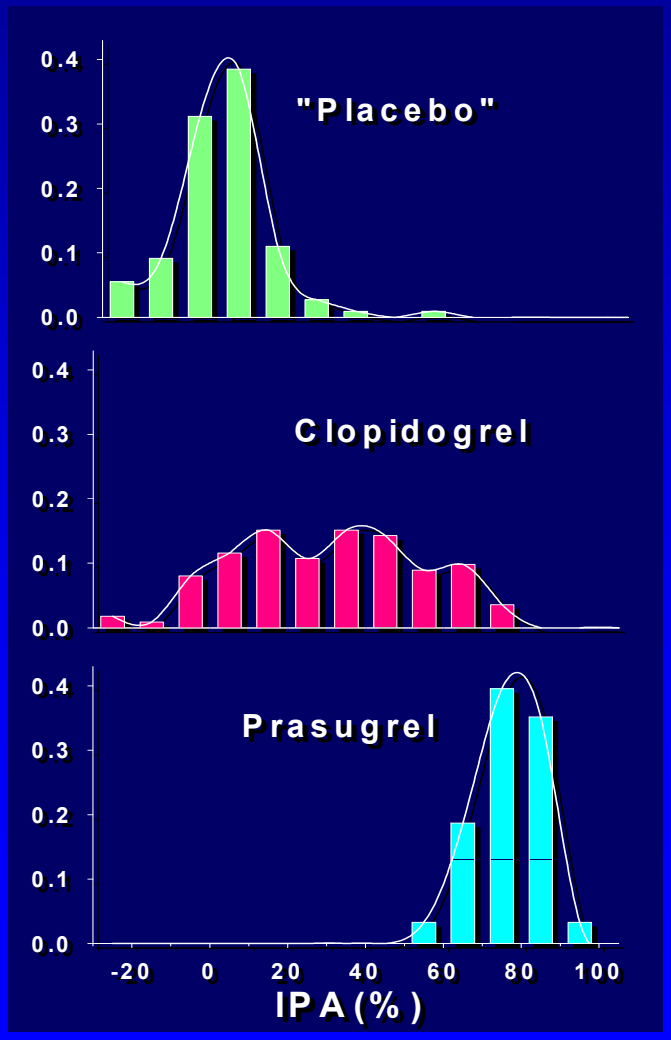


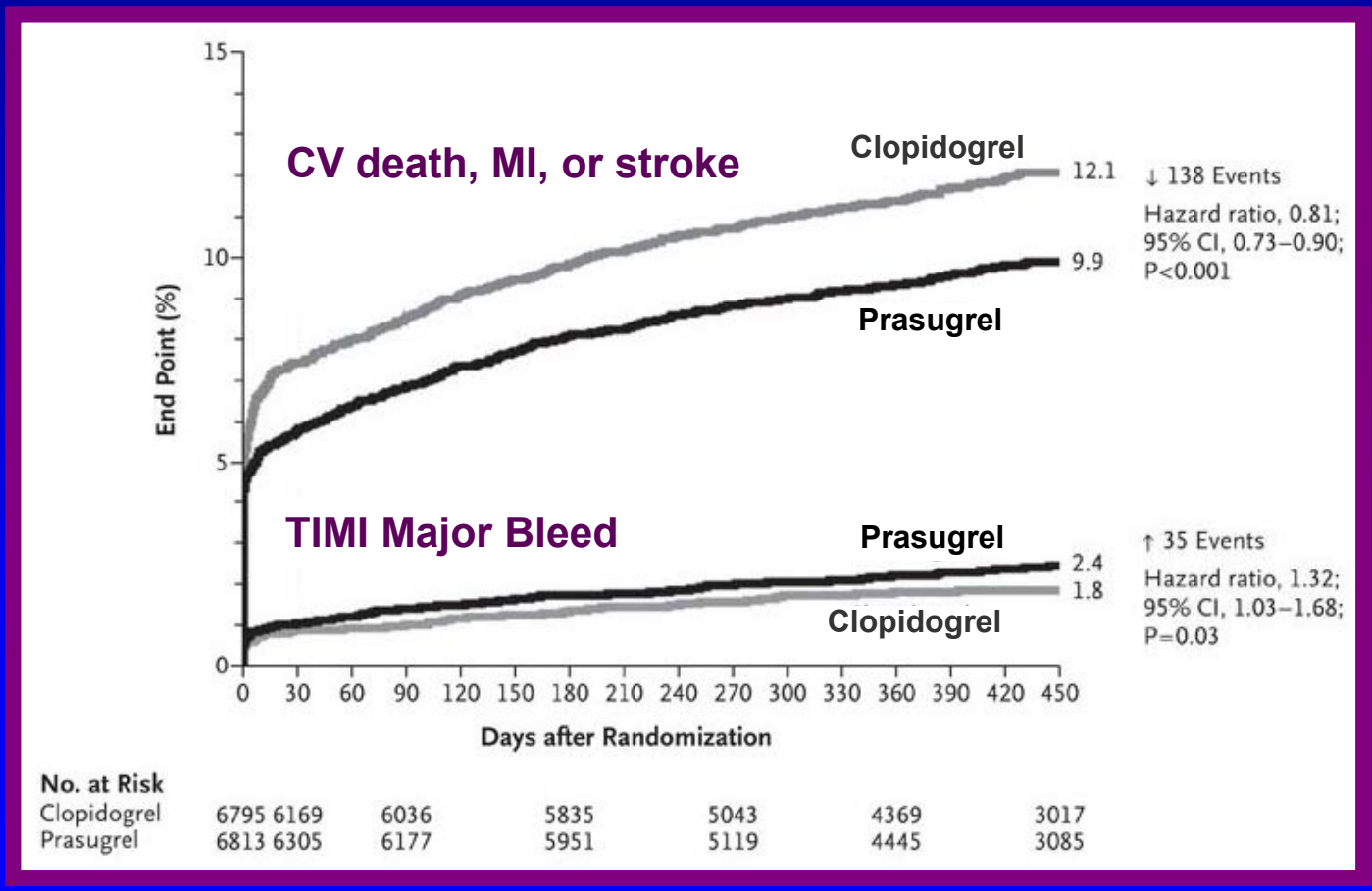
NEJM 2009, 361:1108

Prasugrel

TRITON – TIMI 38 Trial: Prasugrel vs Clopidogrel(300mg)

13,608 Patients - ACS and PCI

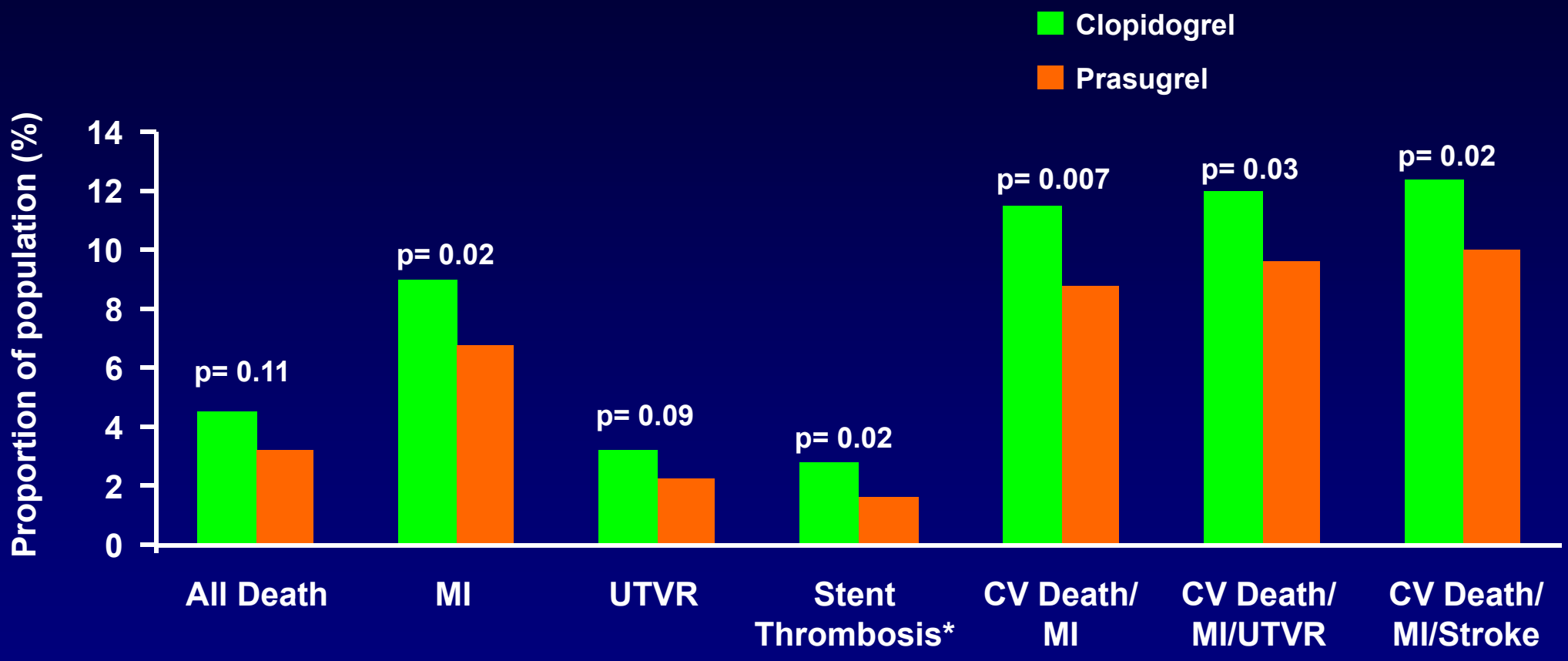




Wiviott S et al. NEJM 2007;357:2001.

TRITON TIMI-38 STEMI cohort

Efficacy endpoints at 15 months

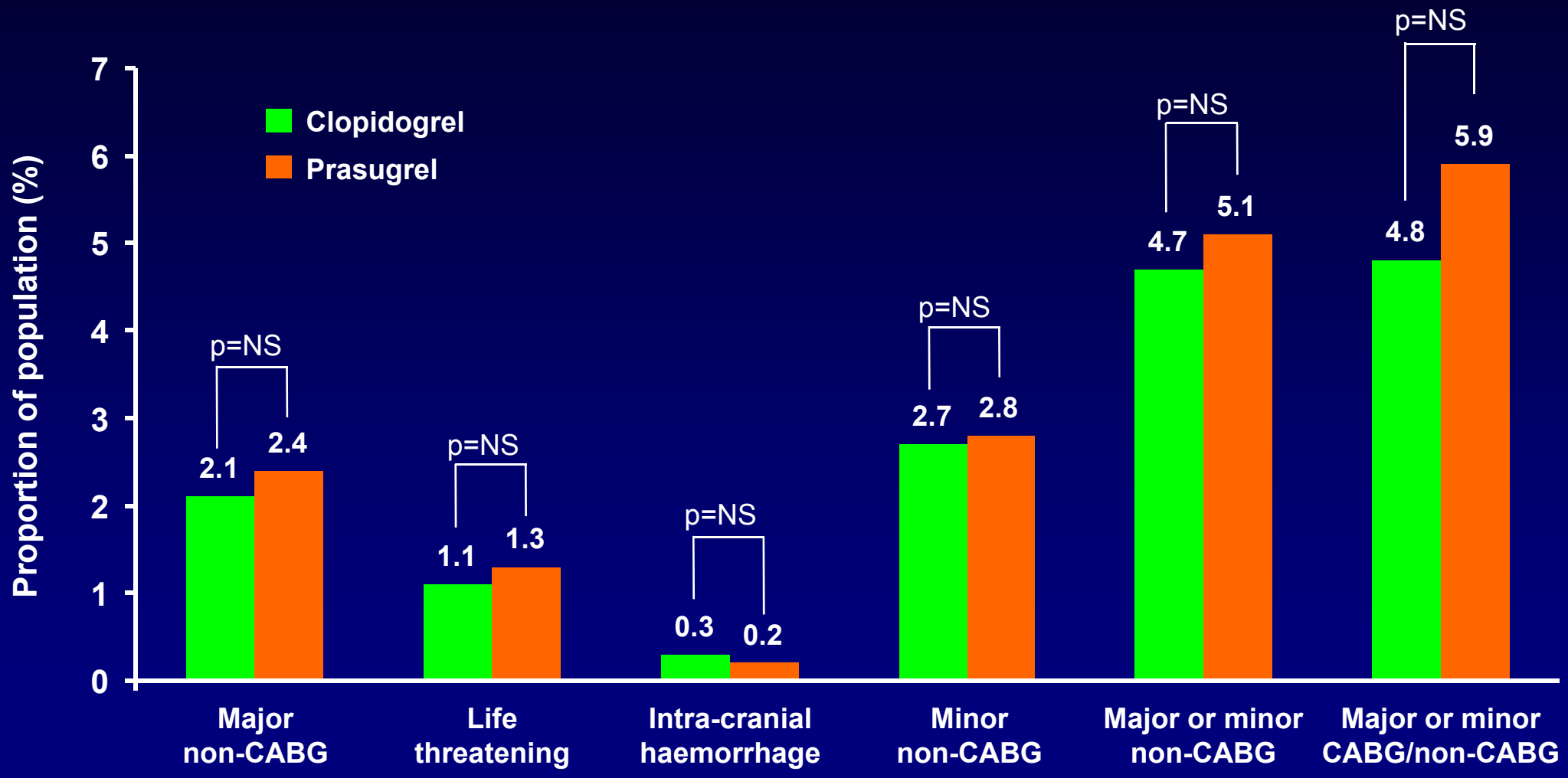


* ARC def/probable

Montalescot et al. ESC 2008

TRITON TIMI-38 STEMI cohort

Bleeding events over 15 months

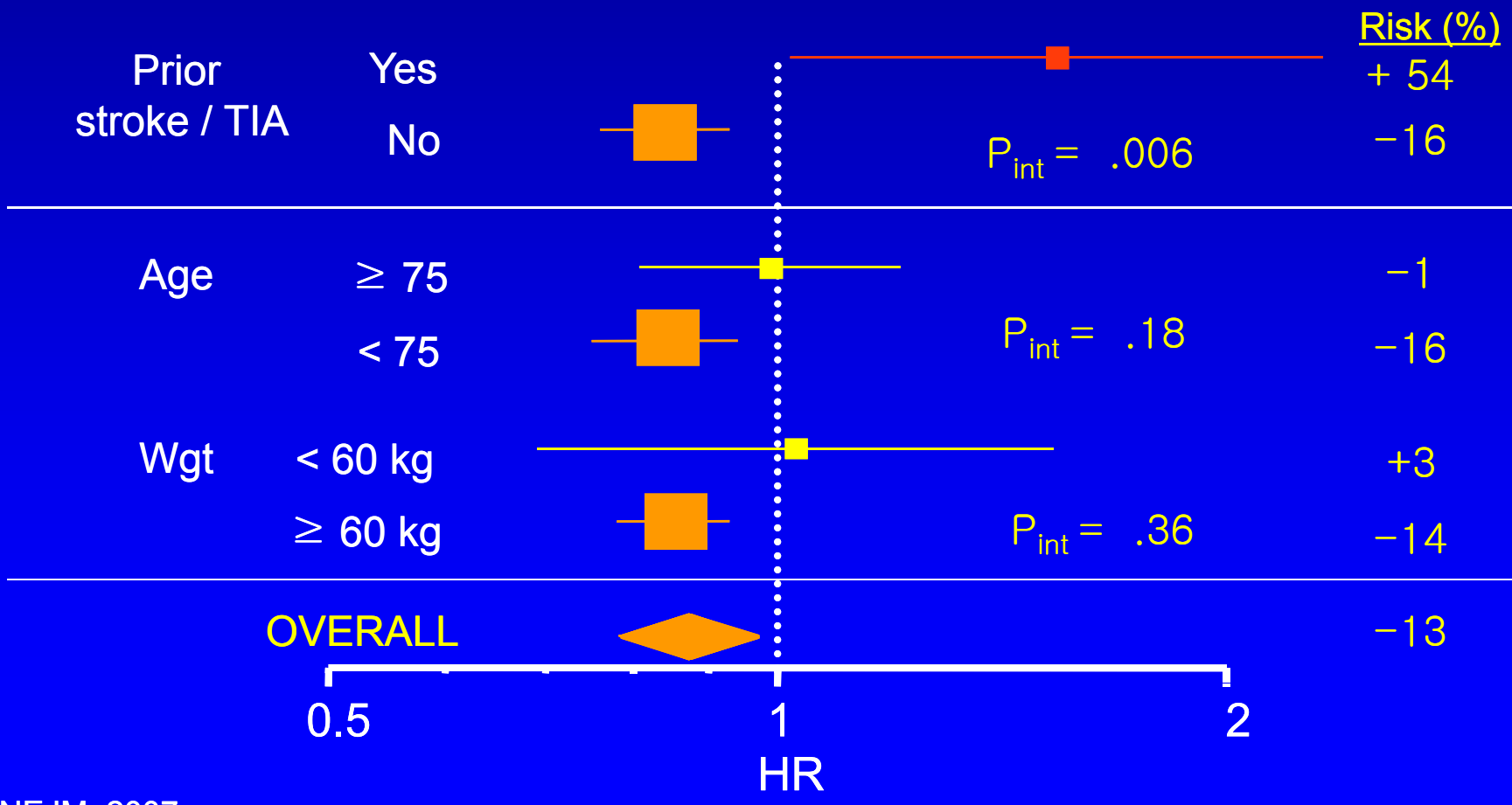


Montalescot et al. ESC 2008

TRITON – TIMI 38 Trial: Prasugrel vs Clopidogrel
13,608 Patients - ACS and PCI

Net Clinical Benefit: Bleeding Risk Subgroups

Post-hoc Analysis



Wiviott SD, NEJM, 2007

Thienopyrine: Class I

2009 Joint STEMI/PCI focused update recommendation

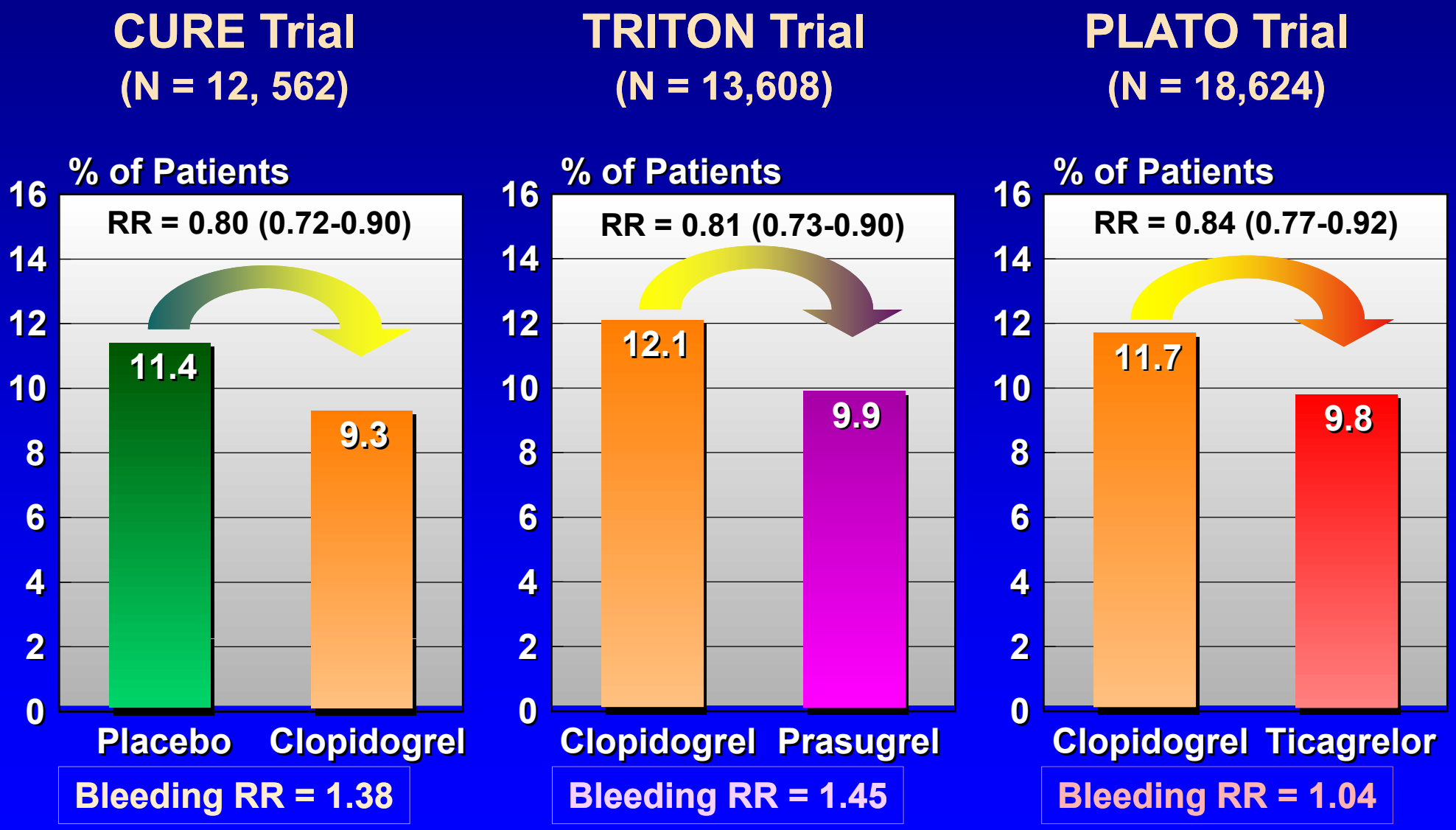
- **A loading dose** of 300- to 600-mg clopidogrel or 60-mg prasugrel should be given as soon as possible for STEMI patients for whom PCI is planned**.** (C)
- **The duration of therapy** should be clopidogrel 75 mg daily or *prasugrel 10 mg* for at least 12 months in patients receiving a BMS or DES(B). (BW<60 kg, prasugrel 5 mg, not generally recommened on > 75 yr)
- Consider earlier discontinuation at risk>benefit
- **The period of withdrawal before CABG** should be at least **5 days** for clopidogrel (B)and at least **7 days** for prasugrel(C)**.**

Thienopyrine

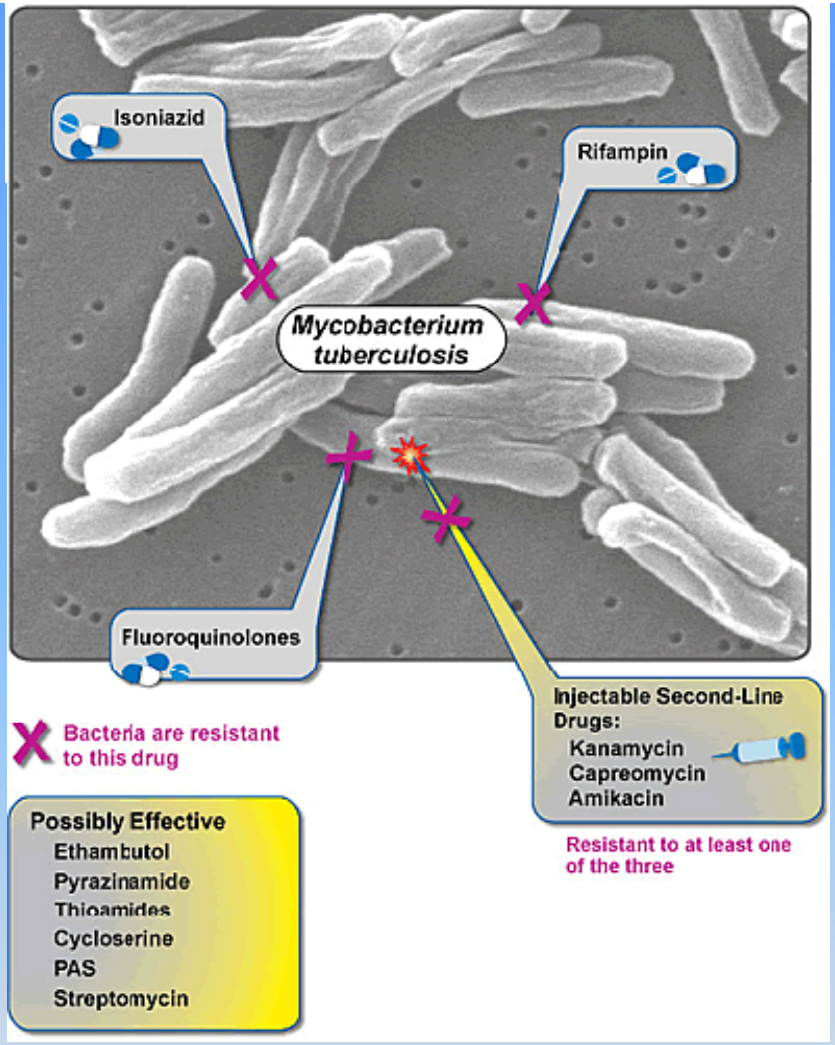
2009 Joint STEMI/PCI focused update recommendation

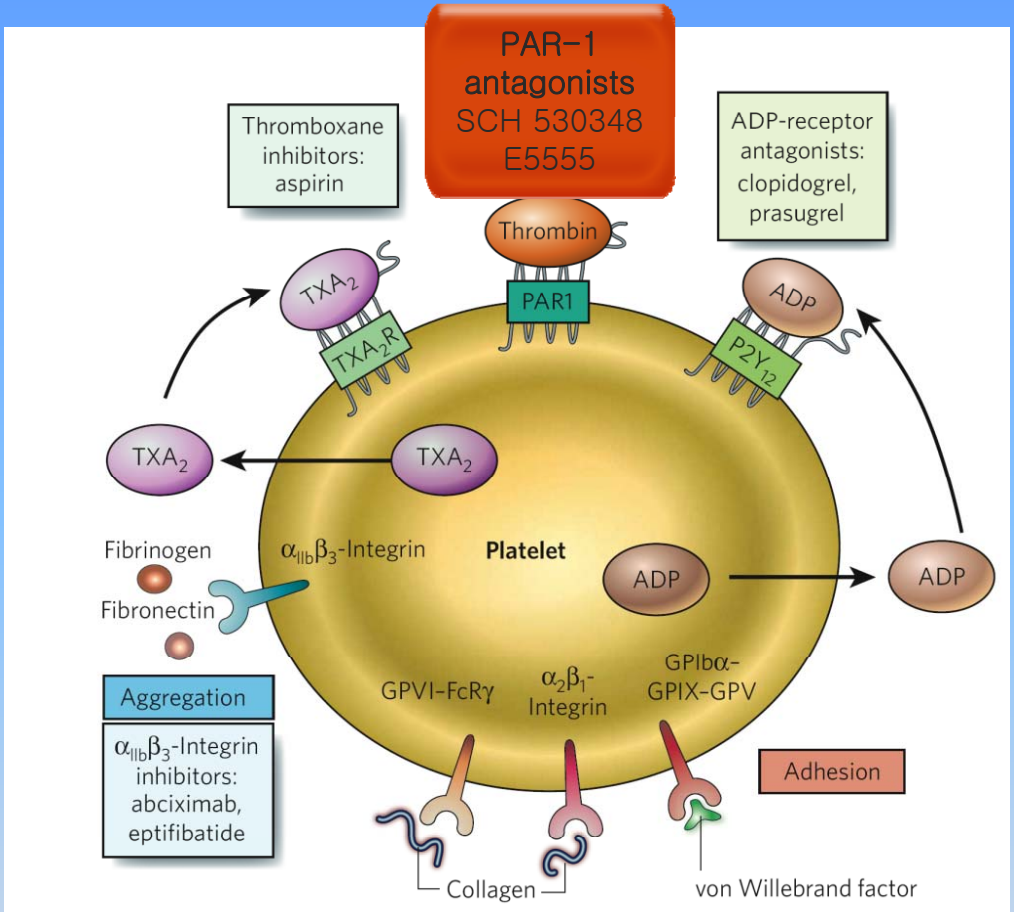
- **Class IIb: Continuation of clopidogrel or prasugrel beyond 15 months** may be considered in patients undergoing DES placement(C).
- **Class III:** In STEMI patients with **a prior history of stroke and TIA** for whom primary PCI is planned, prasugrel is **not recommended** (C).

ADP Inhibitors in ACS – Ischemic Endpoint



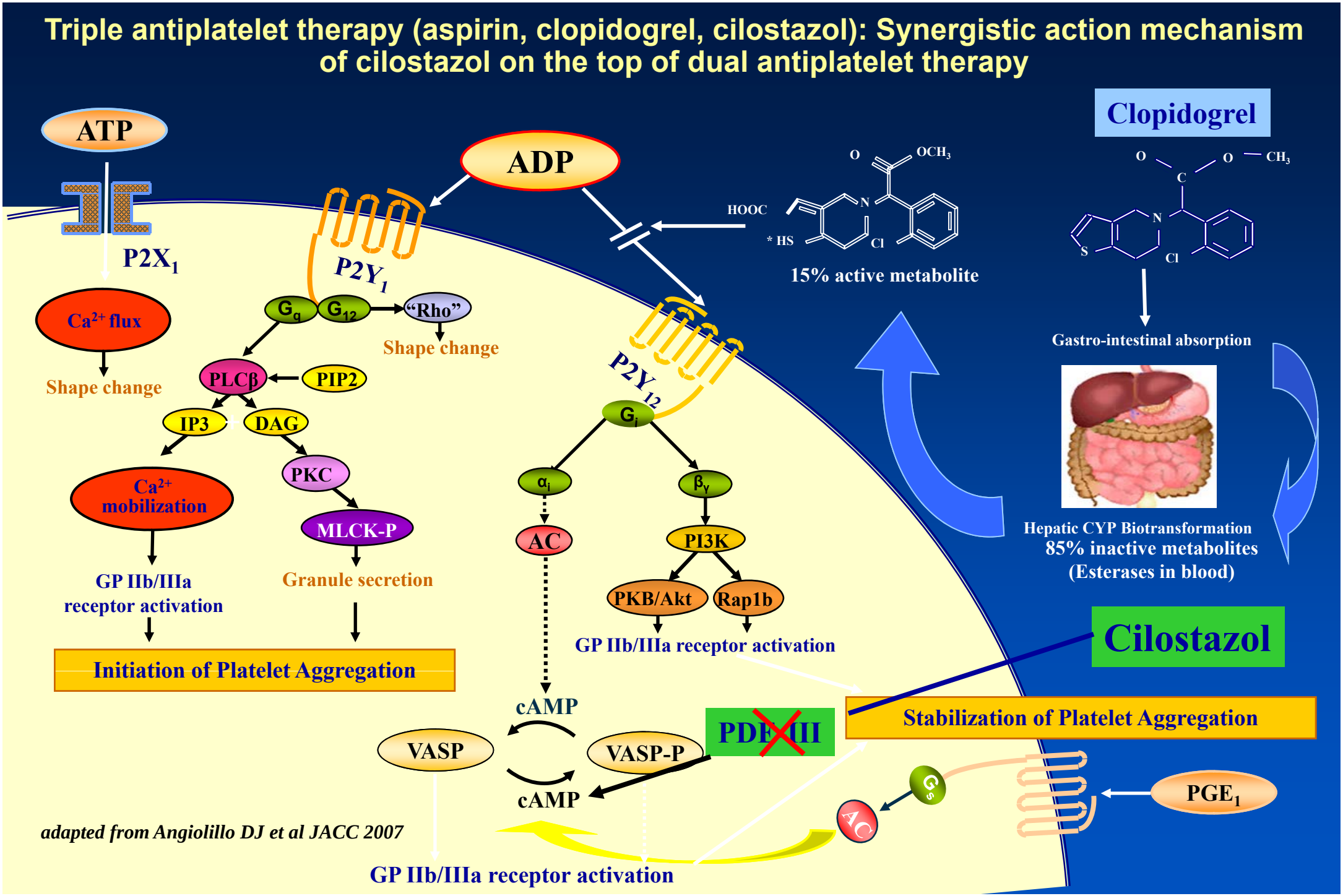
Adapted from Schomig A. NEJM 2009;361:1108



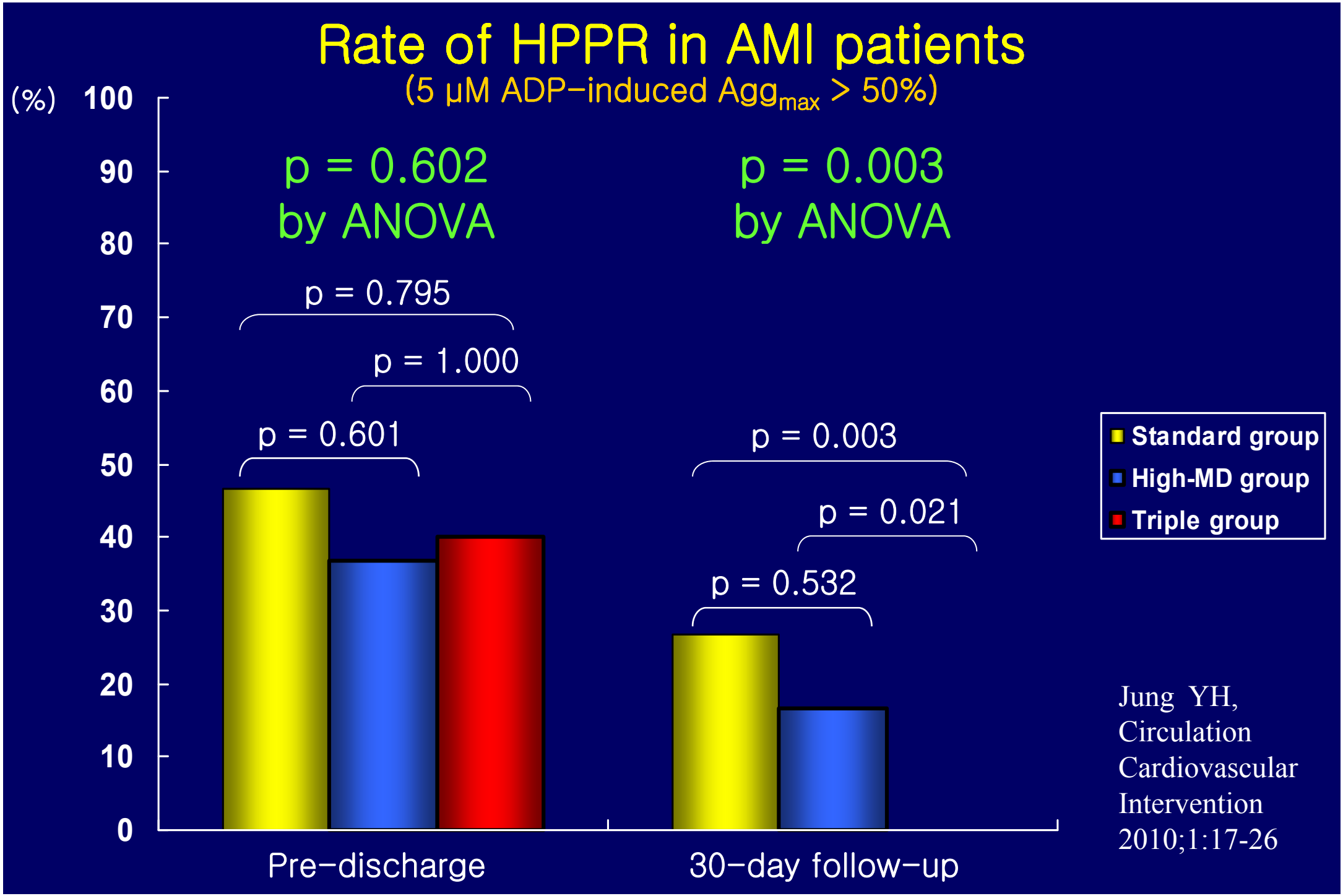


Why not multi-drug strategy for anti-platelet strategy? ⇒ Triple therapy

Triple antiplatelet therapy (aspirin, clopidogrel, cilostazol): Synergistic action mechanism of cilostazol on the top of dual antiplatelet therapy

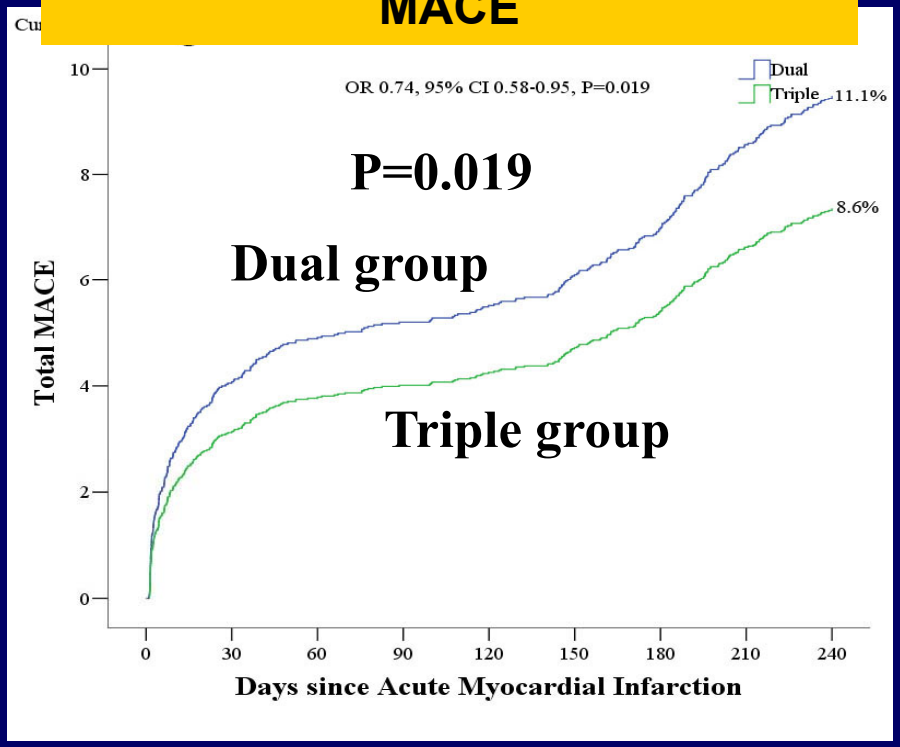


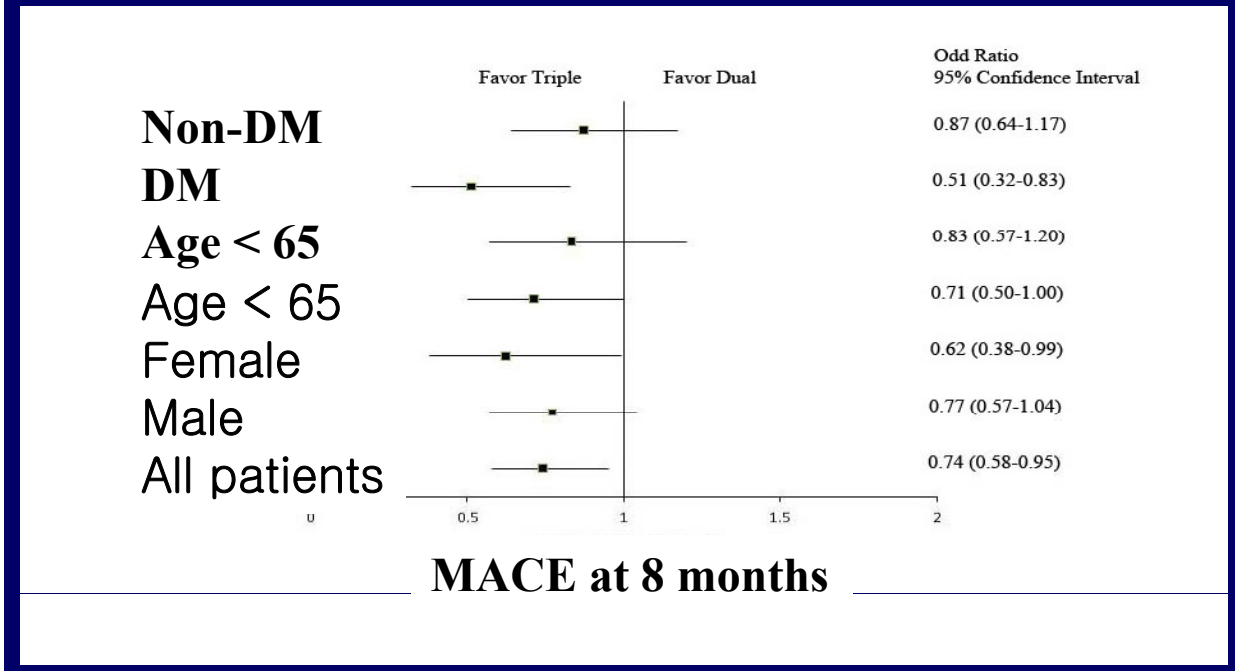
adapted from Angiolillo DJ et al JACC 2007


Rate of HPPR in AMI patients
(5 μM ADP-induced Agg$_{max}$ > 50%)
(%)
100
90
80
70
60
50
40
30
20
10
0
p = 0.602
by ANOVA
p = 0.003
by ANOVA
p = 0.795
p = 1.000
p = 0.601
p = 0.003
p = 0.021
p = 0.532
Standard group
High-MD group
Triple group
Pre-discharge
30-day follow-up
Jung YH,
Circulation
Cardiovascular
Intervention
2010;1:17-26

KAMIR registry
8-month death/MI/repeat revascularization

MACE





MACE at 8 months

Chen KY et al. Circulation;119:3207-14

Prospective Randomized

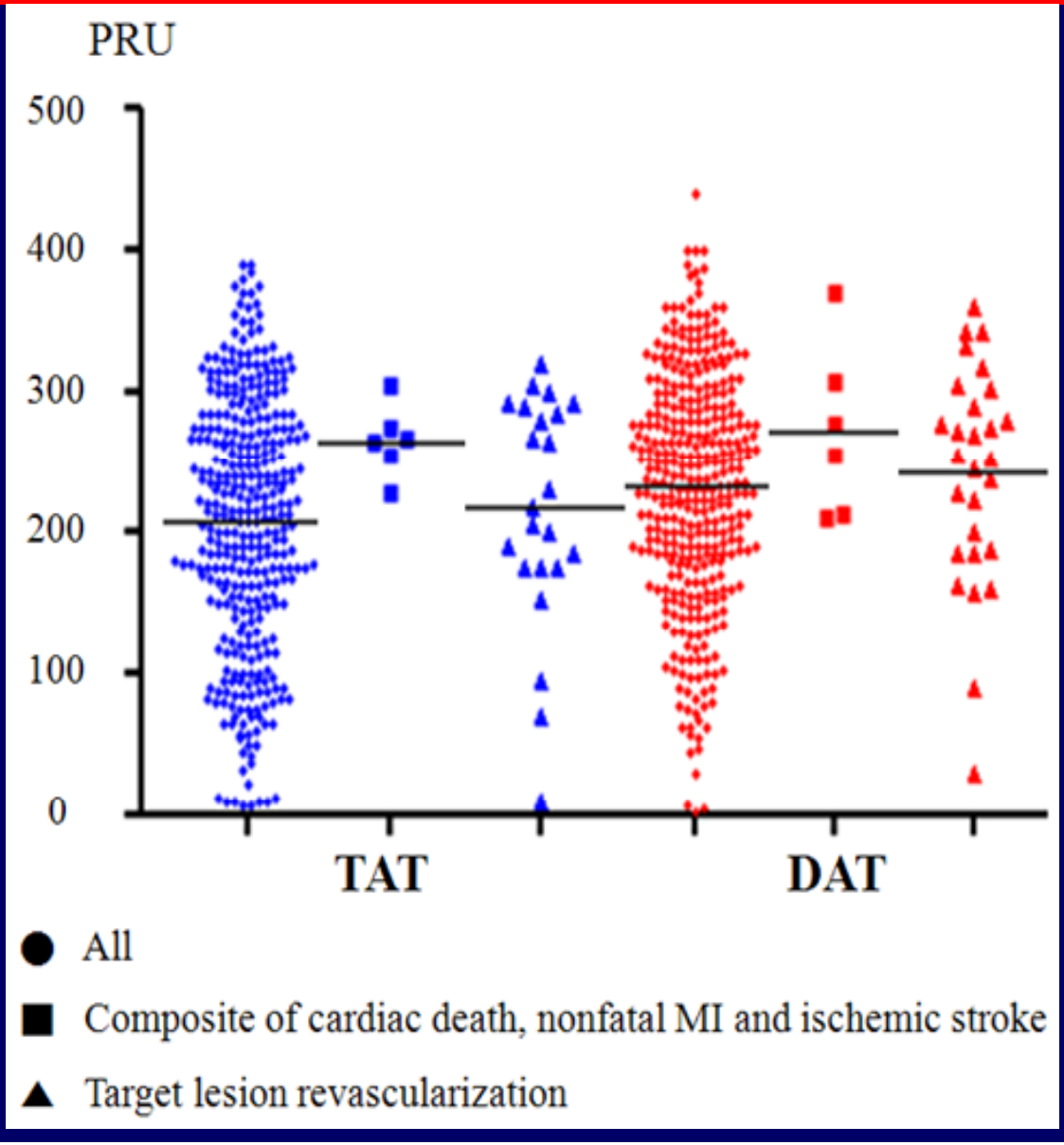
Clinical Outcomes at 12 Months for Triple Antiplatelet Therapy

	Dual (n=608)	Triple (n=604)	*p*
All death	4.1%	2.6%	0.159
CV death	3.3%	1.7%	0.067
MI	0.7%	0.3%	0.687
Stroke	1.6%	0.7%	0.109
Cardiac death/MI/Stroke	5.1%	2.6%	0.027
TVR	10.4%	7.8%	0.118
MACCE	15.1%	10.3%	0.011

Han Y, et al. Am Heart J 2009;157:733-9

CILON-T trial

Distribution of PRU in pts with MACCE



Triple AT
is helpful in HPPR
But has not
enough for some
patient with
MACE

Kim HS, ACC 2010

Development of Thrombin inhibitor

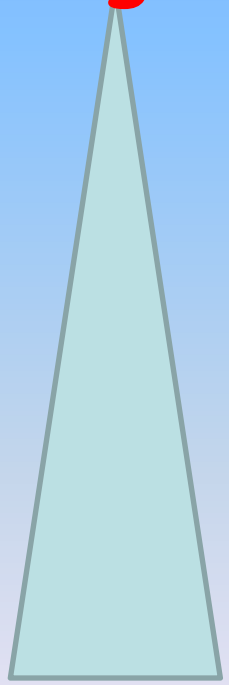
More selective, closer target

Bivaluridin Direct, thrombin inhibitor,

Fondaparinux Indirect, selective inhibitor of Xa

LMWH Indirect, more selective inhibitor of Xa

Heparin Indirect, nonselective inhibitor of thrombus and Xa



Thrombin inhibitor in AMI

Heparin and LMWH

- SYNERGY
- STEEPLE
- ExTRACT–TIMI 25

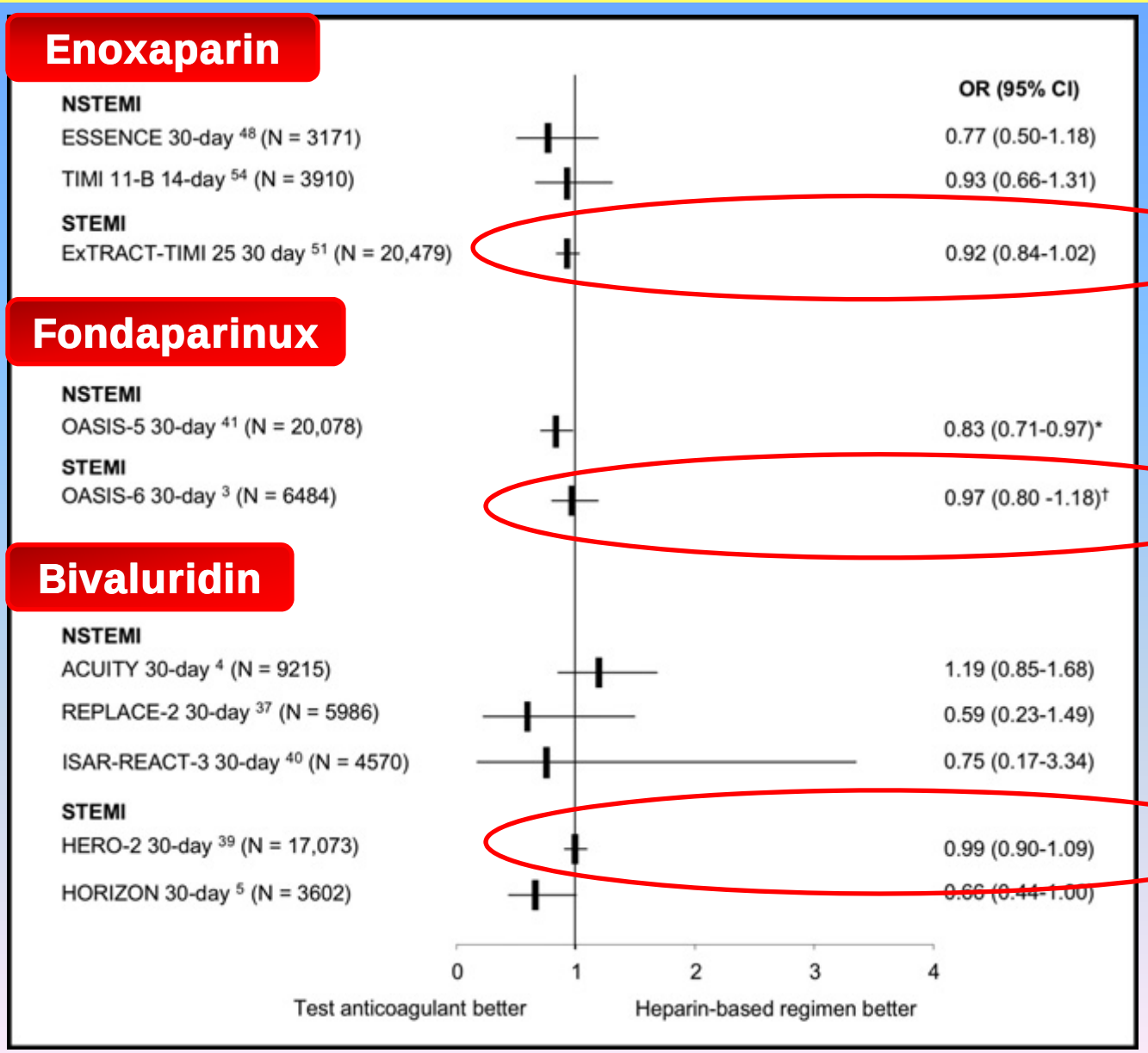
Fondaparinux

- OASIS-6

Bivaluridin

- ACUITY
- HORIZONS-AMI

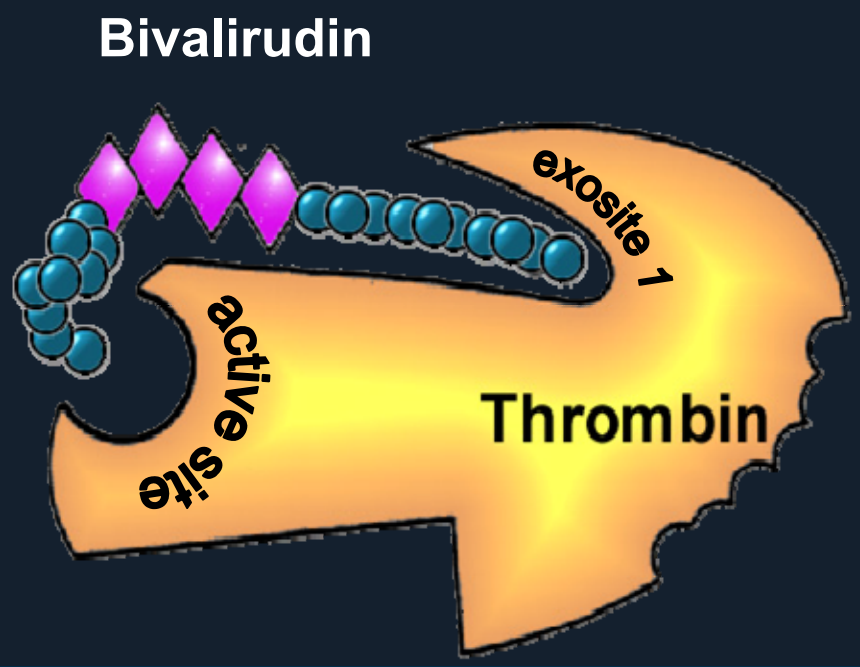
30 day all-cause mortality in ACS trials



The old and broader inhibition (UFH/LMWH) is better than the new!!

Bivalirudin

Bivalent Synthetic Direct Thrombin Inhibitor



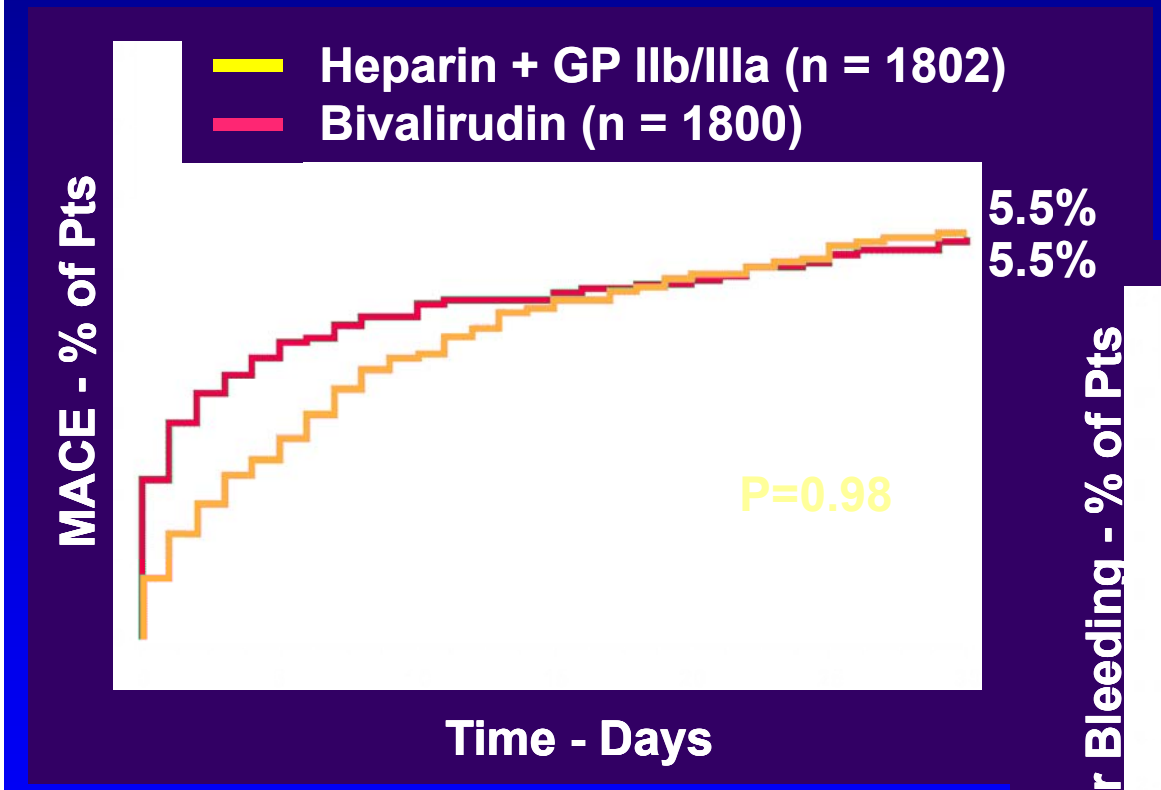
- Specifically inhibits
  - Fluid phase thrombin
  - Clot-bound thrombin
  - Thrombin-mediated Platelet aggregation
- Reversible
- $T_{0.5}$ 25 minutes

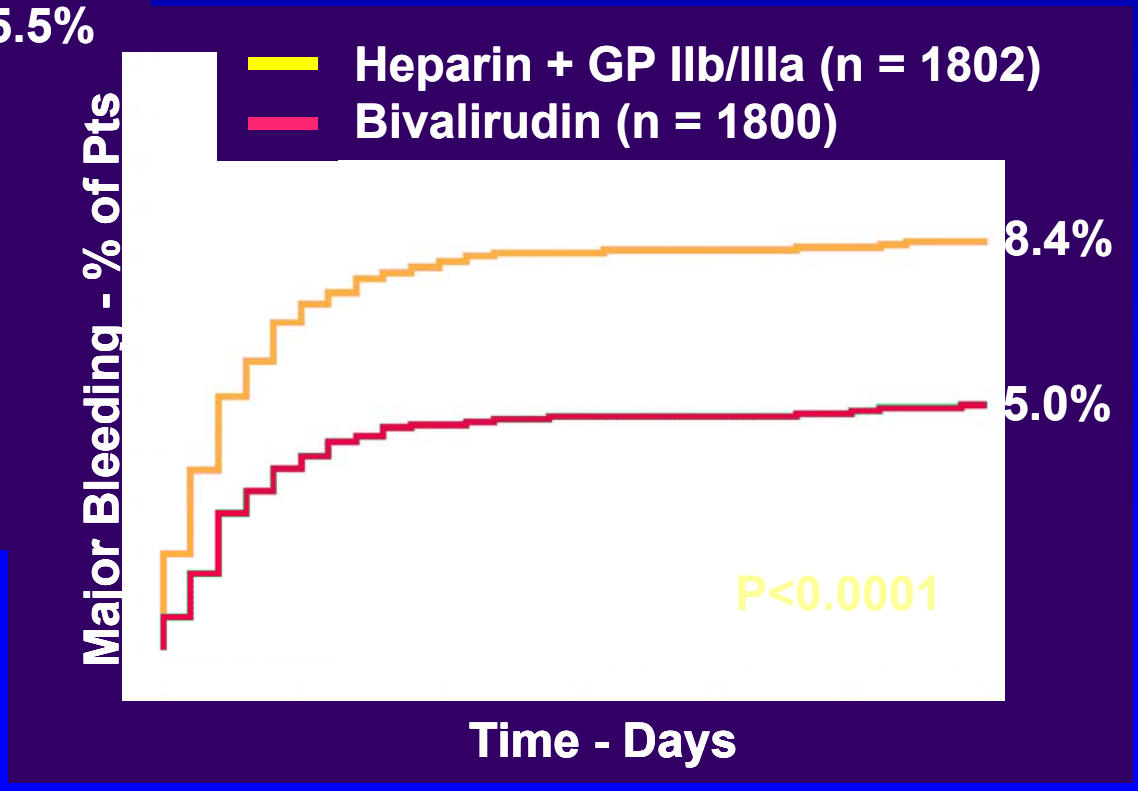
Topol EJ: Textbook of Interventional Cardiology

Bivalirudin vs GP IIb/IIIa in AMI

HORIZONS AMI

Ischemic and Bleeding Endpoints





Parenteral Anticoagulation

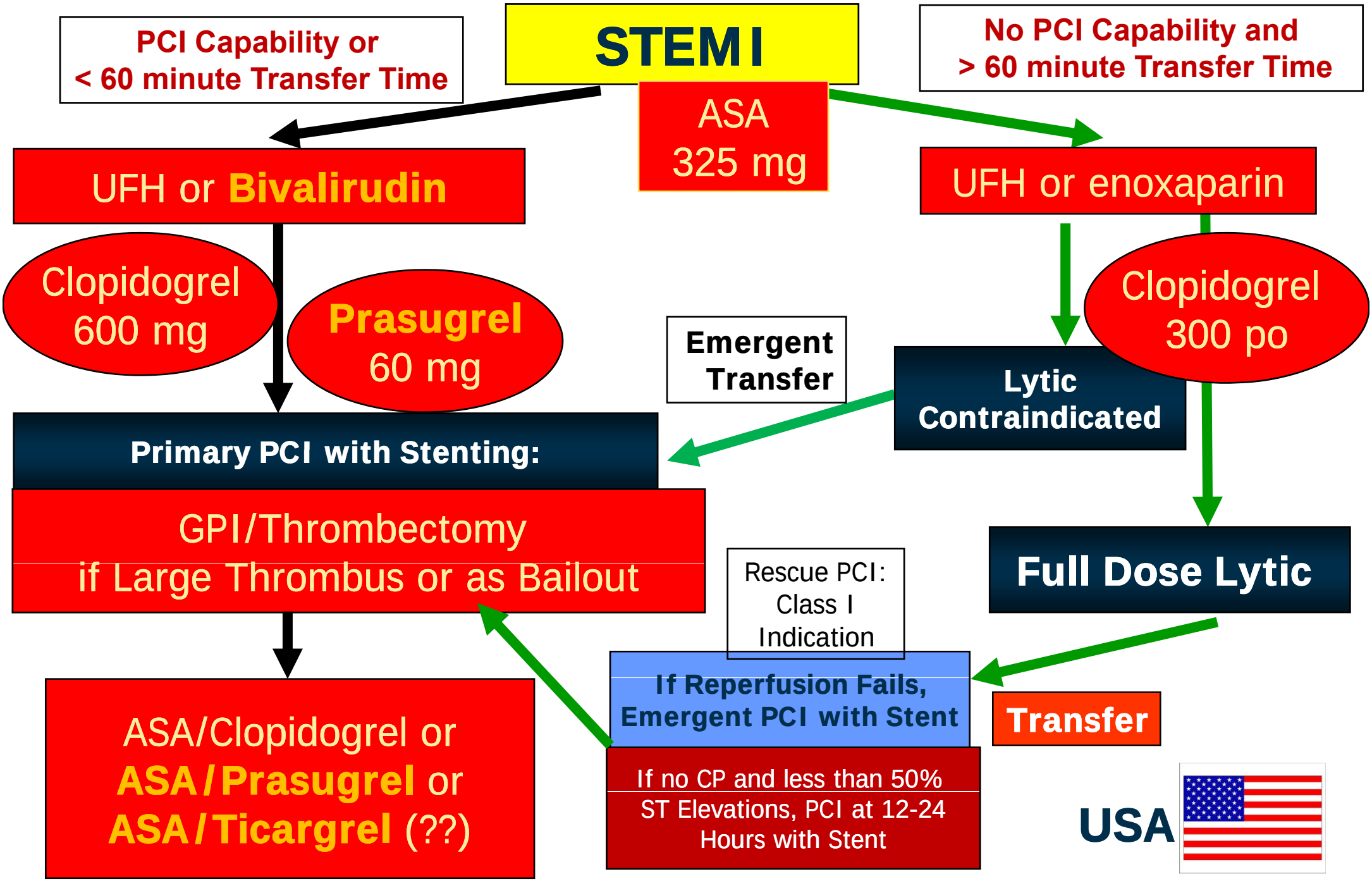
2009 Joint STEMI/PCI focused update recommendation

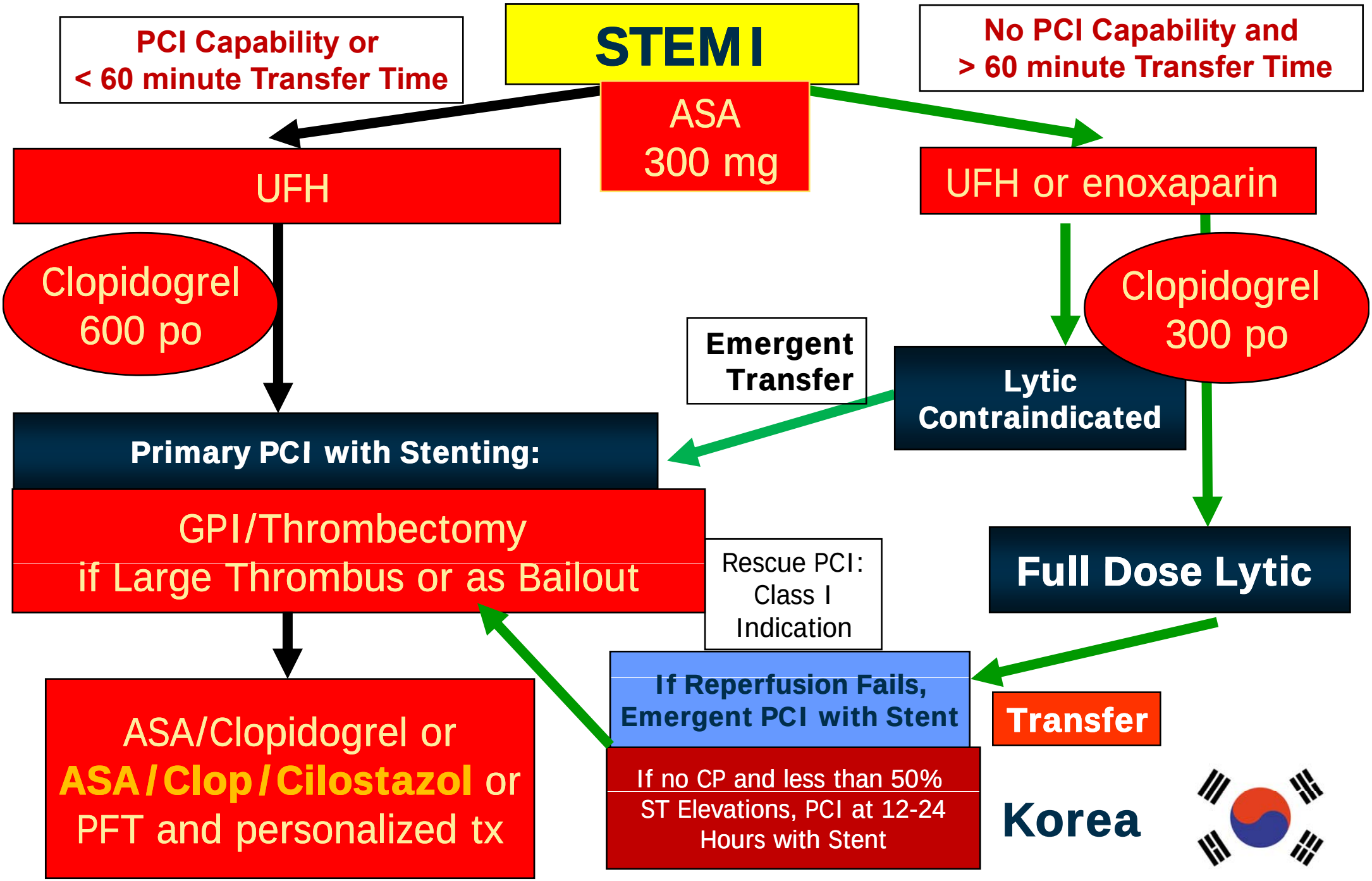
Class I:

- Prior treatment of UFH → Additional bolus of UFH with monitoring **ACT** (C)
- **Bivalirudin** is useful for primary PCI with or without prior treatment of UFH (B)
- **Enoxaparin** and **fondaparinux**: not changed

Class IIa:

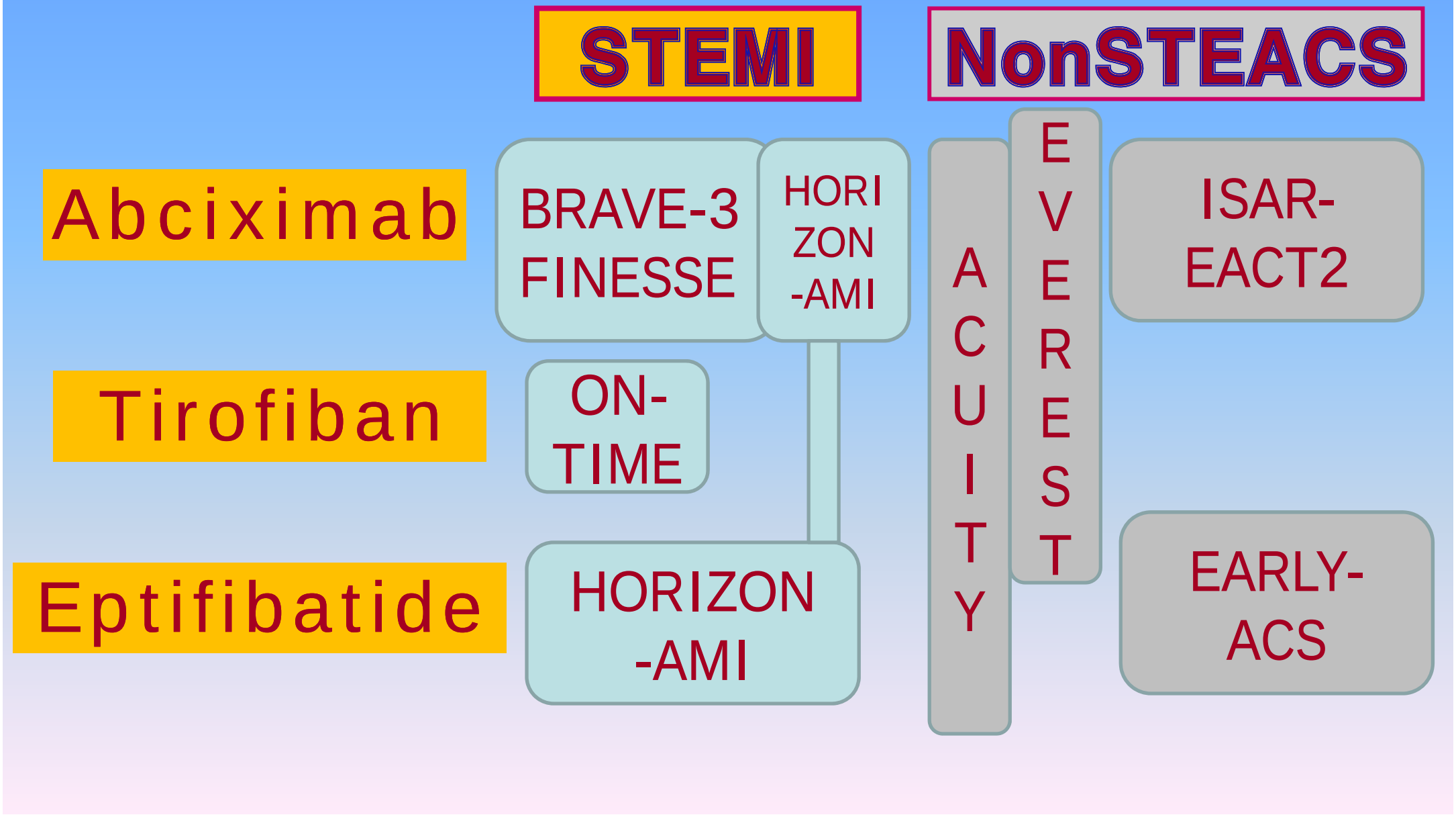
- High risk of bleeding, **bivalirudin** is reasonable (B)


PCI Capability or
< 60 minute Transfer Time
STEMI
No PCI Capability and
> 60 minute Transfer Time
ASA
325 mg
UFH or Bivalirudin
UFH or enoxaparin
Clopidogrel
600 mg
Prasugrel
60 mg
Clopidogrel
300 po
Emergent
Transfer
Lytic
Contraindicated
Primary PCI with Stenting:
GPI/Thrombectomy
if Large Thrombus or as Bailout
Full Dose Lytic
Rescue PCI:
Class I
Indication
If Reperfusion Fails,
Emergent PCI with Stent
Transfer
ASA/Clopidogrel or
ASA/Prasugrel or
ASA/Ticargrel (??)
If no CP and less than 50%
ST Elevations, PCI at 12-24
Hours with Stent
USA


PCI Capability or
< 60 minute Transfer Time
STEMI
ASA
300 mg
No PCI Capability and
> 60 minute Transfer Time
UFH
UFH or enoxaparin
Clopidogrel
600 po
Clopidogrel
300 po
Emergent
Transfer
Lytic
Contraindicated
Primary PCI with Stenting:
GPI/Thrombectomy
if Large Thrombus or as Bailout
Rescue PCI:
Class I
Indication
Full Dose Lytic
If Reperfusion Fails,
Emergent PCI with Stent
Transfer
ASA/Clopidogrel or
ASA/Clop/Cilostazol or
PFT and personalized tx
If no CP and less than 50%
ST Elevations, PCI at 12-24
Hours with Stent
Korea

경청해 주셔서 감사합니다

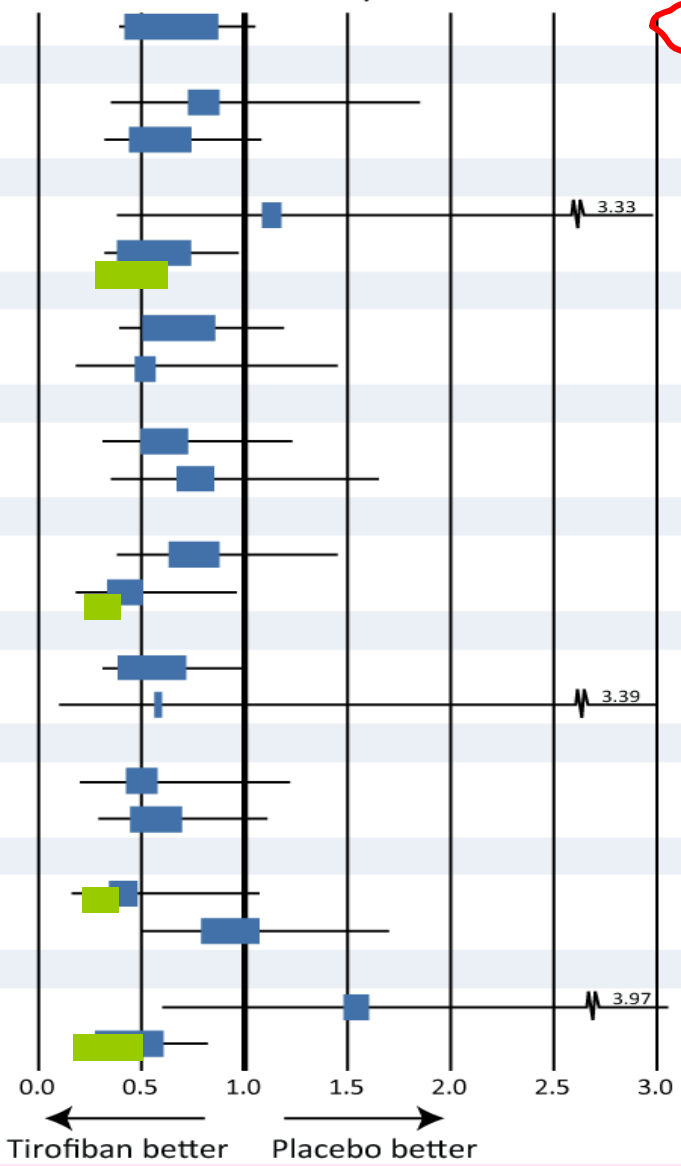
Recent Trials of GPI in AMI



Aspirin 500 mg i.v. or oral
Unfractionated Heparin 5000 IE

Placebo (n=399)

	Tirofiban no./total	Placebo no.	Death within One Year Risk Ratio, 95% Confidence Interval	p-value
All patients	25/670	38/656	0.64 (0.39 - 1.05)	0.078
Sex				
Female	9/154	12/164	0.80 (0.35 - 1.84)	0.597
Male	16/516	26/492	0.59 (0.32 - 1.08)	0.083
Age(years)				
<= 61.6	7/337	6/327	1.13 (0.38 - 3.33)	0.822
> 61.6	18/333	32/329	0.56 (0.32 - 0.97)	0.035
Diabetes				
No	20/595	29/585	0.68 (0.39 - 1.18)	0.169
Yes	5/75	9/69	0.51 (0.18 - 1.45)	0.197
Location				
Anterior MI	12/253	20/259	0.61 (0.31 - 1.23)	0.164
Non anterior MI	11/343	14/331	0.76 (0.35 - 1.65)	0.483
Killip > 1				
No	15/587	19/554	0.75 (0.38 - 1.45)	0.385
Yes	6/69	18/87	0.42 (0.18 - 0.96)	0.039
Timi flow grade before PCI				
0-2	16/473	30/491	0.55 (0.31 - 0.99)	0.047
3	2/134	3/116	0.58 (0.10 - 3.39)	0.665
Time start study drug to balloon inflation/angiography				
<= 55	7/331	14/331	0.50 (0.20 - 1.22)	0.121
> 55	13/326	22/314	0.57 (0.29 - 1.11)	0.093
Time symptom onset to diagnosis				
<= 75	6/340	13/303	0.41 (0.16 - 1.07)	0.059
> 75	18/315	21/340	0.93 (0.50 - 1.70)	0.803
Primary PCI				
No	11/93	6/78	1.54 (0.60 - 3.97)	0.368
Yes	14/577	32/578	0.44 (0.24 - 0.81)	0.007

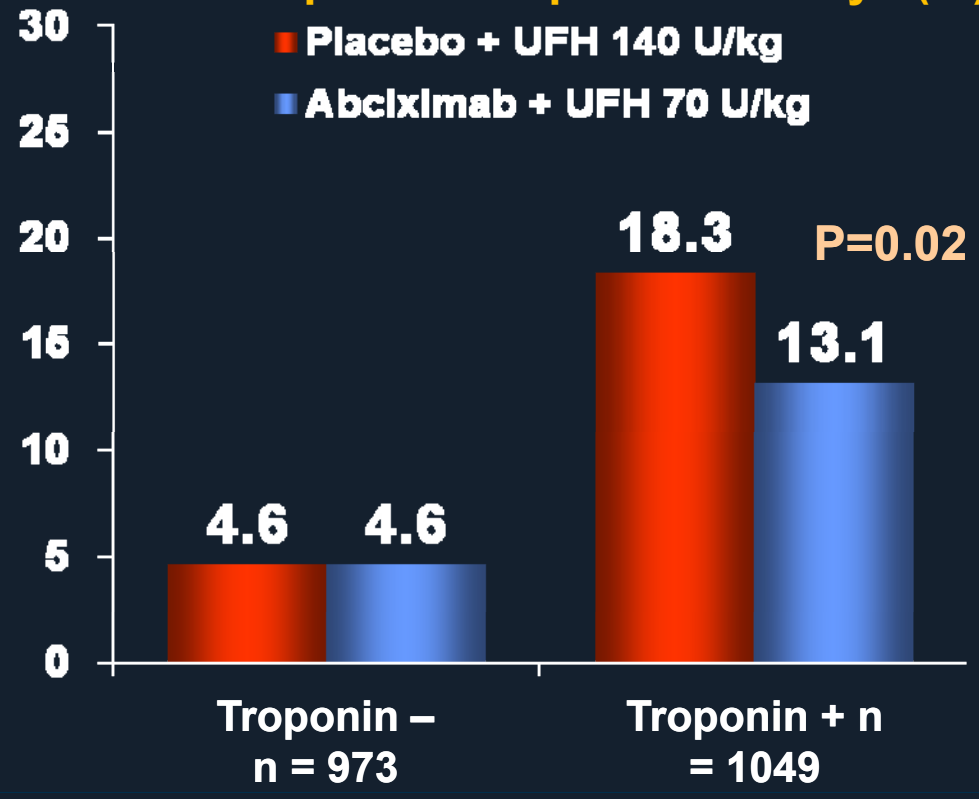


ISAR-REACT 2

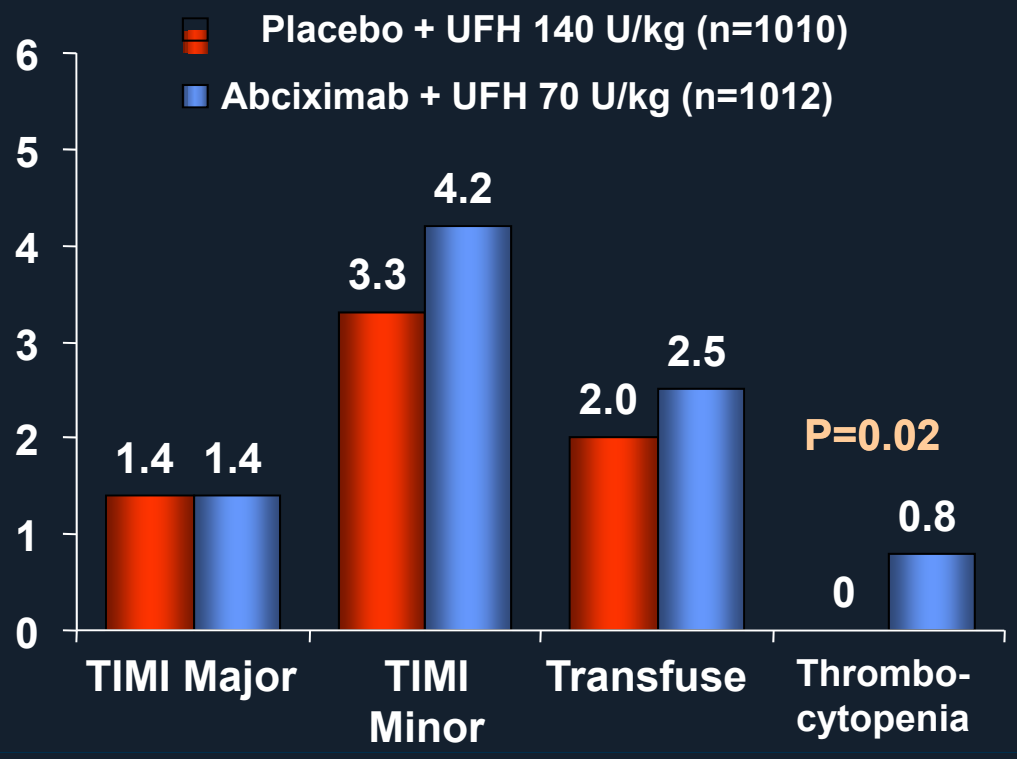
Placebo-controlled randomized trial of abciximab in 2,022 ACS pts pre-loaded with 600 mg clopidogrel for ≥2 hrs

Inclusion: ACS with troponin +, ST-seg changes, or new LBBB

Composite Endpoint – 30 Days (%)

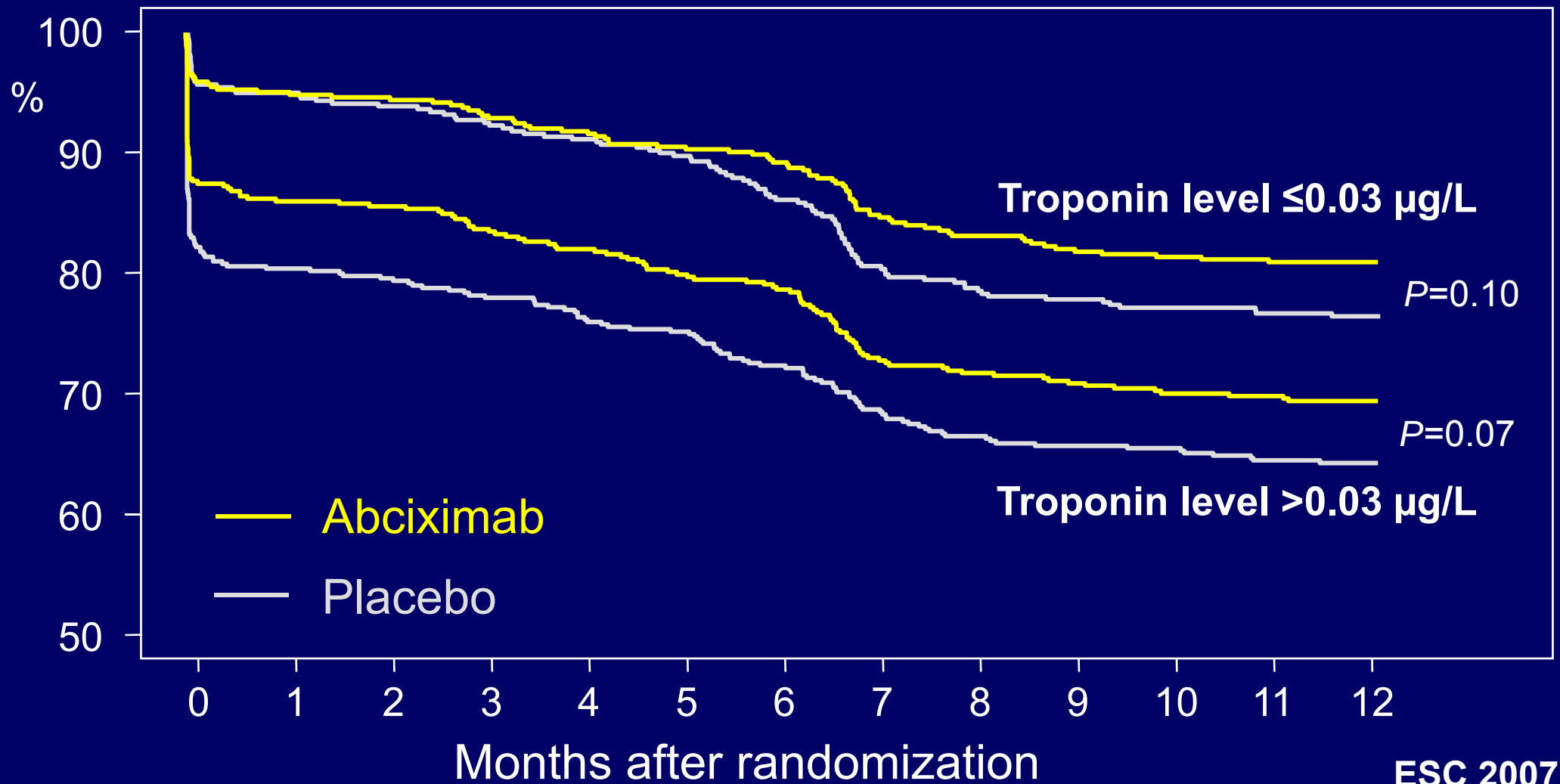


Bleeding Endpoints (%)



Kastrati A et al. *JAMA* 2006;295:1531–8

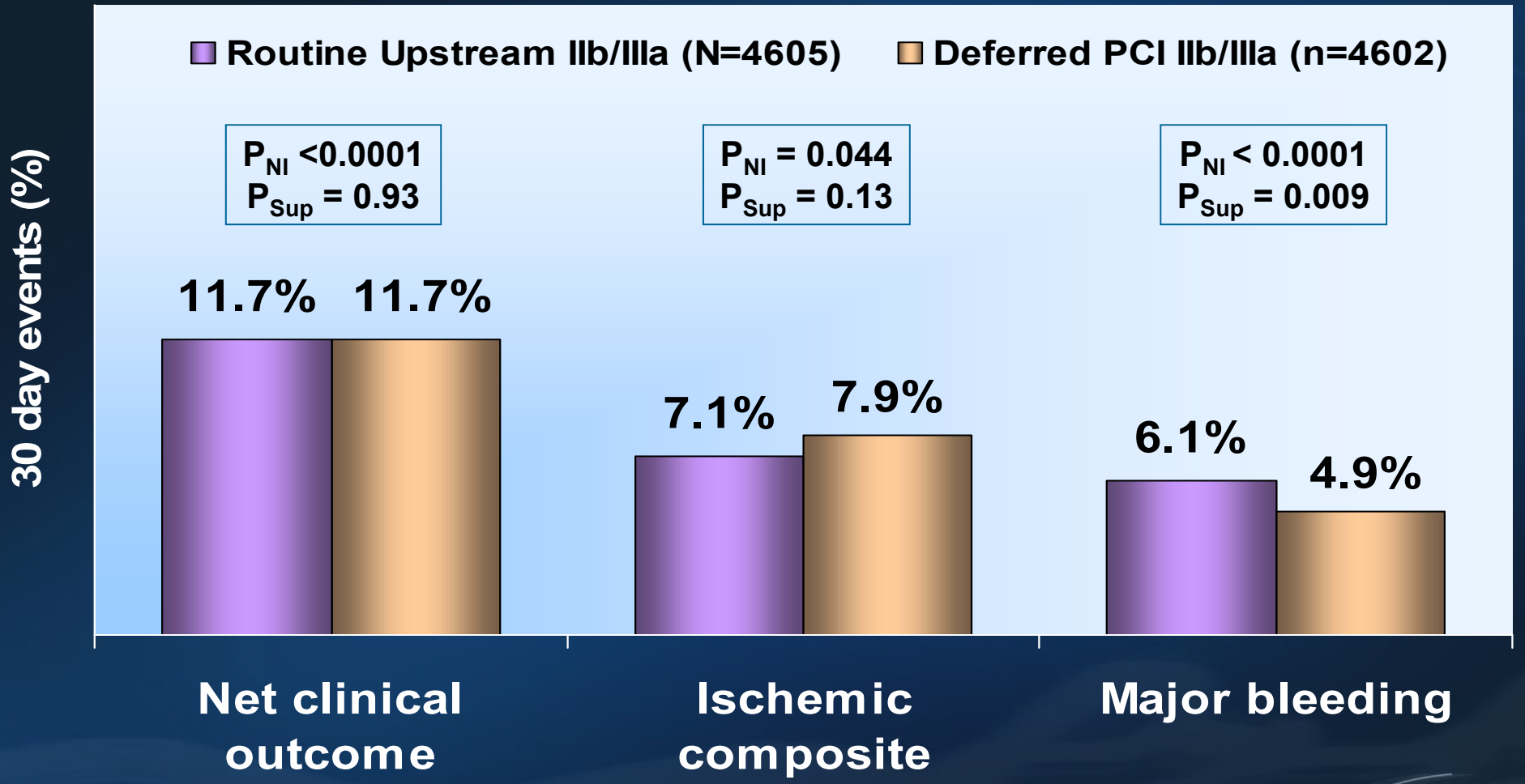
Troponin Level and Benefit With Abciximab after 12 Months



ESC 2007

GPI Timing: Deferred strategy is better

Routine Upstream IIb/IIIa vs. Deferred PCI IIb/IIIa



ACUITY TIMING

Update on antithrombotics in AMI

GPI in Non-STE-ACS

- Moderate- or high- risk NSTE-ACS and if an early invasive strategy: Recommended
- Deferred strategy may be same effect and less bleeding

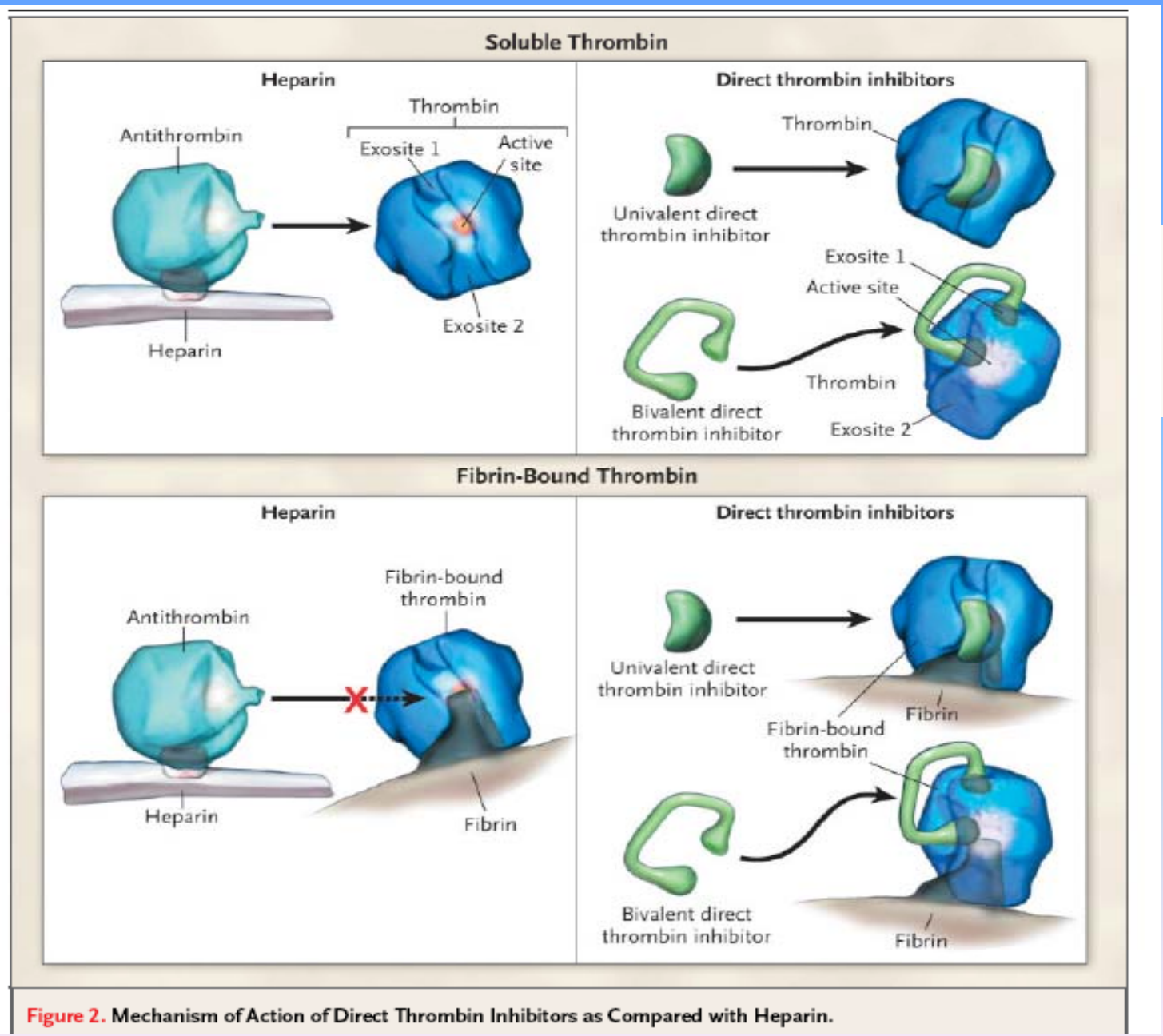


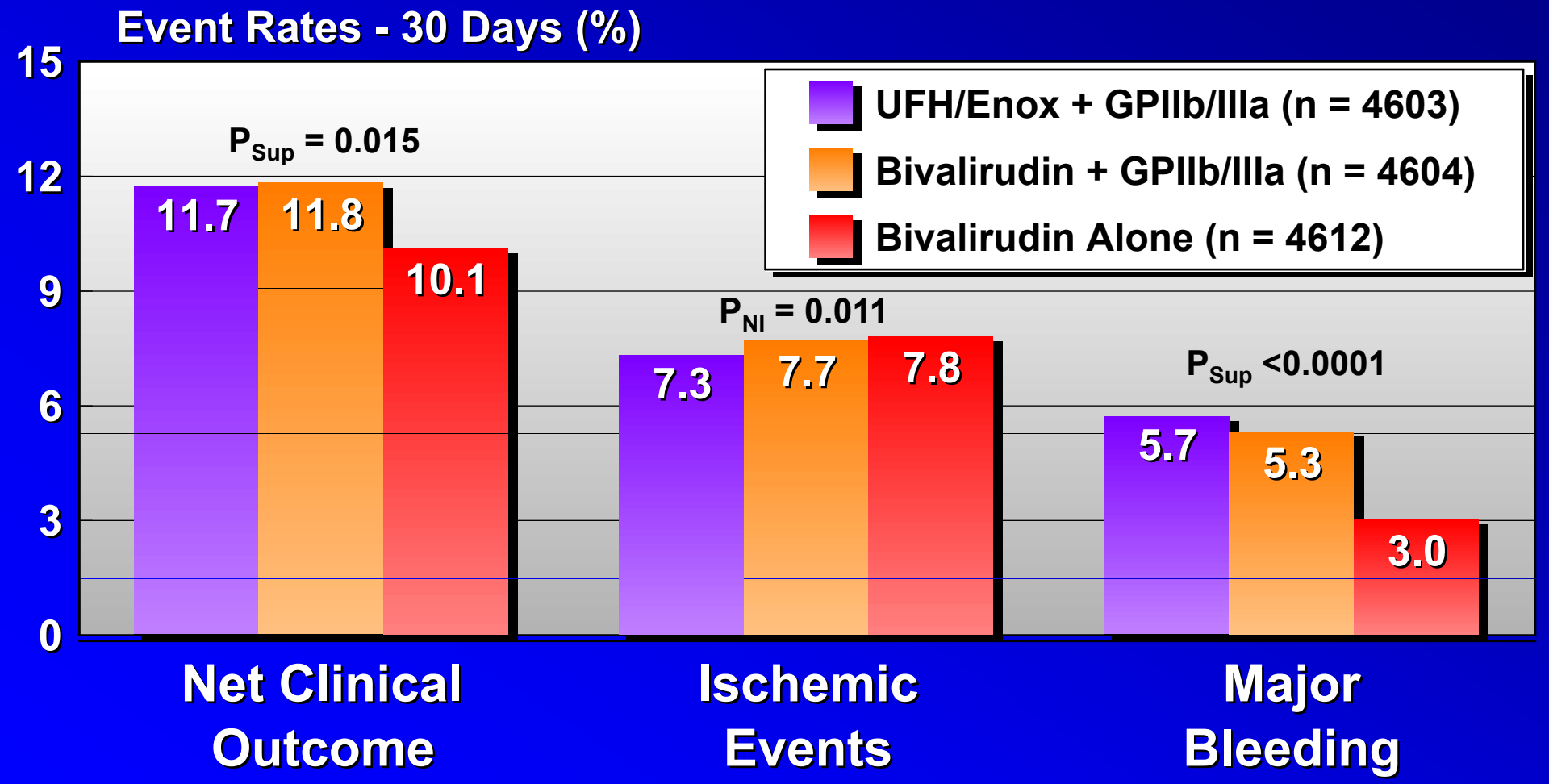
Figure 2. Mechanism of Action of Direct Thrombin Inhibitors as Compared with Heparin.

N Engl J Med 2005;353:1028–40.

ACUITY TRIAL

Bivalirudin in ACS

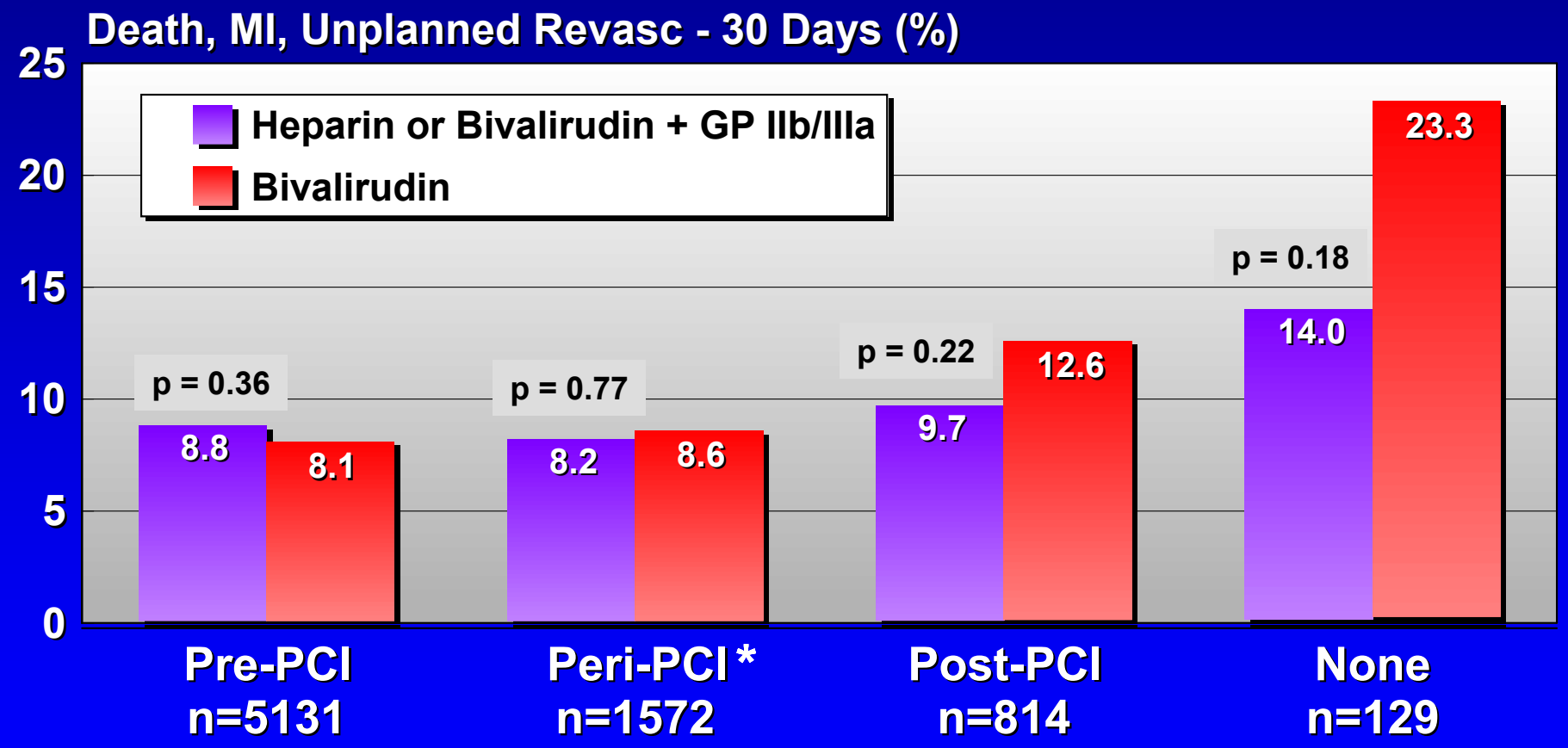
Primary Endpoints - 30 Days



Stone et al. NEJM 2006;355:2203.

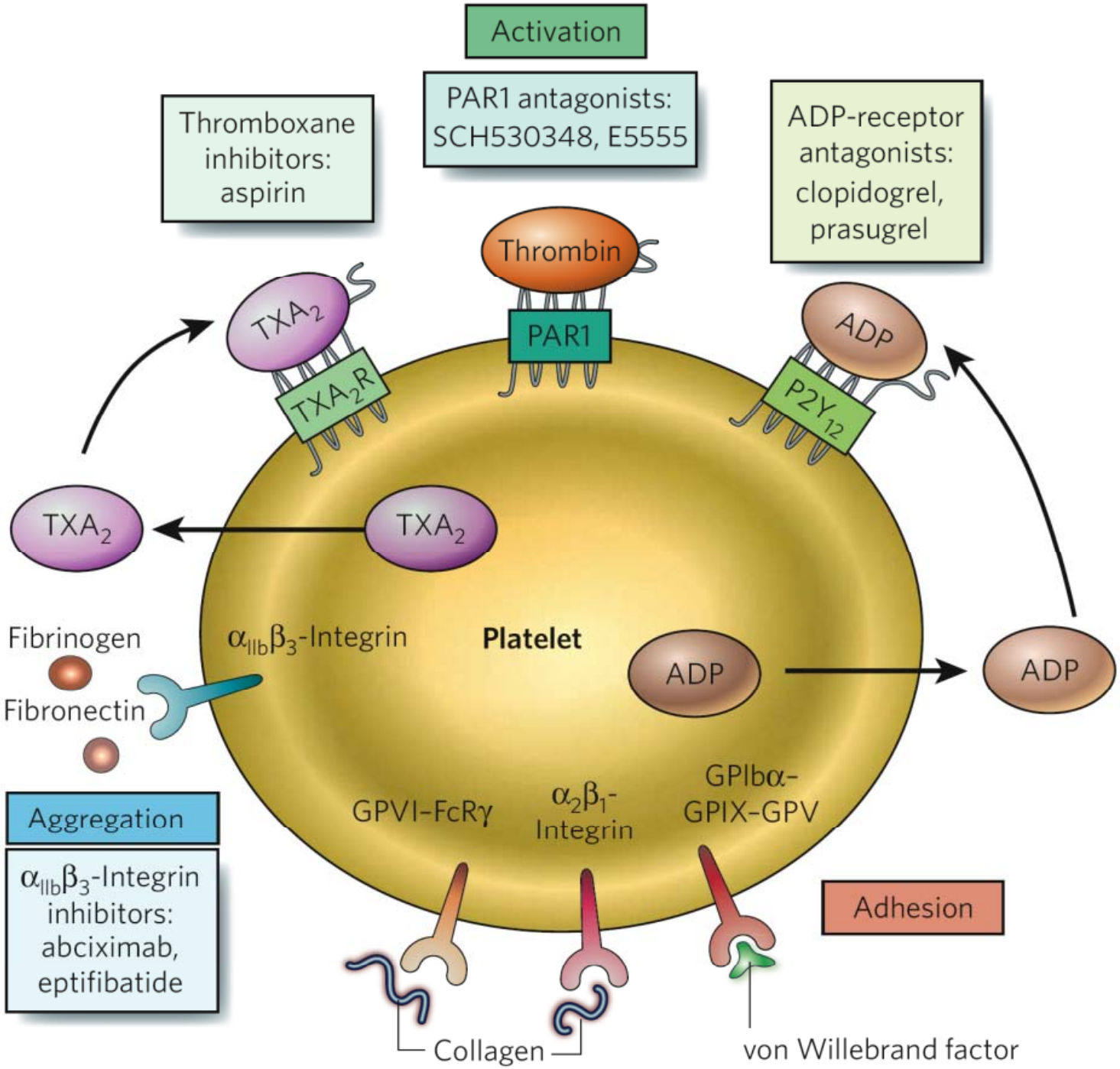
ACUITY Trial – Bivalirudin in ACS

Ischemic Outcome by Clopidogrel Timing

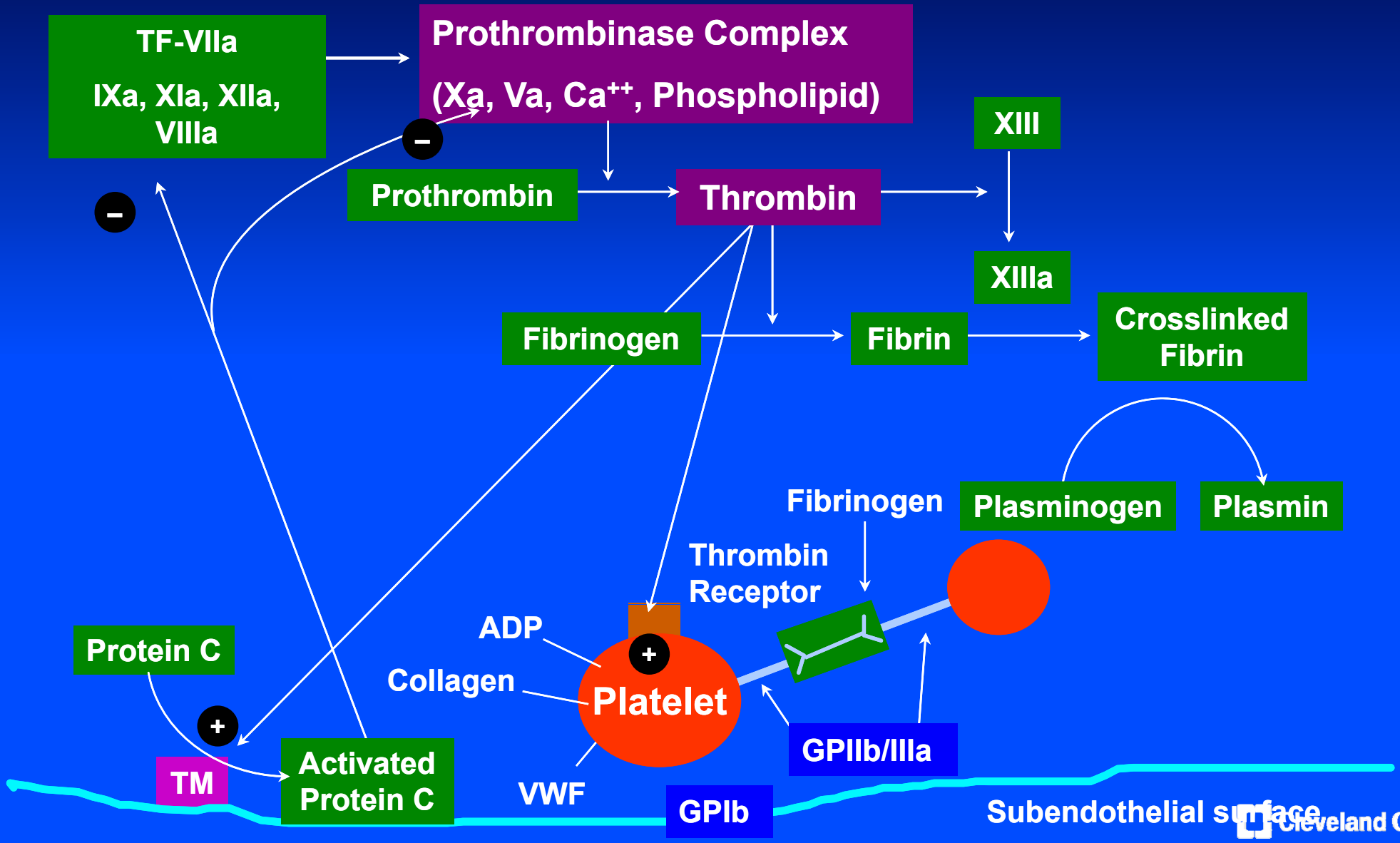


* Peri-PCI = after angio but <30 min after PCI

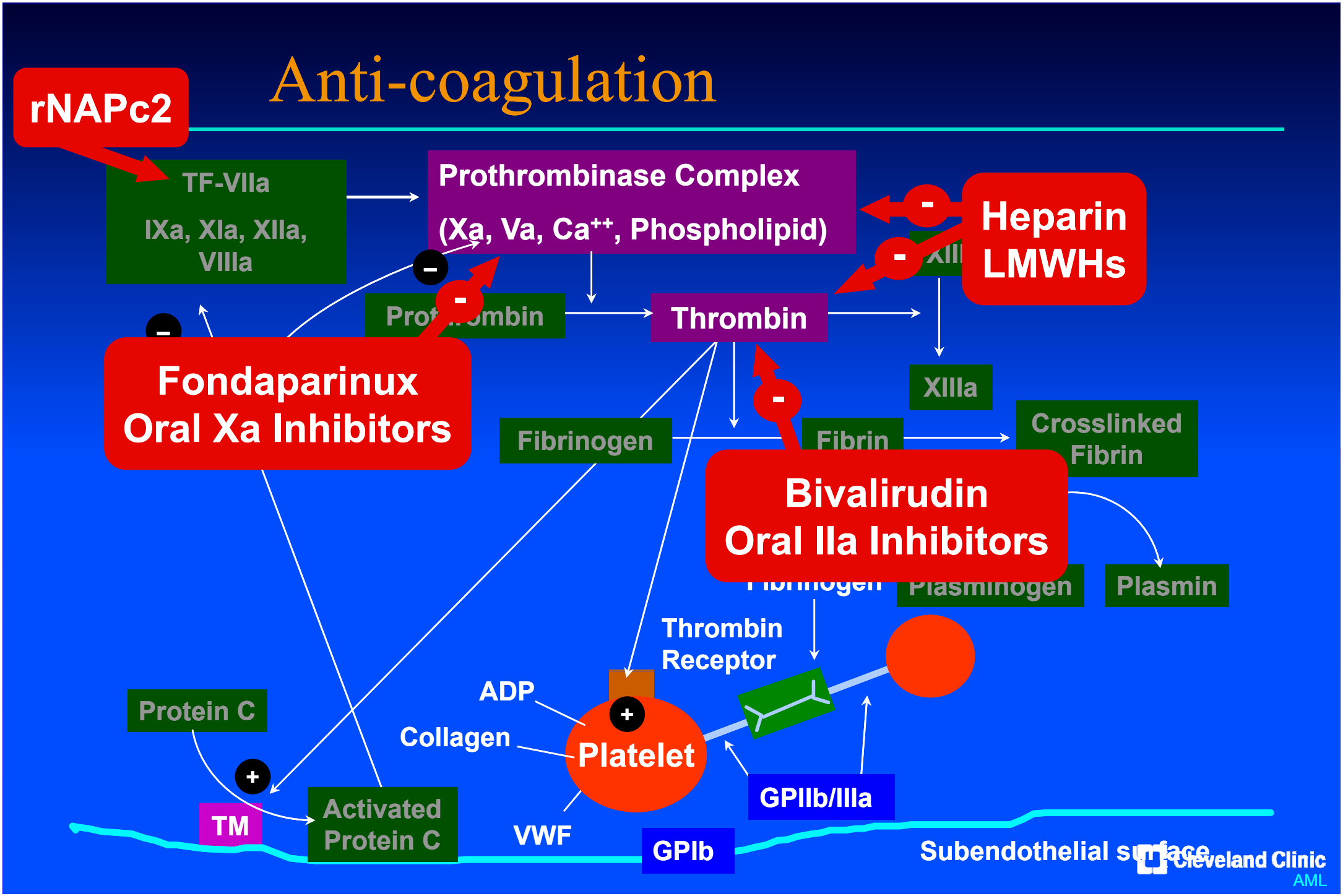
Lincoff et al. JACC Intervention 2008:1:639.


Activation
Thromboxane inhibitors: aspirin
PAR1 antagonists: SCH530348, E5555
ADP-receptor antagonists: clopidogrel, prasugrel
Thrombin
PAR1
TXA_2
TXA_2R
ADP
$P2Y_{12}$
TXA_2
TXA_2
Fibrinogen
Fibronectin
$\alpha_{IIb}\beta_3$-Integrin
Platelet
ADP
ADP
Aggregation
$\alpha_{IIb}\beta_3$-Integrin inhibitors: abciximab, eptifibatide
GPVI-FcRγ
$\alpha_2\beta_1$-Integrin
GPIbα-GPIX-GPV
Adhesion
Collagen
von Willebrand factor

Coagulation Cascade



Anti-coagulation



New ADP inhibitors

Drug	Ticlopidine	Clopidogrel	Prasugrel	Ticagrelor
Bioavailability (%)	80–90	>50	80–100	?
Protein binding (%)	98	94–98	?	?
Half-life (hours)	12.6	7–8	3.7[a]	12
Metabolism	90% hepatic, no active meta-bolites	Hepatic active metabolites	Hepatic active metabolites, 70% renal excretion	Orally active
Onset of antiaggregation	<4 days	2 hours	30 minutes	2 hours
Steady state of aggregation	8–11 days	3–7 days[b]	3 days	2–3 days
Phase	approved	approved	approved	3
Reversibility	-	-	-	+

[a] Median half-times reported for the active metabolite R-138727. [b] After administration of loading dose (300 mg to 600 mg).

Zurn CS, Thromb Haemost 2010; 103: 496–506

Glycoprotein Inhibitor in STEMI

Abciximab

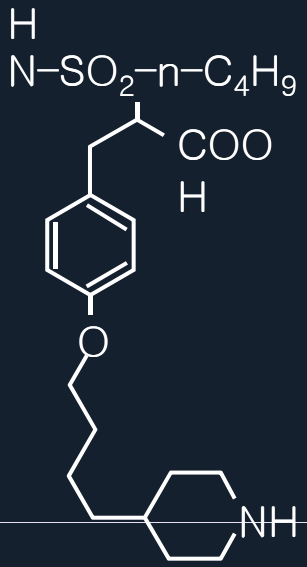
Chimeric Monoclonal Antibody

MW ≈ 50,000 D

Tirofiban

Nonpeptide Tyrosine Derivative

MW ≈ 500 D



Eptifibatide

Cyclic Heptapeptide

MW ≈ 800 D