קורס השתלמות לאחיות וטכנאים מחדרי צנתור –06/2010

תרופות נוגדות קרישה וטסיות בחולים העוברים צנתור כלילי התערבותי

ד"ר אלי לב

מנהל שרות הצנתורים

בי"ח השרון, מרכז רפואי רבין

3 Major systems involved in thrombosis and hemostasis

- **Vessel wall**
  - **Endothelium**
- **Platelets**
- **Coagulation cascade**

Anti-platelet Properties of the Endothelium

- Covers highly thrombogenic basement membrane (type IV collagen, TF)

  Uninjured endothelium does not bind platelets

- NO from uninjured endothelium inhibit platelet aggregation and adhesion, PGI2 (prostacyclin) inhibits platelet aggregation

- TFPI – tissue factor pathway inhibitor – released from endothelial cells

3 Major systems involved

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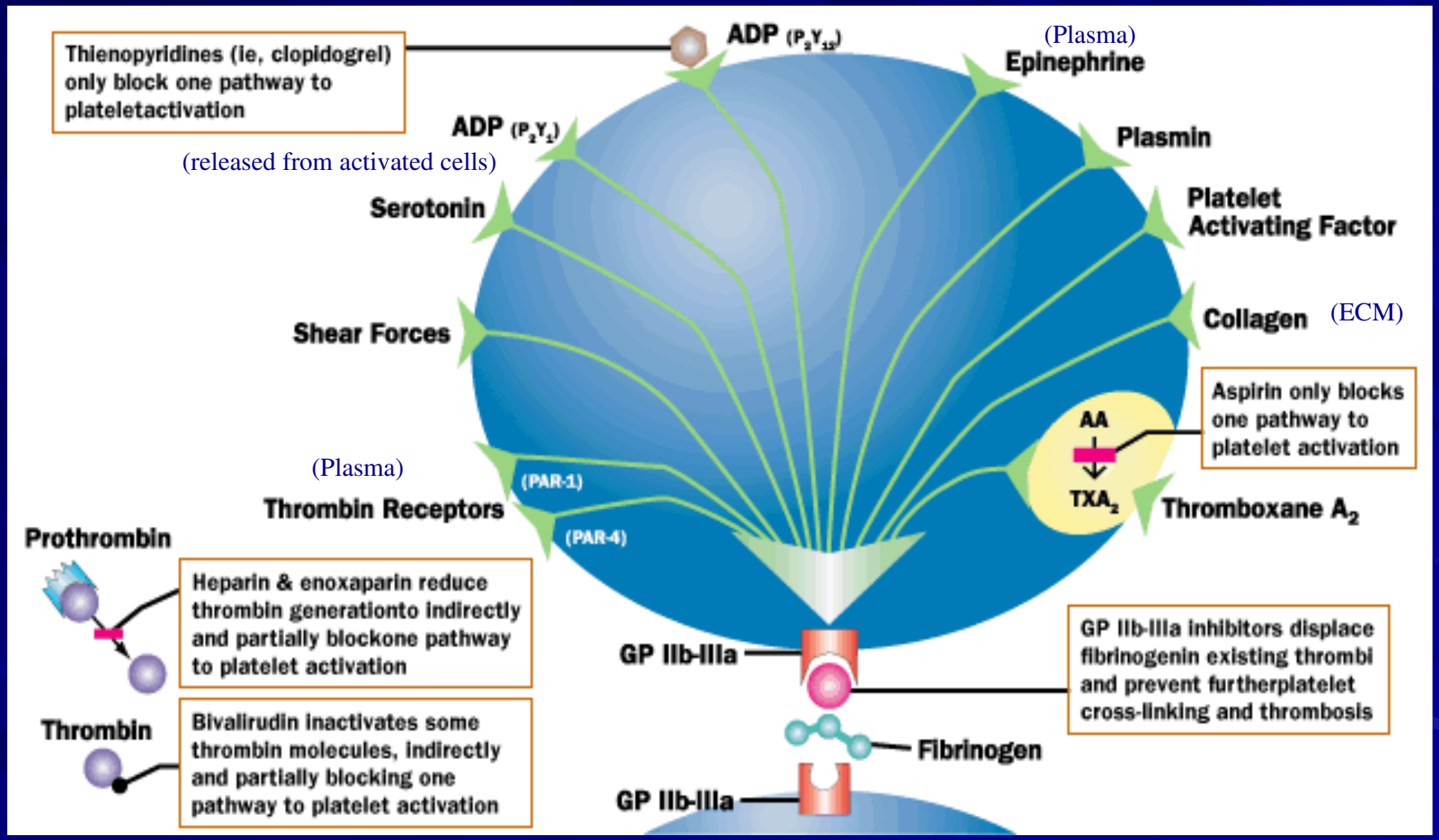
Platelets

- Adhesion
- Activation
- Aggregation

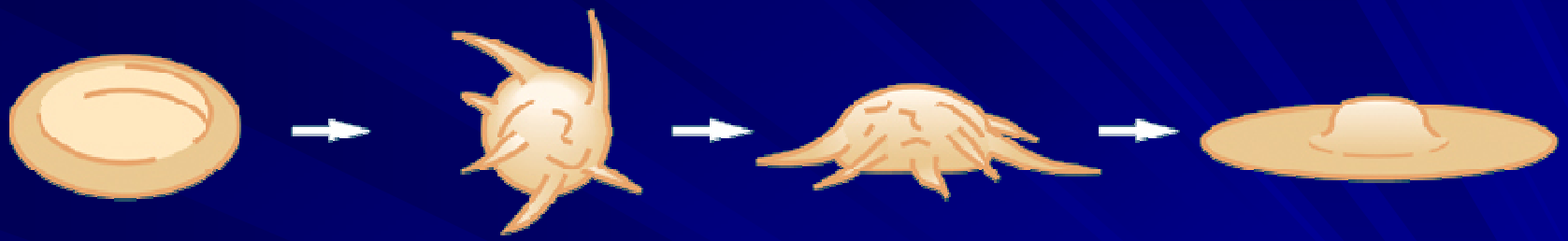
Platelet Adhesion

- Platelets are the first cells to adhere to injured vascular wall (subendothelium)
- Adhesion is mediated by vWF
- Binding occurs only under high shear stress conditions !

Platelet Activation



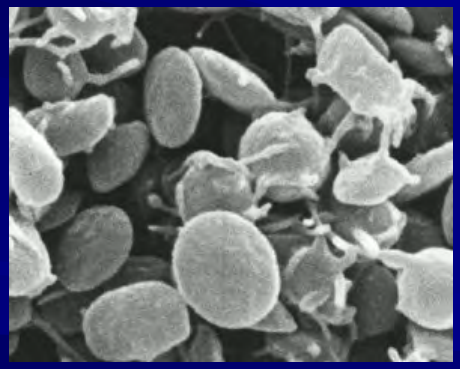
Platelet Aggregation



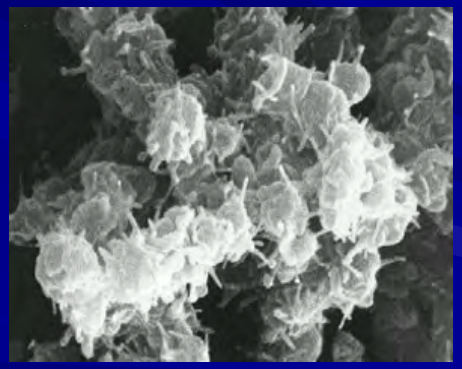
Flowing disc-shaped platelet → Rolling ball-shaped platelet → Hemisphere-shaped platelet → Spreading platelet

FIRM, BUT REVERSIBLE ADHESION

IRREVERSIBLE ADHESION



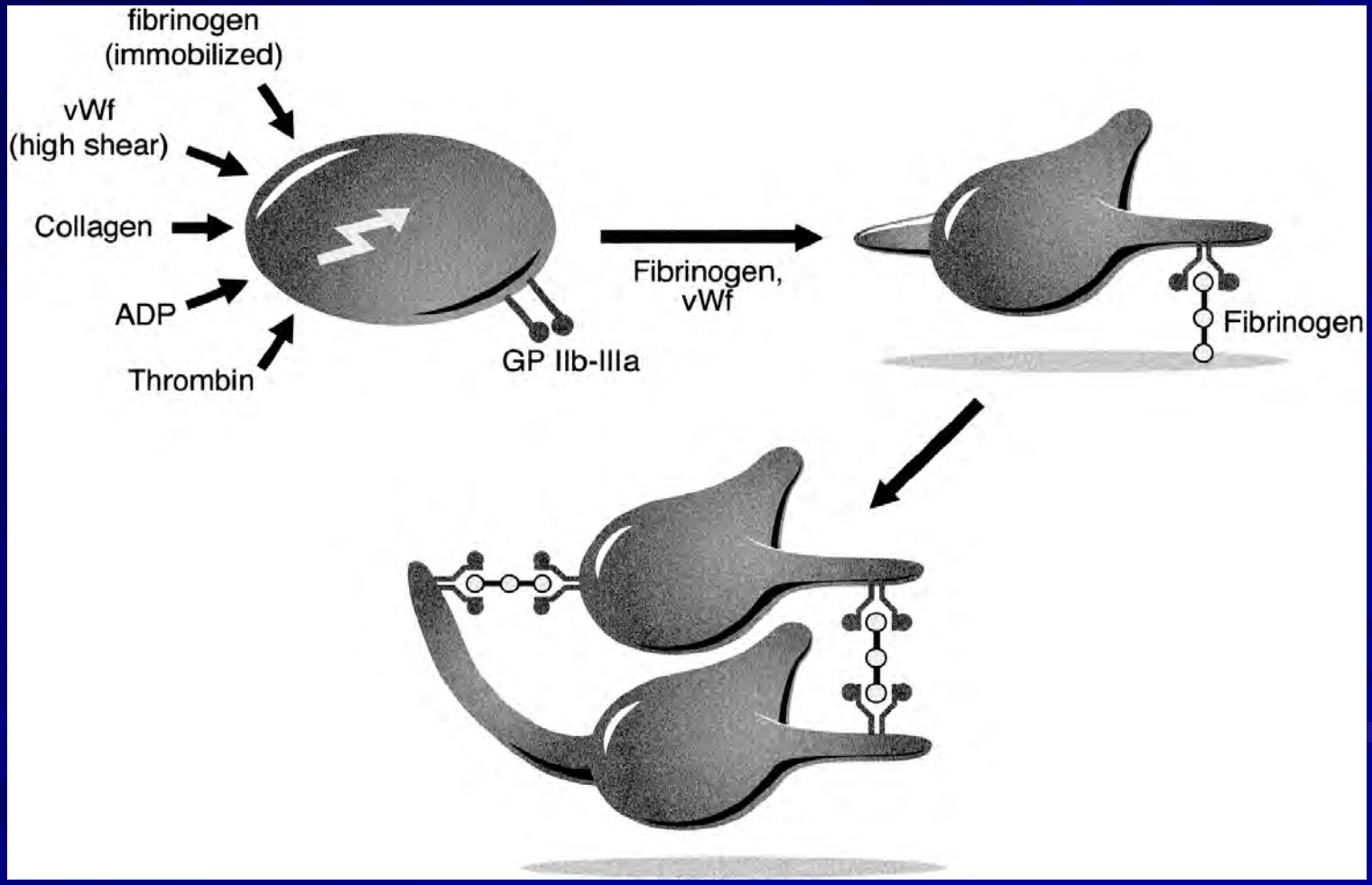
Scanning electron micrograph of discoid, dormant platelets



Activated, aggregating platelets illustrating fibrin strands

1. Kuwahara M *et al. Arterioscler Thromb Vasc Biol* 2002; 22: 329–34.

Platelet Aggregation



3 Major systems involved

- **Vessel wall**
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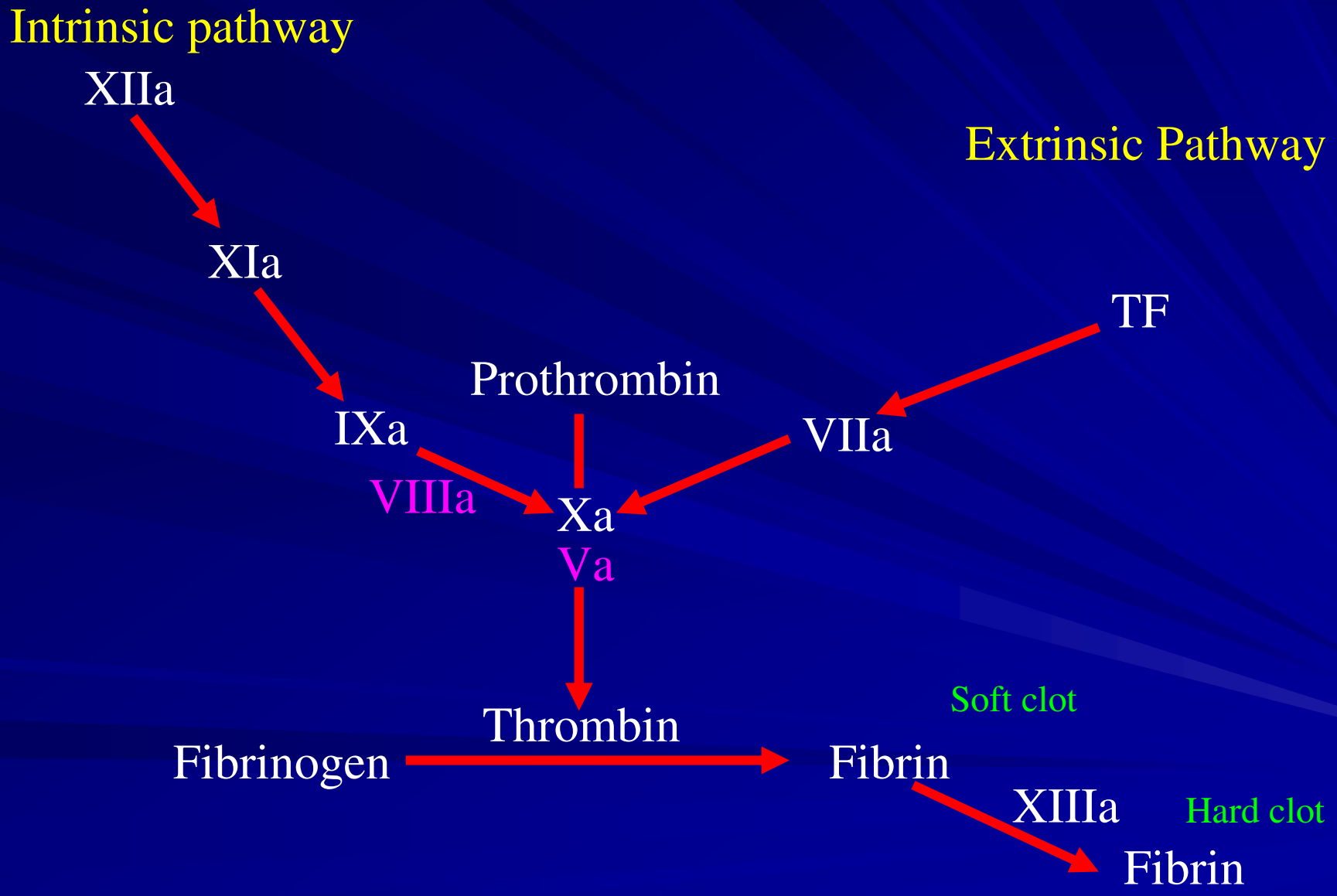
- **Coagulation cascade**

"Classic Coagulation Cascade"

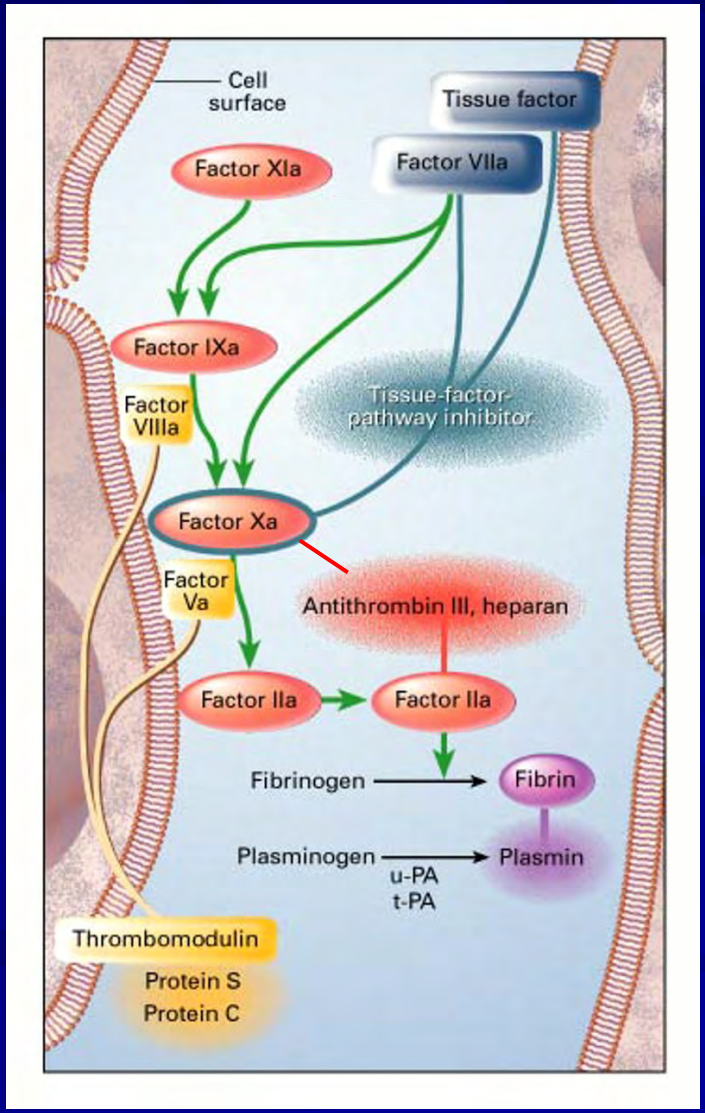


"Classic Coagulation Cascade"

- **Enzymatic cascade** (amplification)
- **Several serine protease complexes**
  - Produced by liver (most)
  - Several require Vit K (IIa, VIIa, IXa, Xa)
- **Requires Ca^{2+}**
- **Localized to site of injury**
- **Reversible (via production of plasmin)**

"Classic Coagulation Cascade"

Localization to sites of vascular injury. Protease complexes assemble on PL membranes of activated platelets, endothelial cells and monocytes. (The coagulation cascade occurs very slowly in fluid phase plasma and with resting cells)

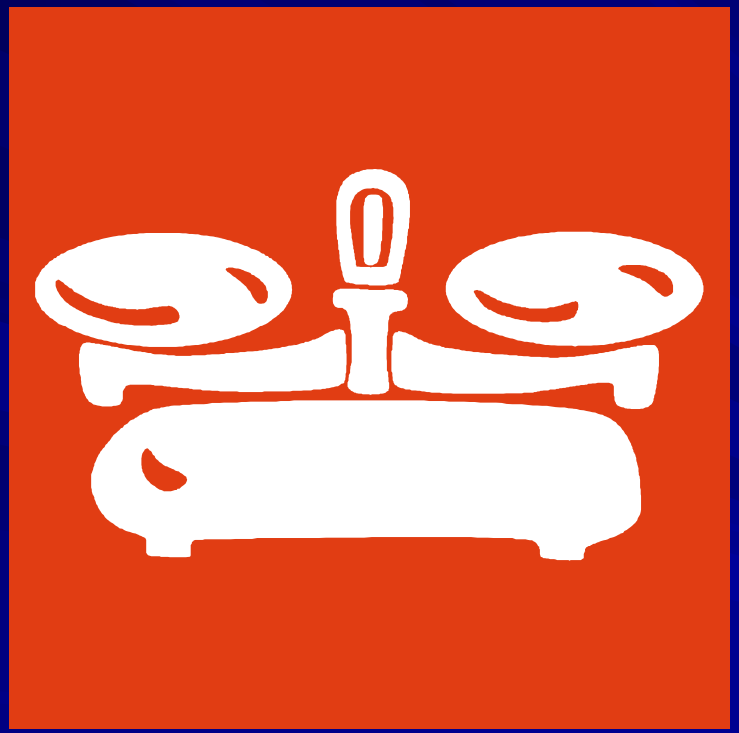


4 major Anti-thrombotic Pathways (TFPI, Prot C/S, ATIII, Plasmin)

Rosenberg et al NEJM 1999

“The Great Balance”

Thrombotic Complications

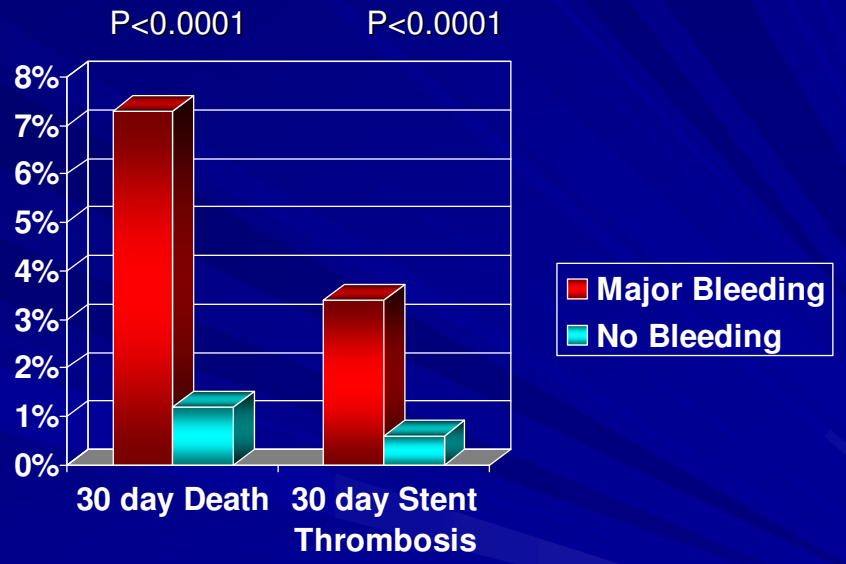


Bleeding Complications

Significance of Major Bleeding

- **ACUITY Trial:** bivalirudin vs. bivalirudin + GPIIb/IIIa inhibitors vs. heparin + GPIIb/IIIa inhibitors in 13,819 moderate-high risk ACS patients

- Major bleeding was an independent predictor of death at 30 days (OR 7.6 !! 95% CI 4.7-12.2, P<0.0001)



Manoukian et al, JACC 2007

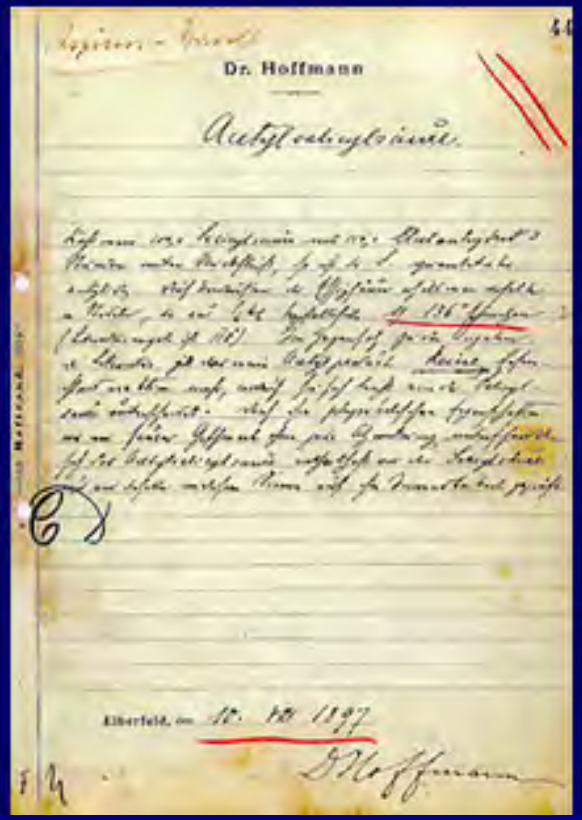
An original package of Bayer Aspirin sold in the United States from 1909.

Each pill is 5 grains, or ~ 325mg.

Developed by Felix Hoffrman, Bayer Co. , 1897

Aspirin

(From the German acetylspirsaure + chemical suffix – in)

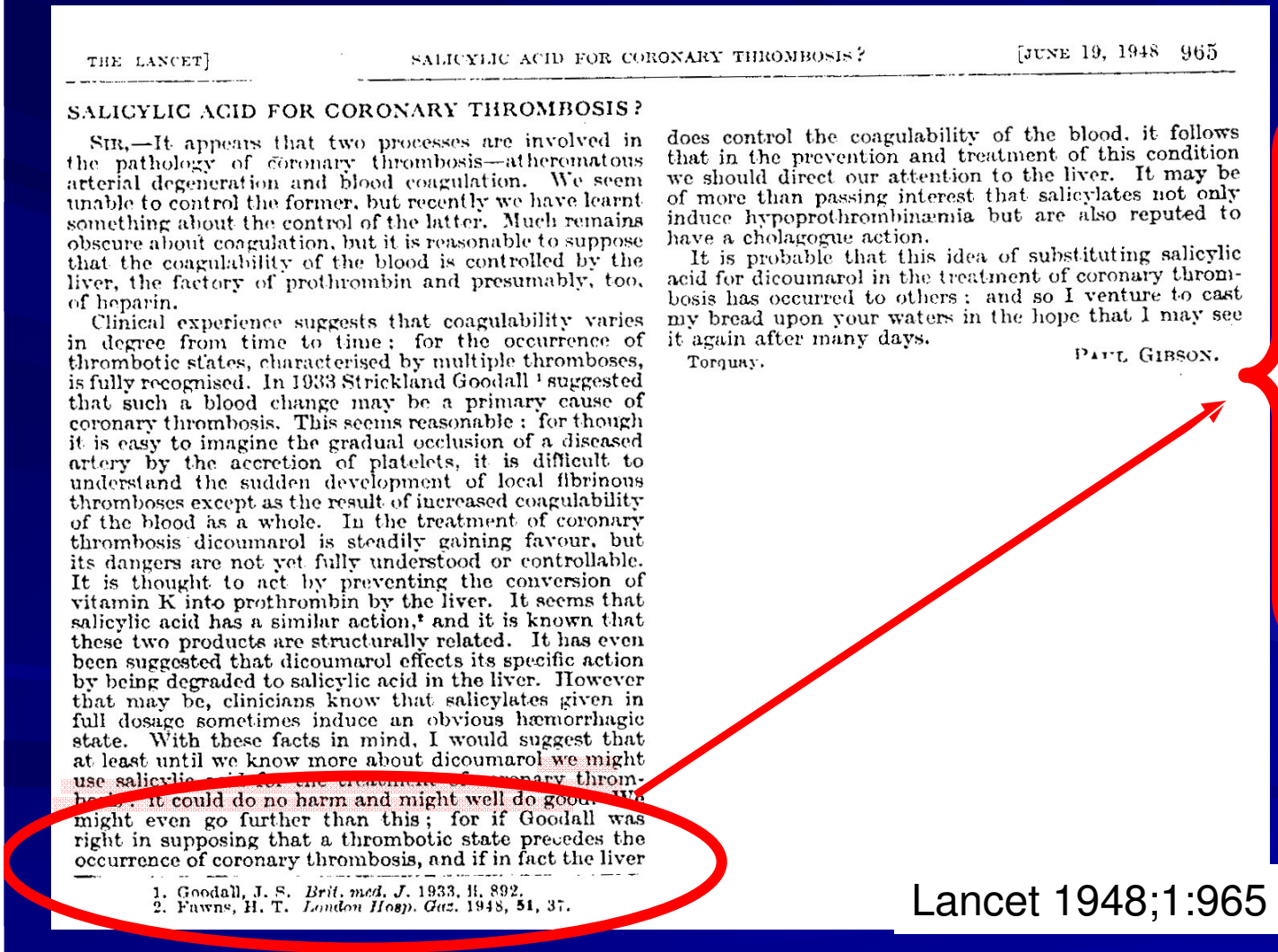

Dr. Hoffmann

Acetylsalicylsäure.

First synthesized in pure form by Felix Hoffman of Friedr. Bayer & Co. in 1897.

Courtesy of Dr S. Steinhubl, U. Kentucky

Early Citations Predicted the Value of Aspirin Therapy to Inhibit Platelet Aggregation



THE LANCET] SALICYLIC ACID FOR CORONARY THROMBOSIS? [JUNE 19, 1948 965

SALICYLIC ACID FOR CORONARY THROMBOSIS?

SIR,—It appears that two processes are involved in the pathology of coronary thrombosis—atheromatous arterial degeneration and blood coagulation. We seem unable to control the former, but recently we have learnt something about the control of the latter. Much remains obscure about coagulation, but it is reasonable to suppose that the coagulability of the blood is controlled by the liver, the factory of prothrombin and presumably, too, of heparin.

Clinical experience suggests that coagulability varies in degree from time to time; for the occurrence of thrombotic states, characterised by multiple thromboses, is fully recognised. In 1933 Strickland Goodall [1] suggested that such a blood change may be a primary cause of coronary thrombosis. This seems reasonable: for though it is easy to imagine the gradual occlusion of a diseased artery by the accretion of platelets, it is difficult to understand the sudden development of local fibrinous thromboses except as the result of increased coagulability of the blood as a whole. In the treatment of coronary thrombosis dicoumarol is steadily gaining favour, but its dangers are not yet fully understood or controllable. It is thought to act by preventing the conversion of vitamin K into prothrombin by the liver. It seems that salicylic acid has a similar action,[2] and it is known that these two products are structurally related. It has even been suggested that dicoumarol effects its specific action by being degraded to salicylic acid in the liver. However that may be, clinicians know that salicylates given in full dosage sometimes induce an obvious hæmorrhagic state. With these facts in mind, I would suggest that at least until we know more about dicoumarol we might use salicylic acid for the treatment of coronary thrombosis: it could do no harm and might well do good. We might even go further than this; for if Goodall was right in supposing that a thrombotic state precedes the occurrence of coronary thrombosis, and if in fact the liver does control the coagulability of the blood, it follows that in the prevention and treatment of this condition we should direct our attention to the liver. It may be of more than passing interest that salicylates not only induce hypoprothrombinæmia but are also reputed to have a cholagogue action.

It is probable that this idea of substituting salicylic acid for dicoumarol in the treatment of coronary thrombosis has occurred to others; and so I venture to cast my bread upon your waters in the hope that I may see it again after many days.

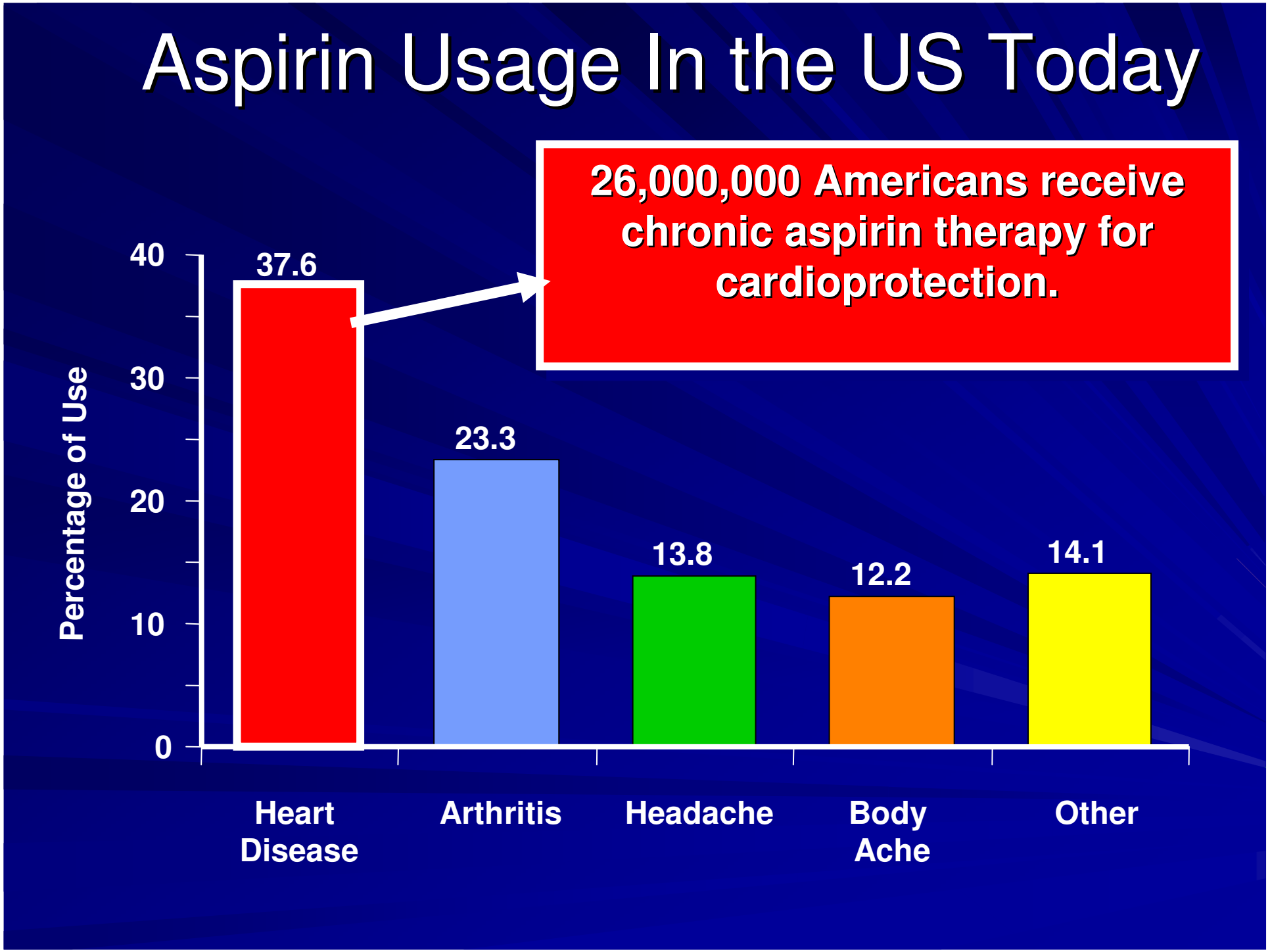
Torquay. PAUL GIBSON.

1. Goodall, J. S. *Brit. med. J.* 1933, ii, 892.
2. Fawns, H. T. *London Hosp. Gaz.* 1948, **51**, 37.

"...we might use salicylic acid for the treatment of coronary thrombosis: it could do no harm and might well do good."

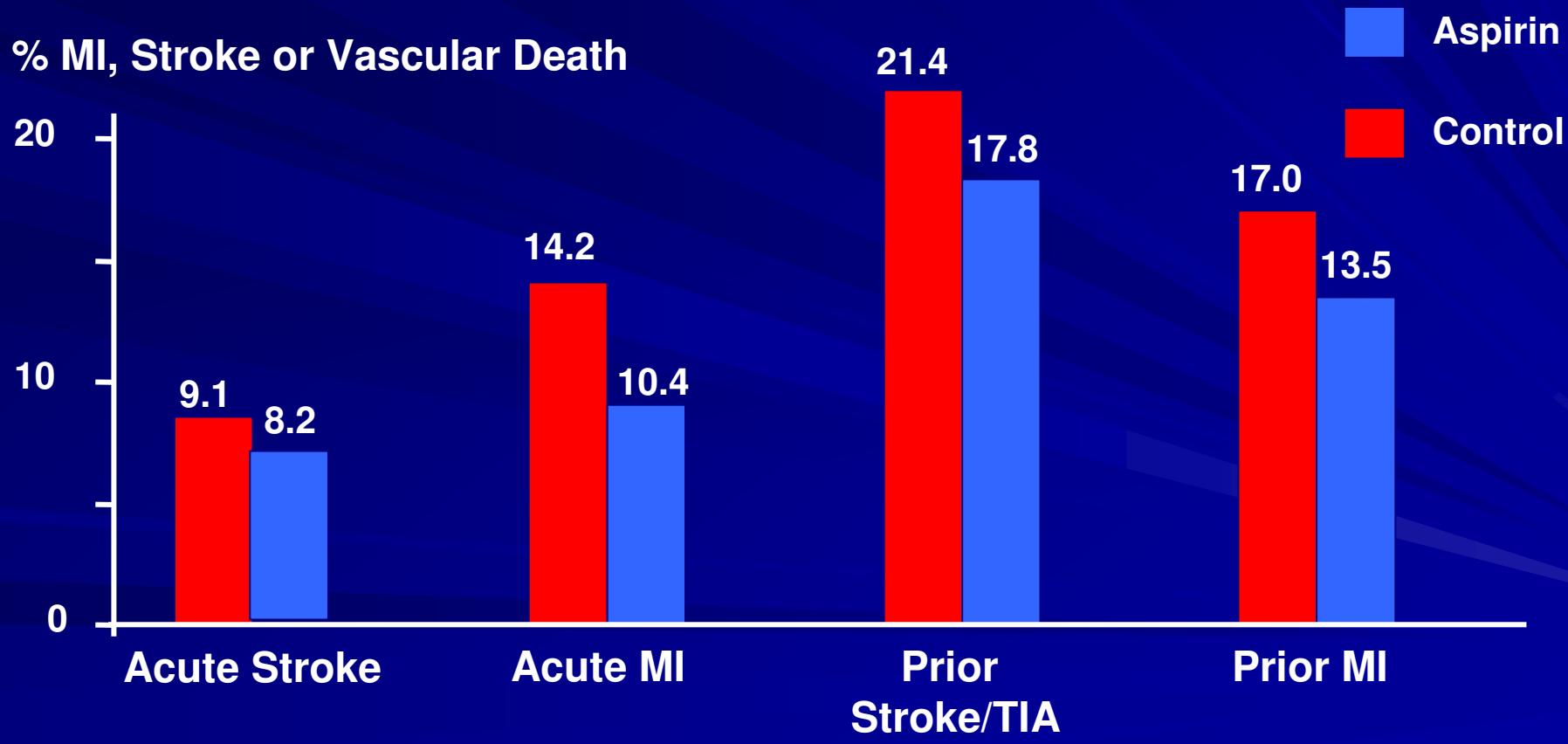
Lancet 1948;1:965

Aspirin Usage In the US Today



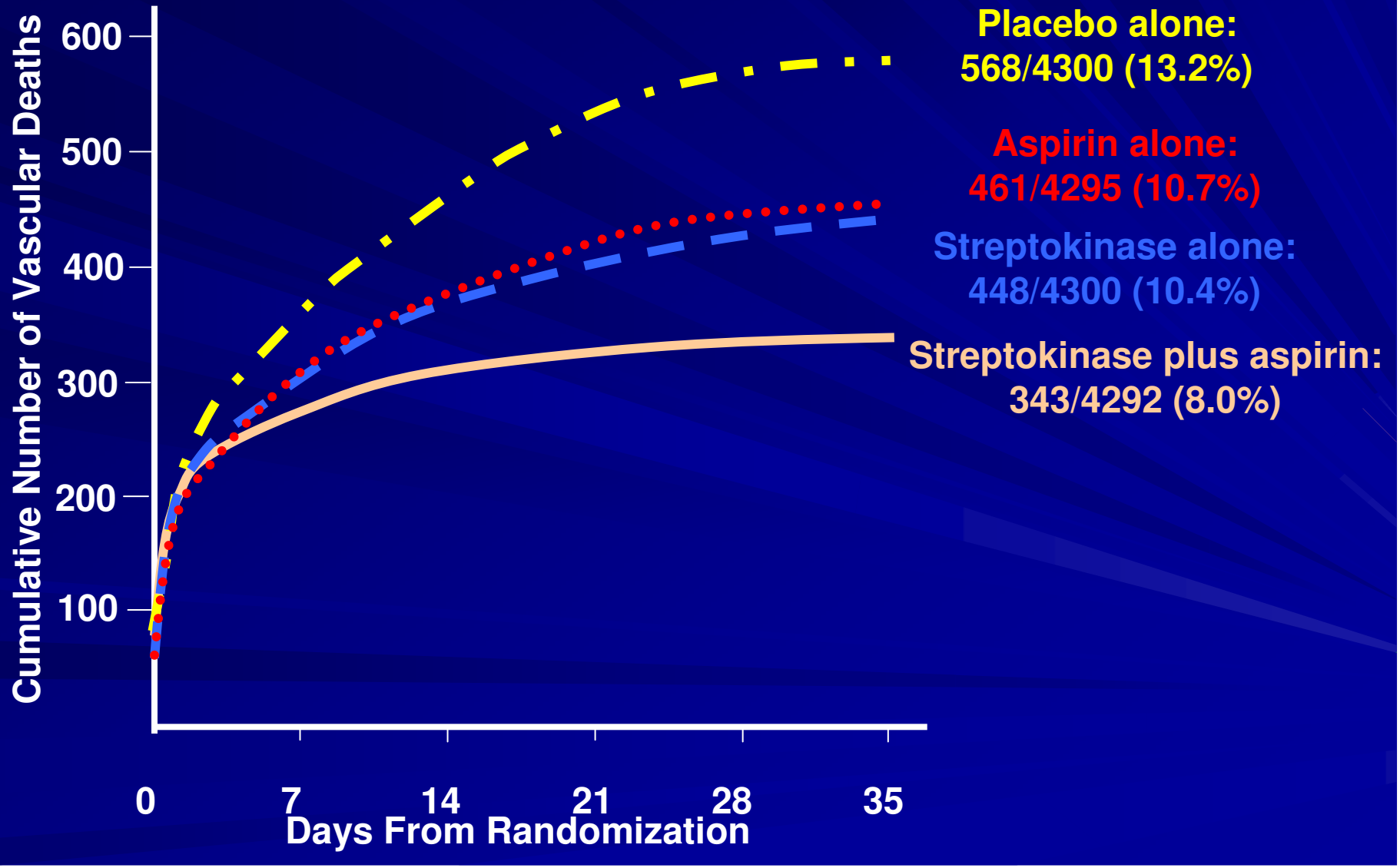
Antithrombotic Trialists' Collaboration

Overview of 195 randomized trials, including 212,000 patients (135,640 high-risk). Overall odds reduction 22%.

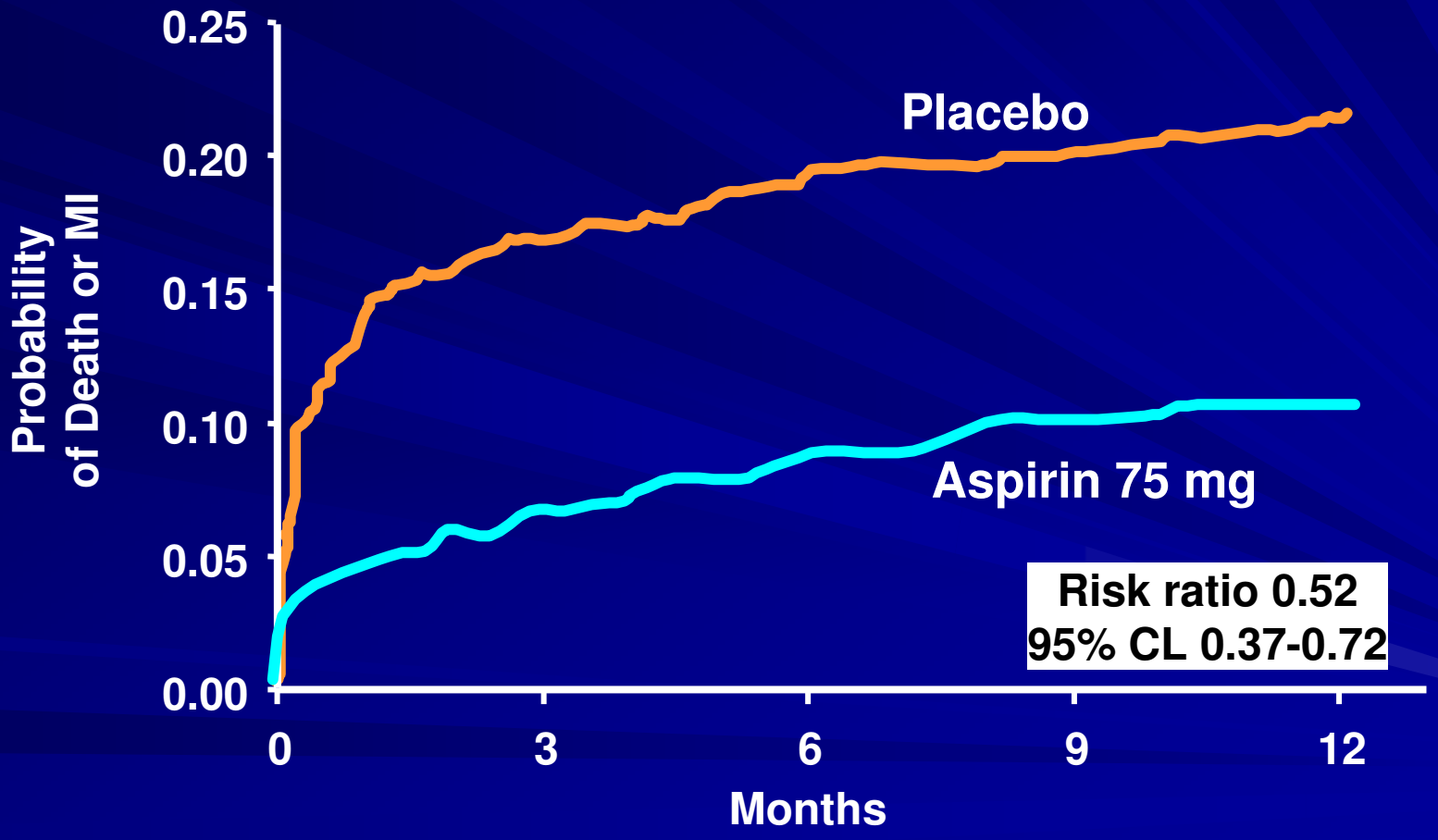


Antithrombotic Trialists' Collaboration. *BMJ* 2002; 324: 71–86.

Aspirin in Acute Myocardial Infarction: ISIS-2 (Lancet 1988;2:349-60)



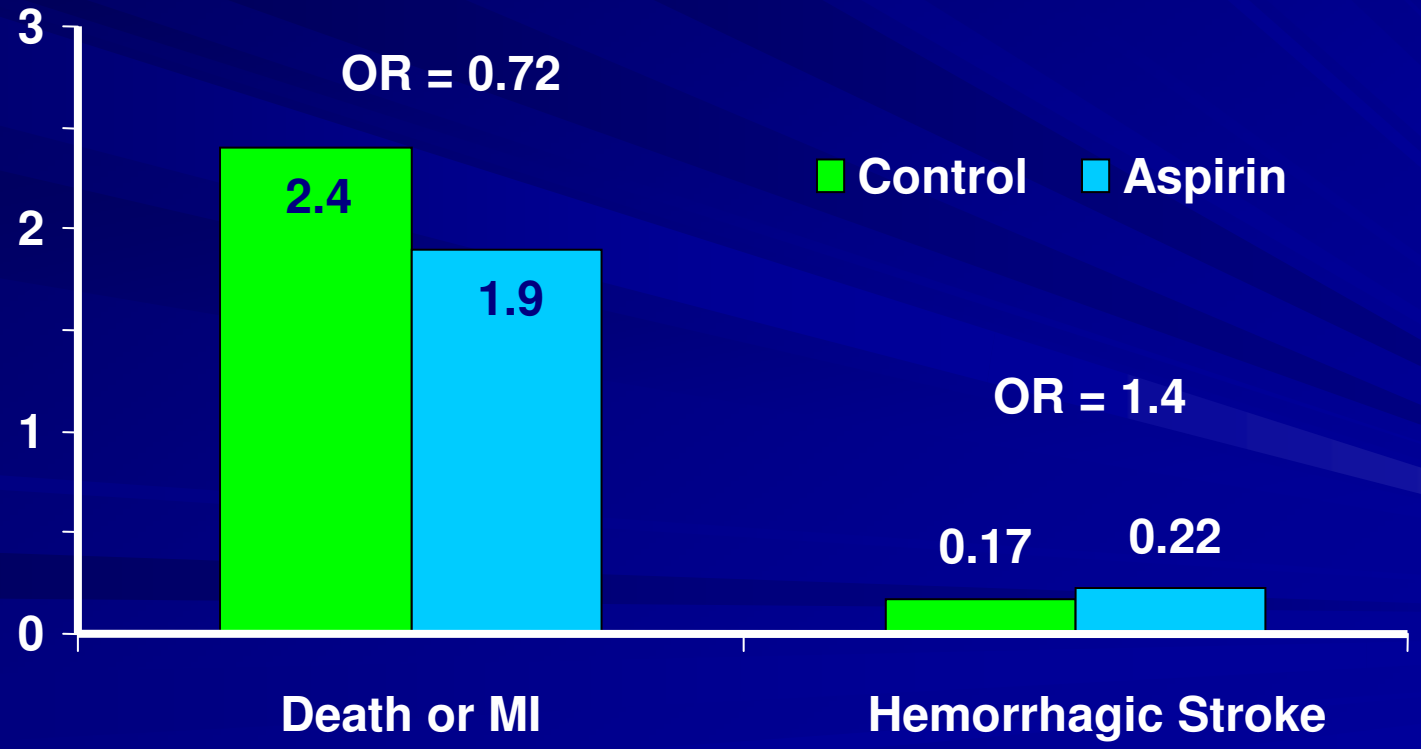
Aspirin in the Treatment of ACS



Wallentin LC, et al. JACC 1991;18:1587-93.

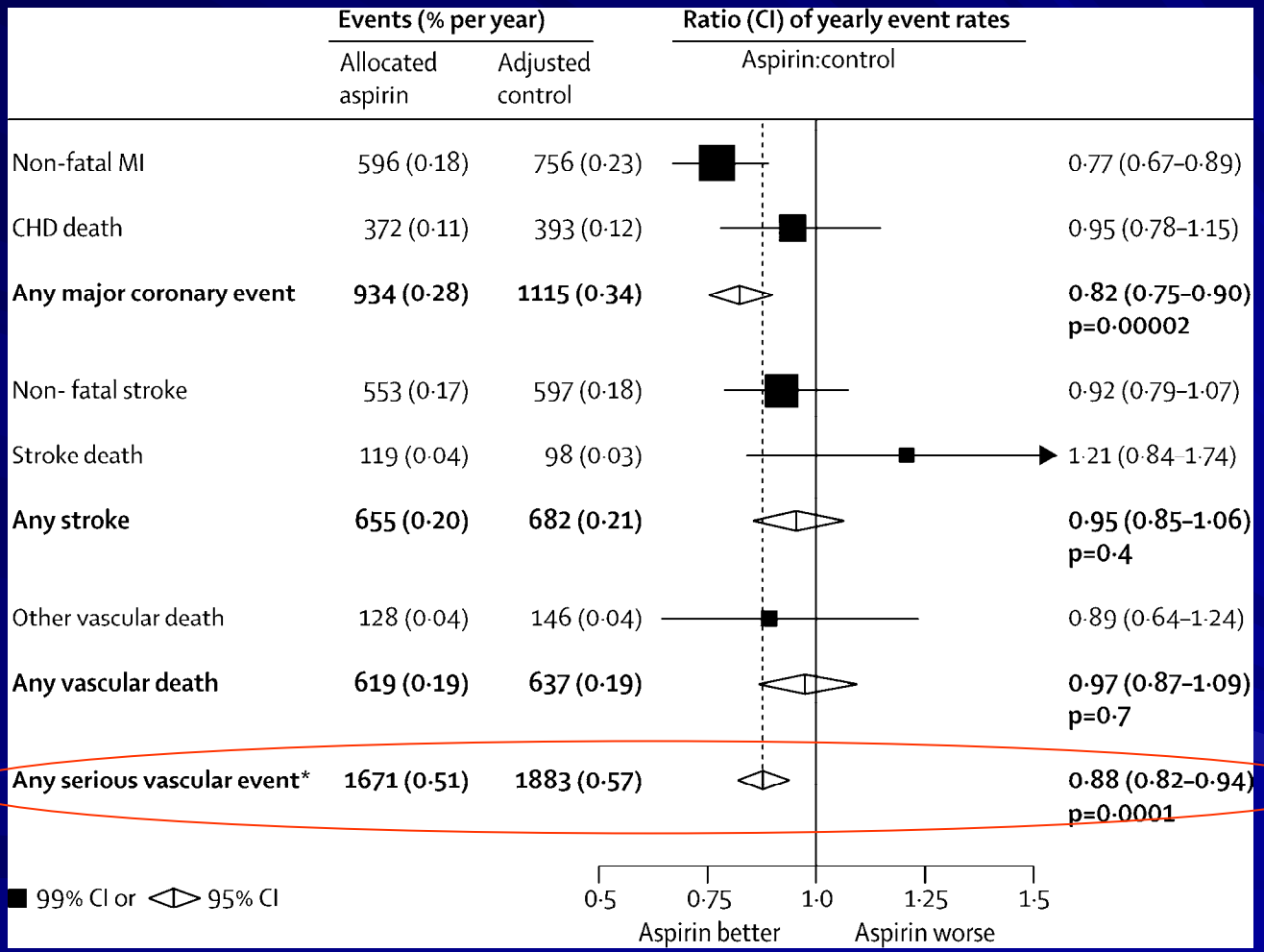
Aspirin in Primary Prevention

Data from 5 randomized trials, with over 50,000 individuals, with doses of 75 – 500 mg daily, 3-7 years f/u.



ATT Collaboration – Lancet 2009

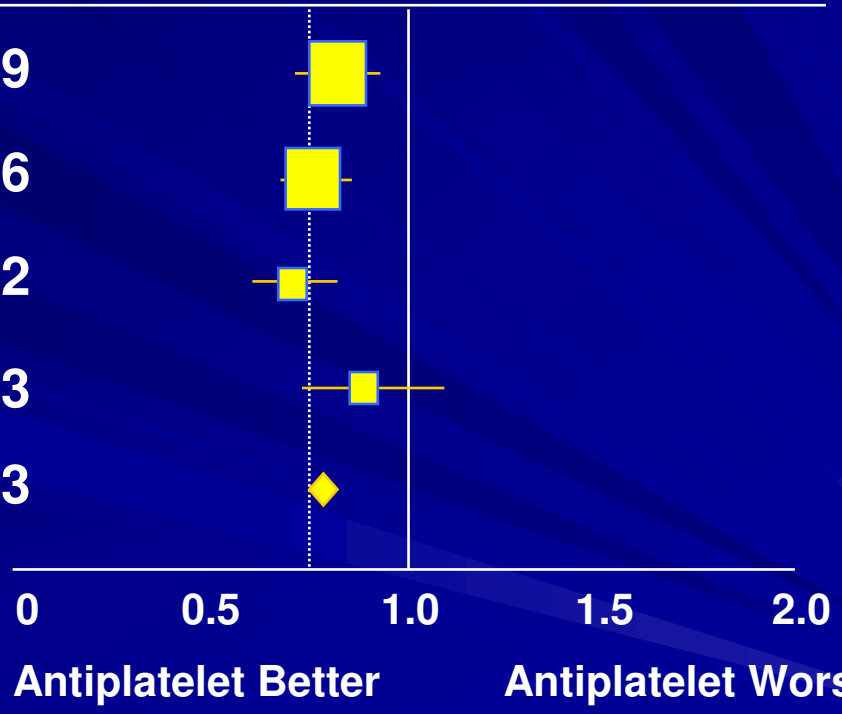
6 primary prevention trials



12% proportional reduction in serious vascular events

Comparison of ASA Doses on Vascular Events in High-Risk Patients

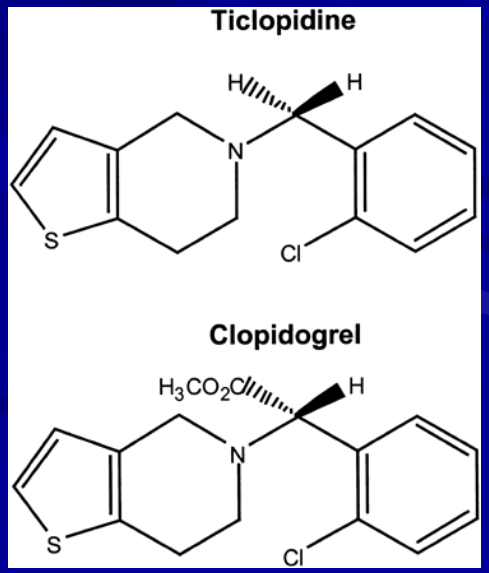
Aspirin Dose	No. of Trials	OR* (%)
500-1500 mg	34	19
160-325 mg	19	26
75-150 mg	12	32
<75 mg	3	13
Any aspirin	65	23



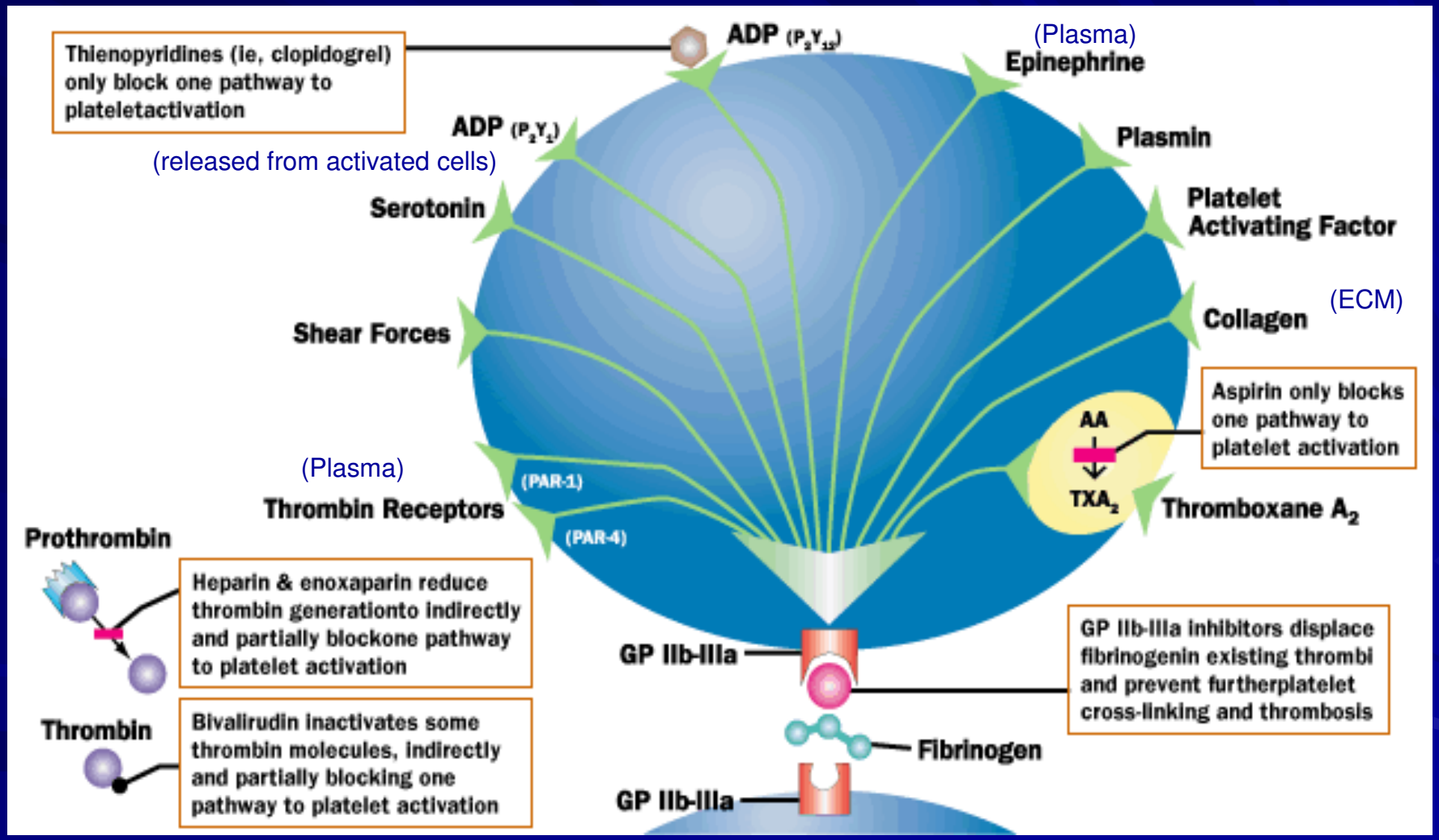
* Odds reduction.
Treatment effect *P*<.0001.
ASA, acetylsalicylic acid.
Adapted with permission from BMJ Publishing Group. Antithrombotic Trialists' Collaboration. *BMJ.* 2002;324:71-86.

CLOPIDOGREL (PLAVIX)

- A thienopyridine , inhibits ADP induced platelet aggregation
- The specific target of inhibition appears to be the $P2Y_{12}$ receptor
- Fewer side effects than ticlopidine



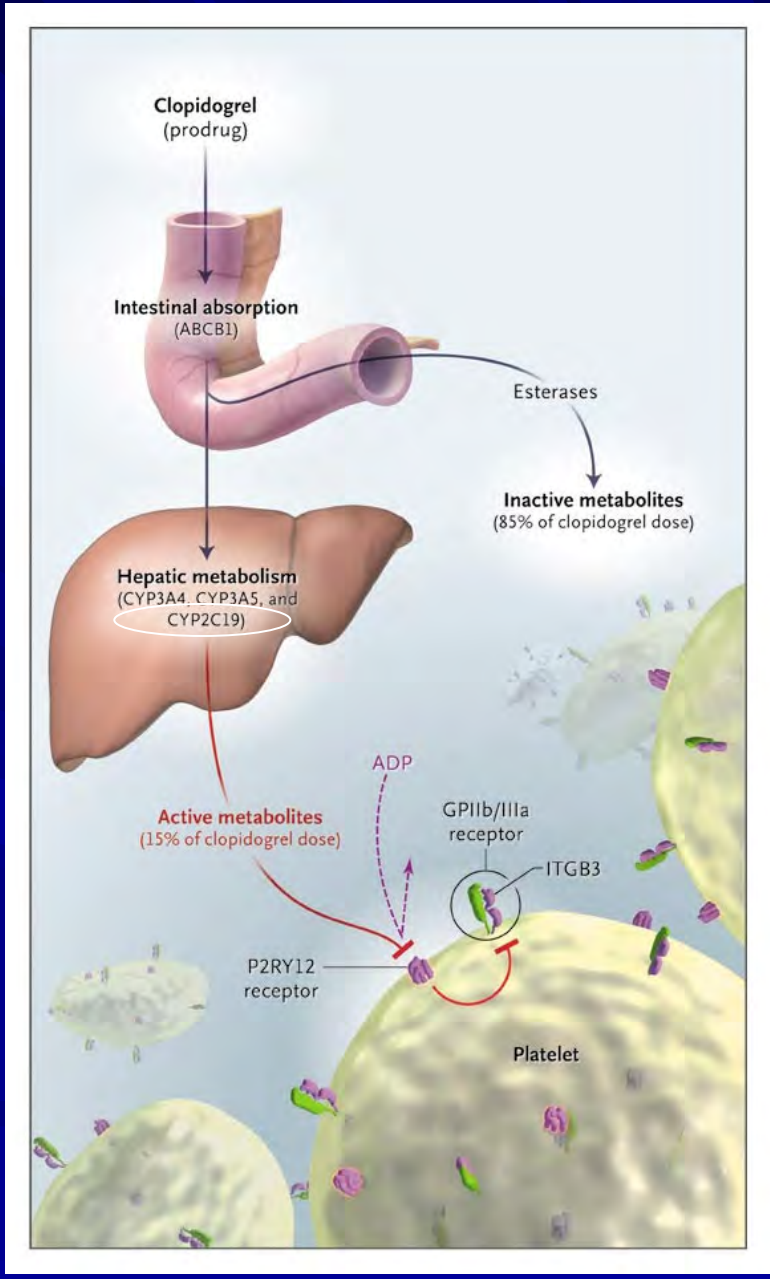
Platelet Activation



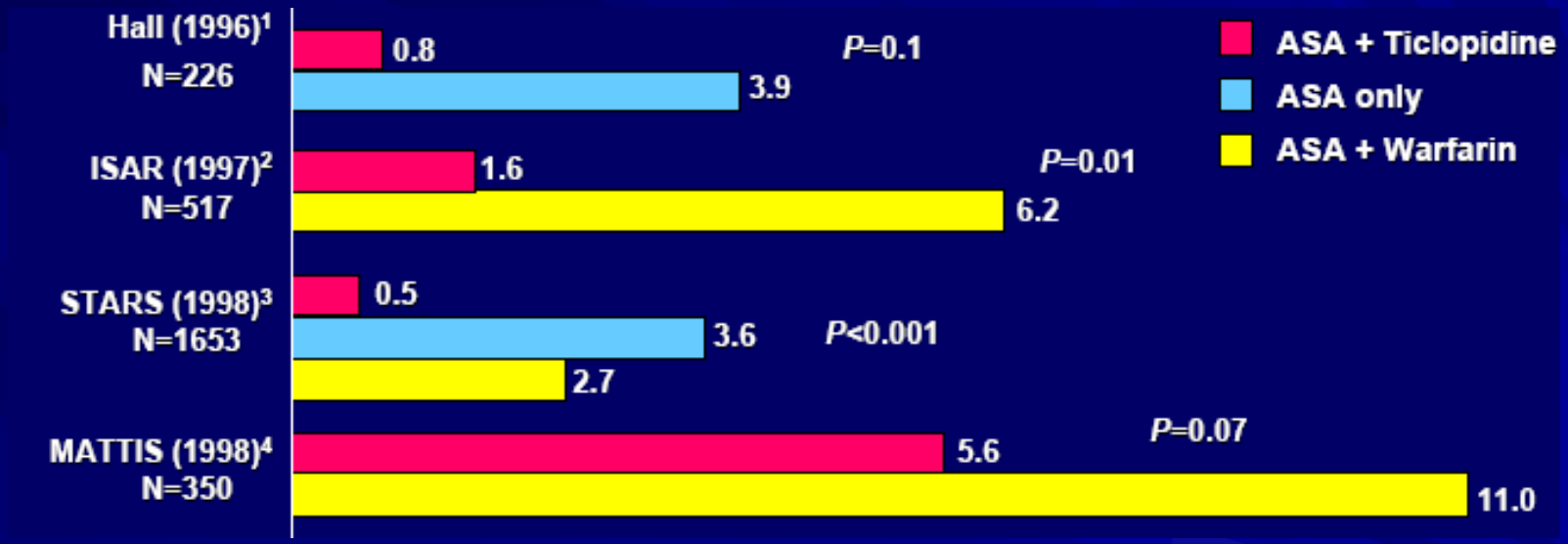
Pharmacokinetic properties

- Requires metabolism by the hepatic cytochrome P450-1A enzyme system to acquire activity
- Peak plasma concentrations of the main circulating metabolite, an inactive carboxylic acid derivative occur at 1 hour.
- Platelet inhibition effect of 600 mg bolus after ~2-4 hrs, of 300 mg bolus after ~6 hrs

Clopidogrel metabolism

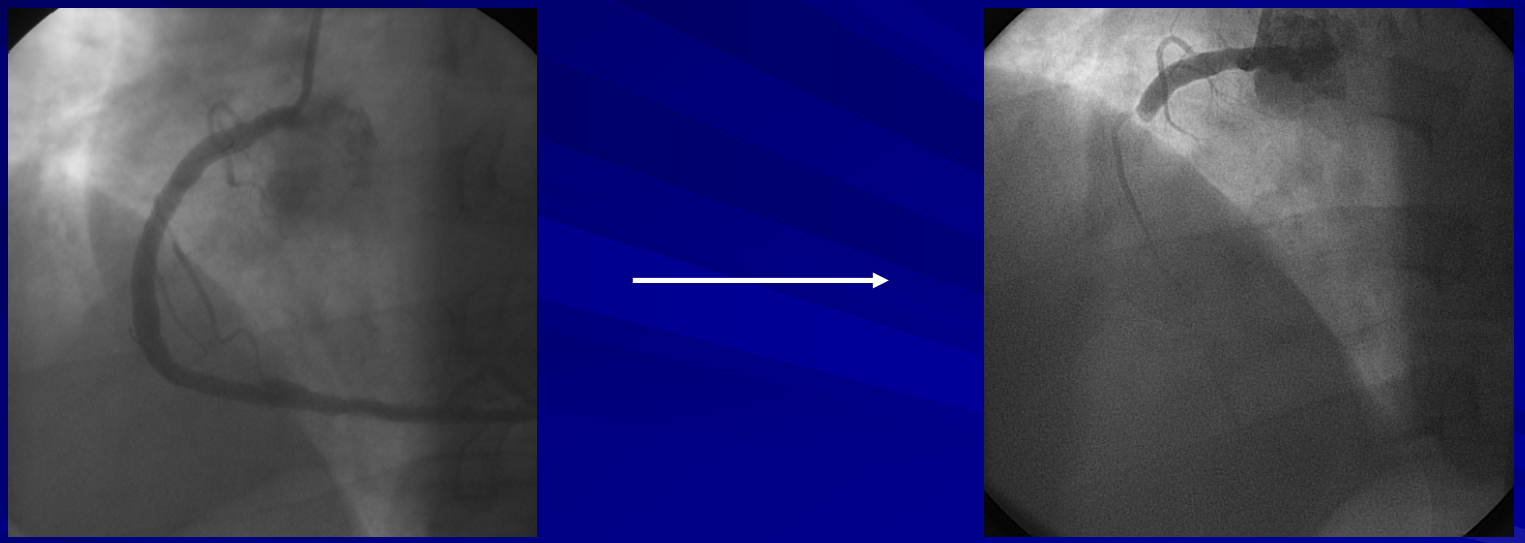


Efficacy of anti-platelet agents in reducing coronary events after stenting

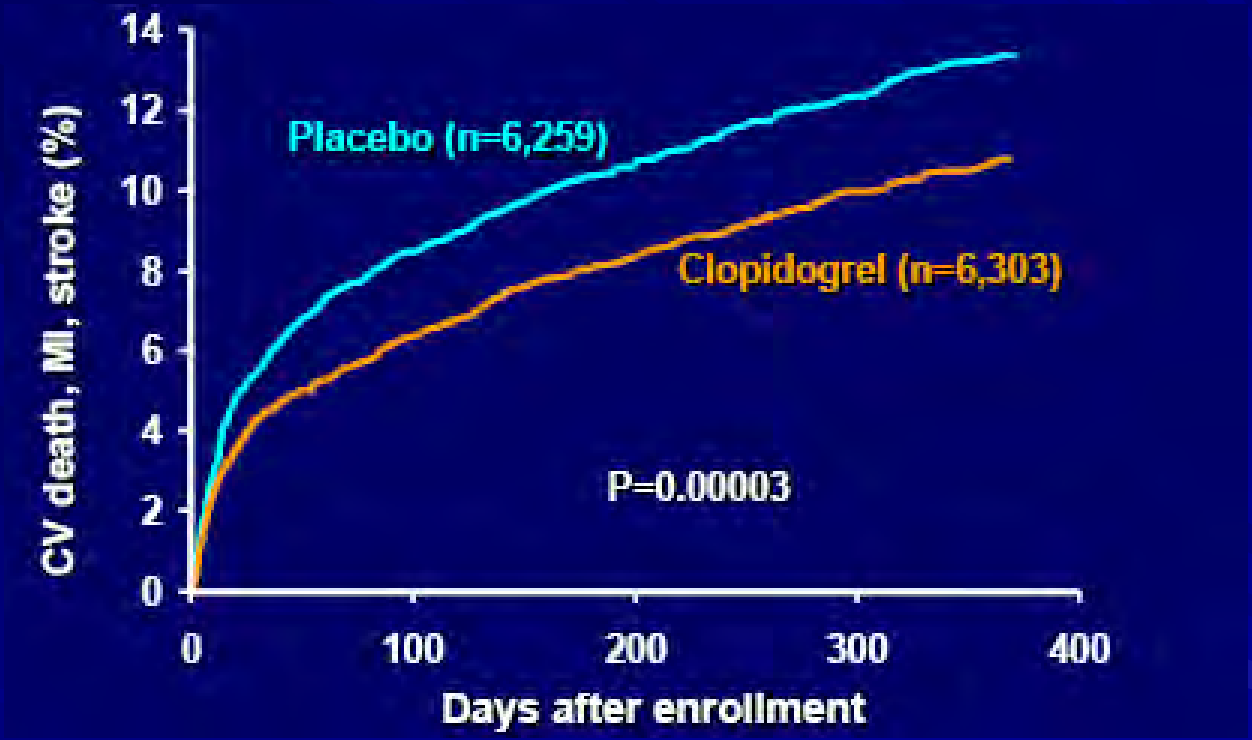


[1] Hall P, et al. *Circulation*. 1996;93:215-222.
[2] Schömig A, et al. *N Engl J Med*. 1996;335:1084-
[3] Leon M, et al. *N Engl J Med*. 1998:339:1665-71
[4] Urban P. et al. *Circulation*. 1998 98:2126-2132.

Stent Thrombosis

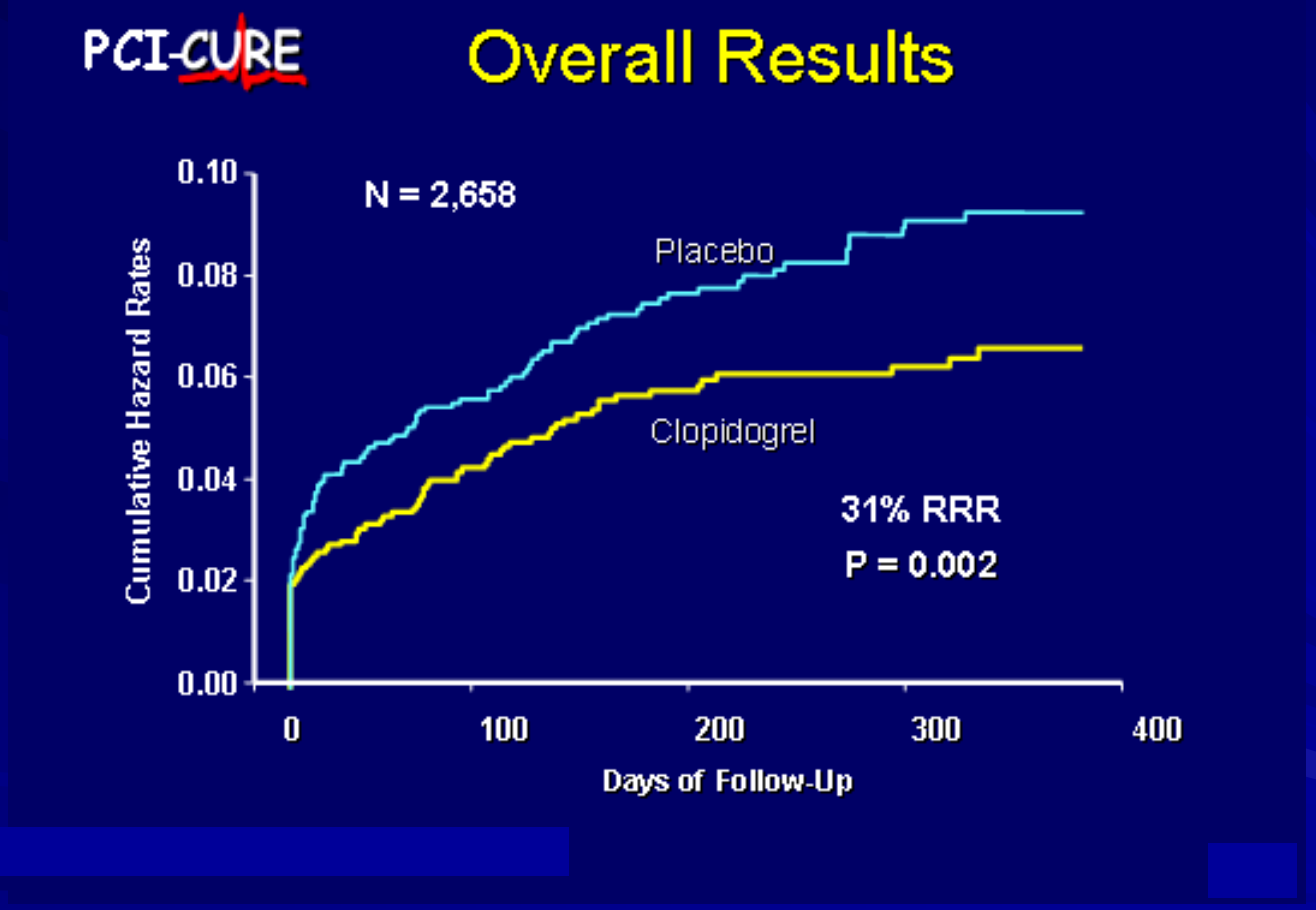


CURE TRIAL – ACS pts



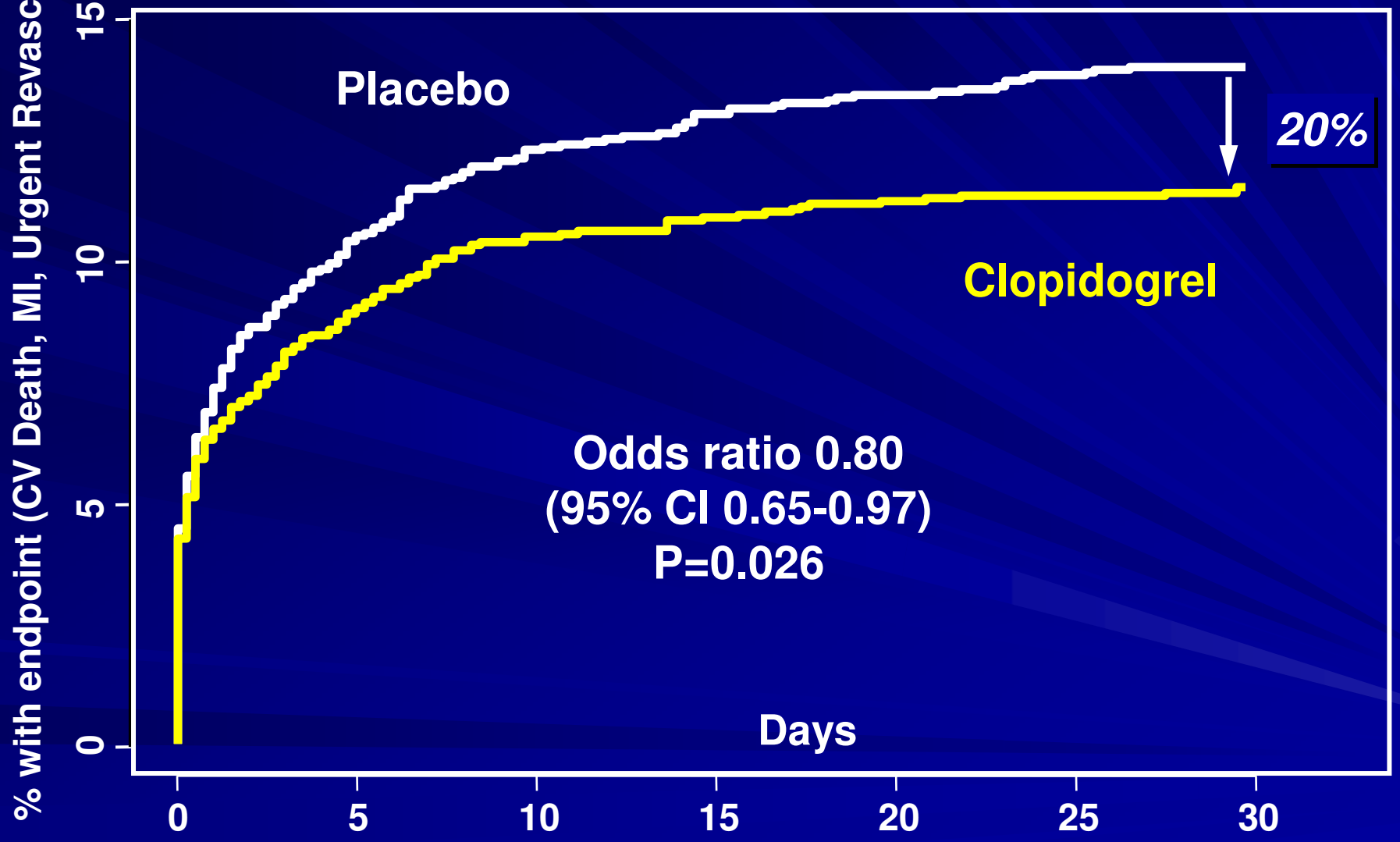
20 % reduction in primary endpoint (N Engl J Med. 2001;345:494-502)

PCI-CURE TRIAL – ACS pts



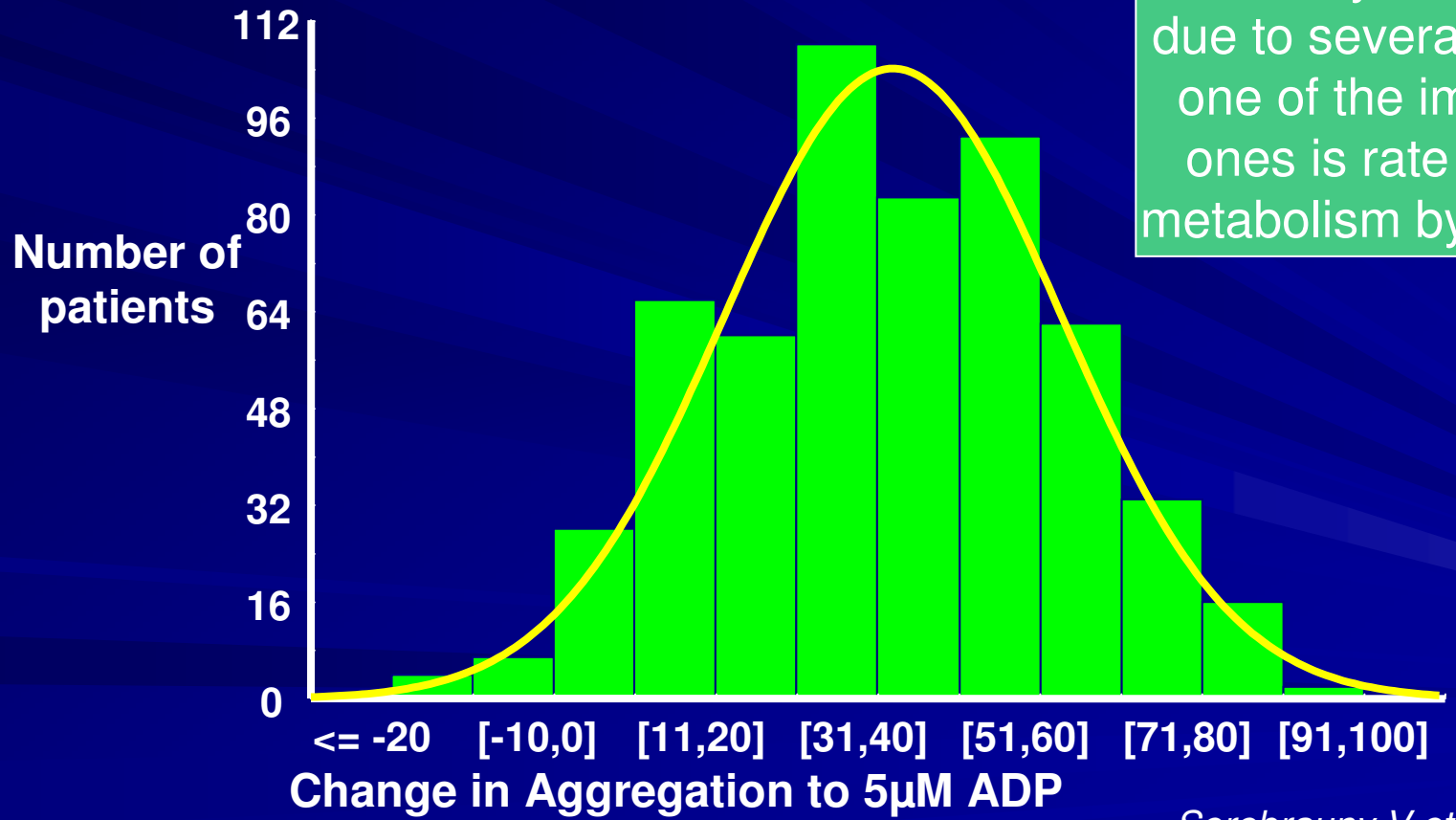
Pretreatment with clopidogrel vs. no pretreatment
Reduction in CV death, MI or urgent TVR
CURE Investigatots, Lancet 2001 358: 527-33

CLARITY TRIAL – STEMI pts



Sabatine et al. *N Engl J Med* 2005;352:1179-1189.

Distribution of Response to **Clopidogrel**
(544 patients, platelet aggregation)

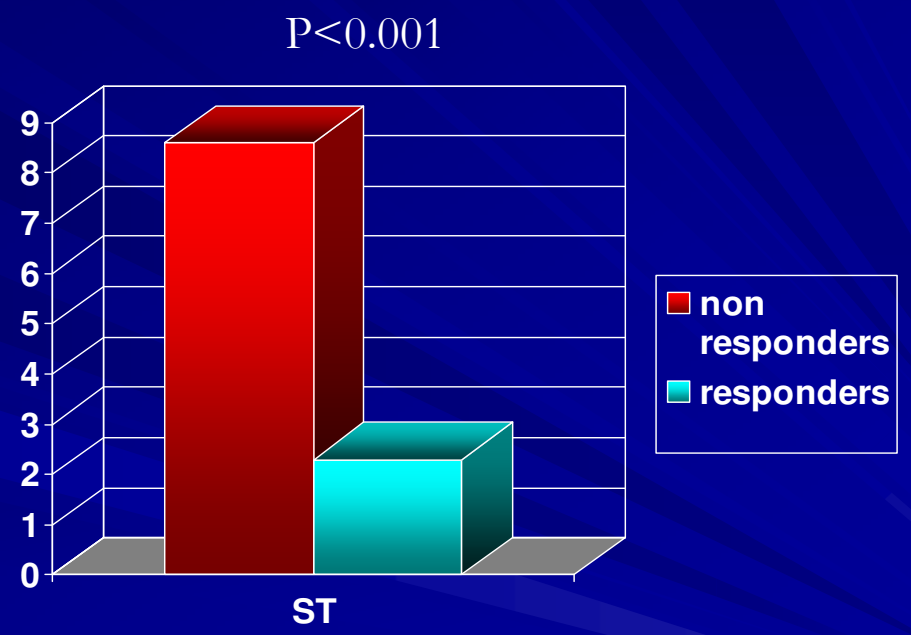


Variability in response due to several factors - one of the important ones is rate of drug metabolism by cyt. P450

Serebrauny V et al. JACC 2004

Impact of Clopidogrel Response on Stent Thrombosis

- 804 pts who had successful PCI with DES implantation
- Loaded with 600 mg clopidogrel, platelet reactivity to ADP assessed 12-18 hrs after loading
- 105 pts (13%) not responsive to clopidogrel
- **ST incidence: 8.6% vs. 2.3%** **(non responders vs responders)**



Buonamici et al , JACC 2007

Prasugrel: Active Metabolite Formation Faster Onset of IPA

Sem Vasc Med 3:113, 2003

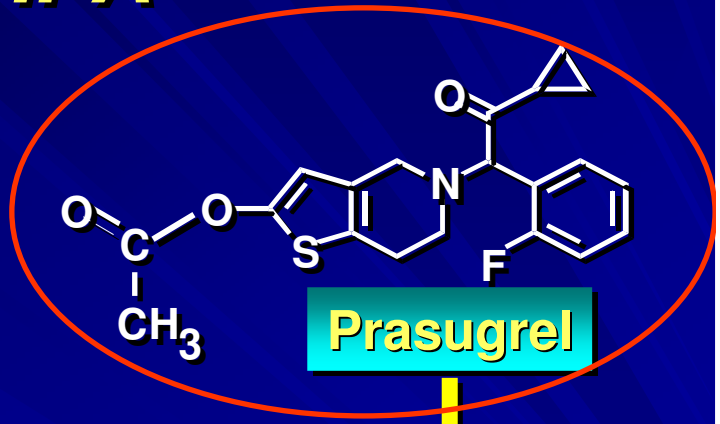
Clopidogrel

85% Inactive Metabolites (hydrolysis)

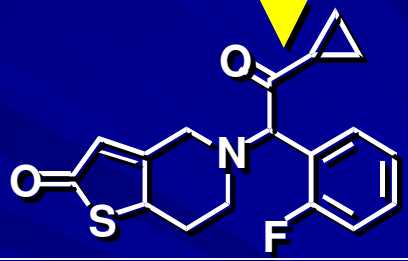
Pro-drug

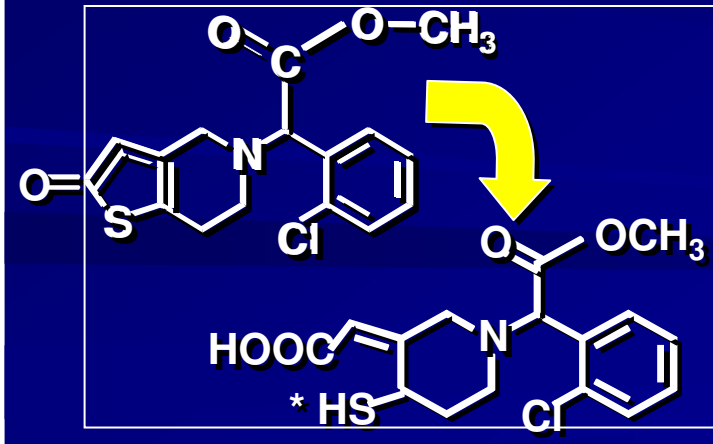
Pre-hepatic metabolism - Hydrolysis

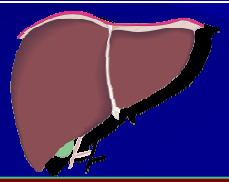
Esterases in blood



Prasugrel



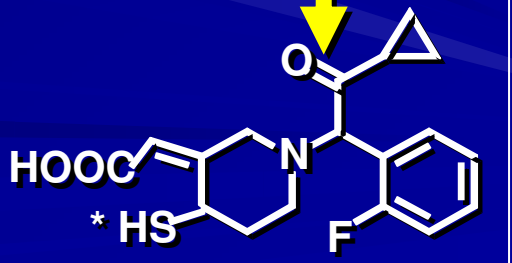




Hepatic Metabolism

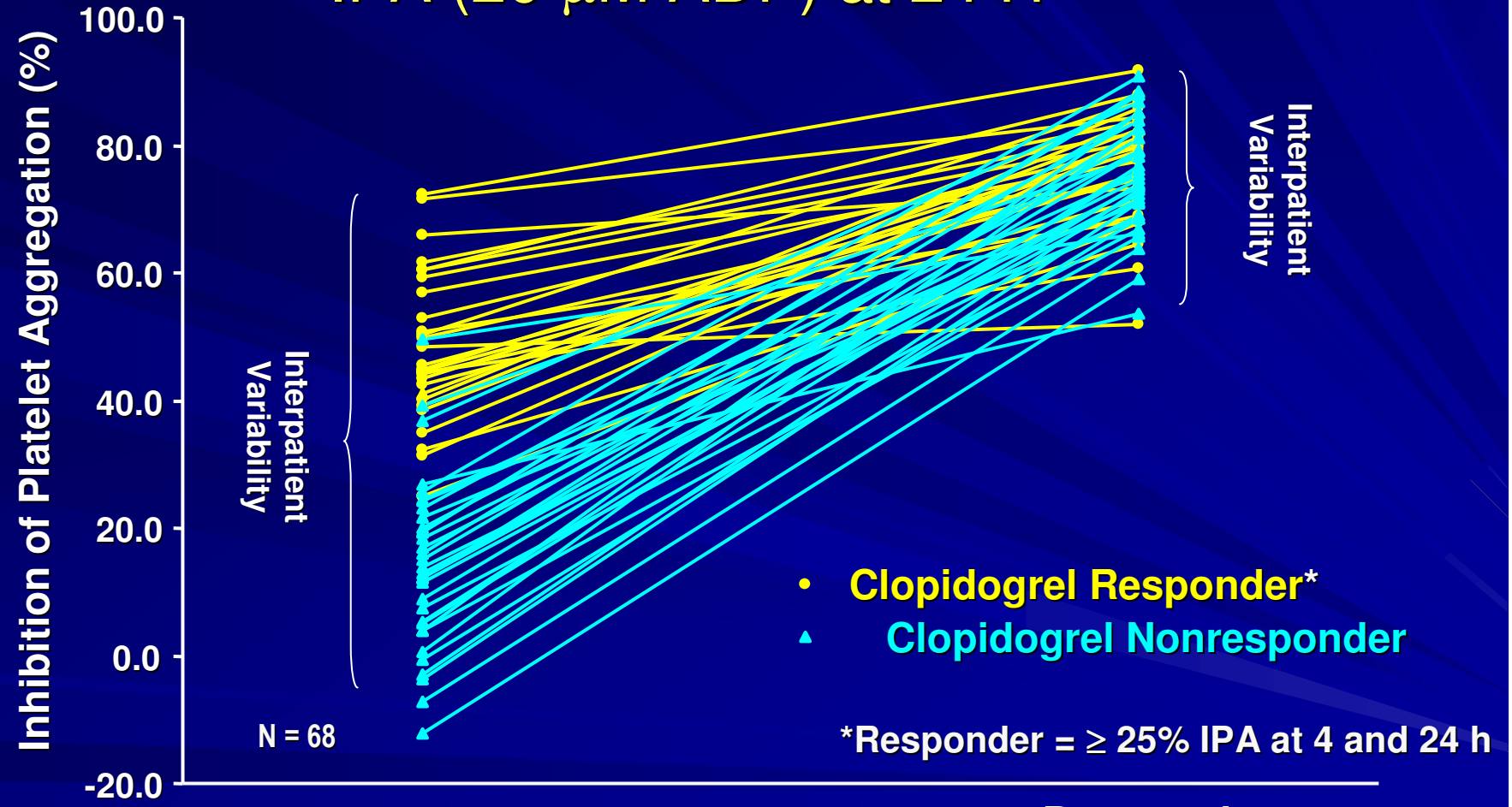
Cytochrome P450

Active Metabolite



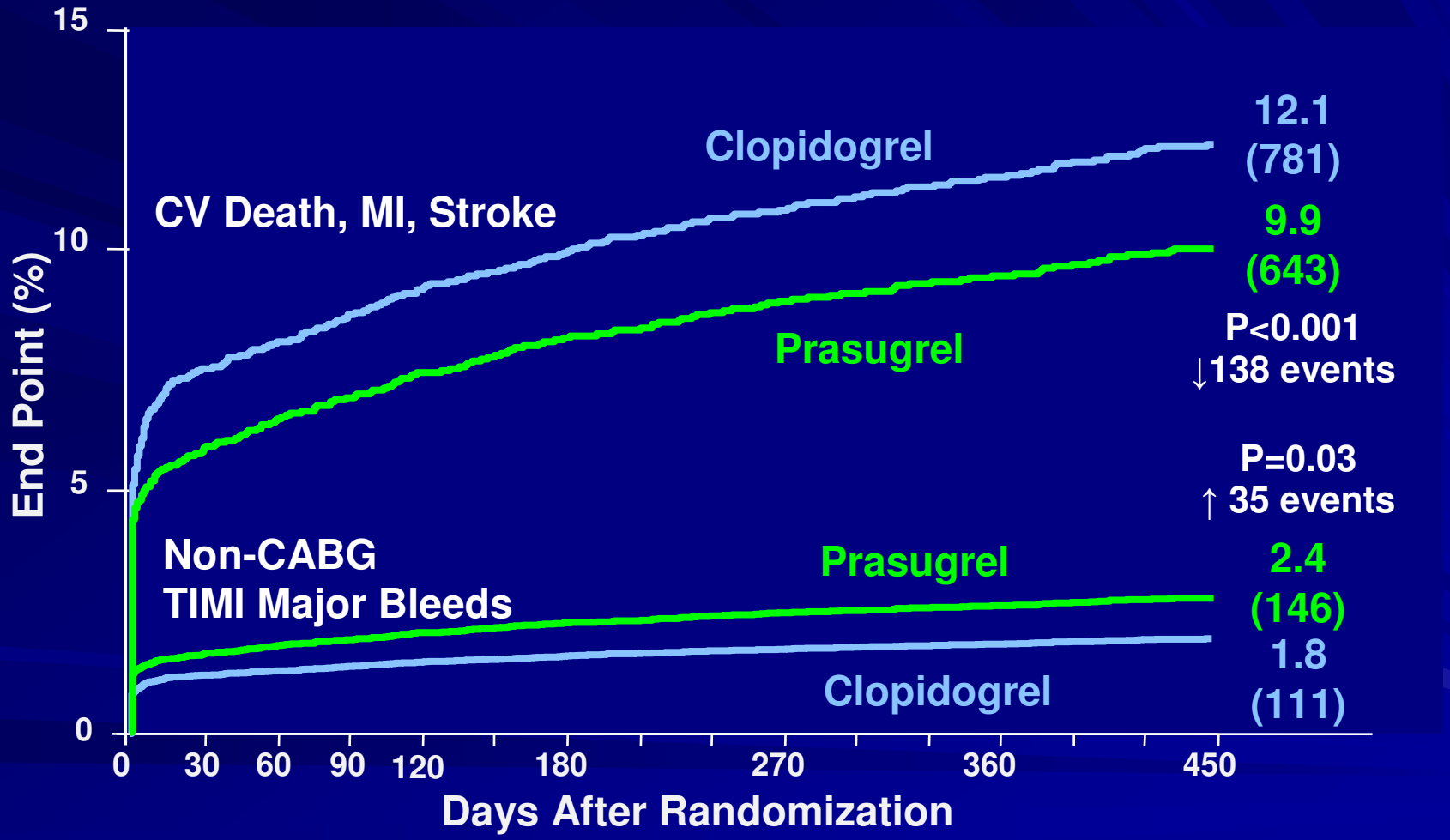
Healthy Volunteer Crossover Study (n=68)

IPA (20 μM ADP) at 24 H



Brandt J et al. AHJ 2007

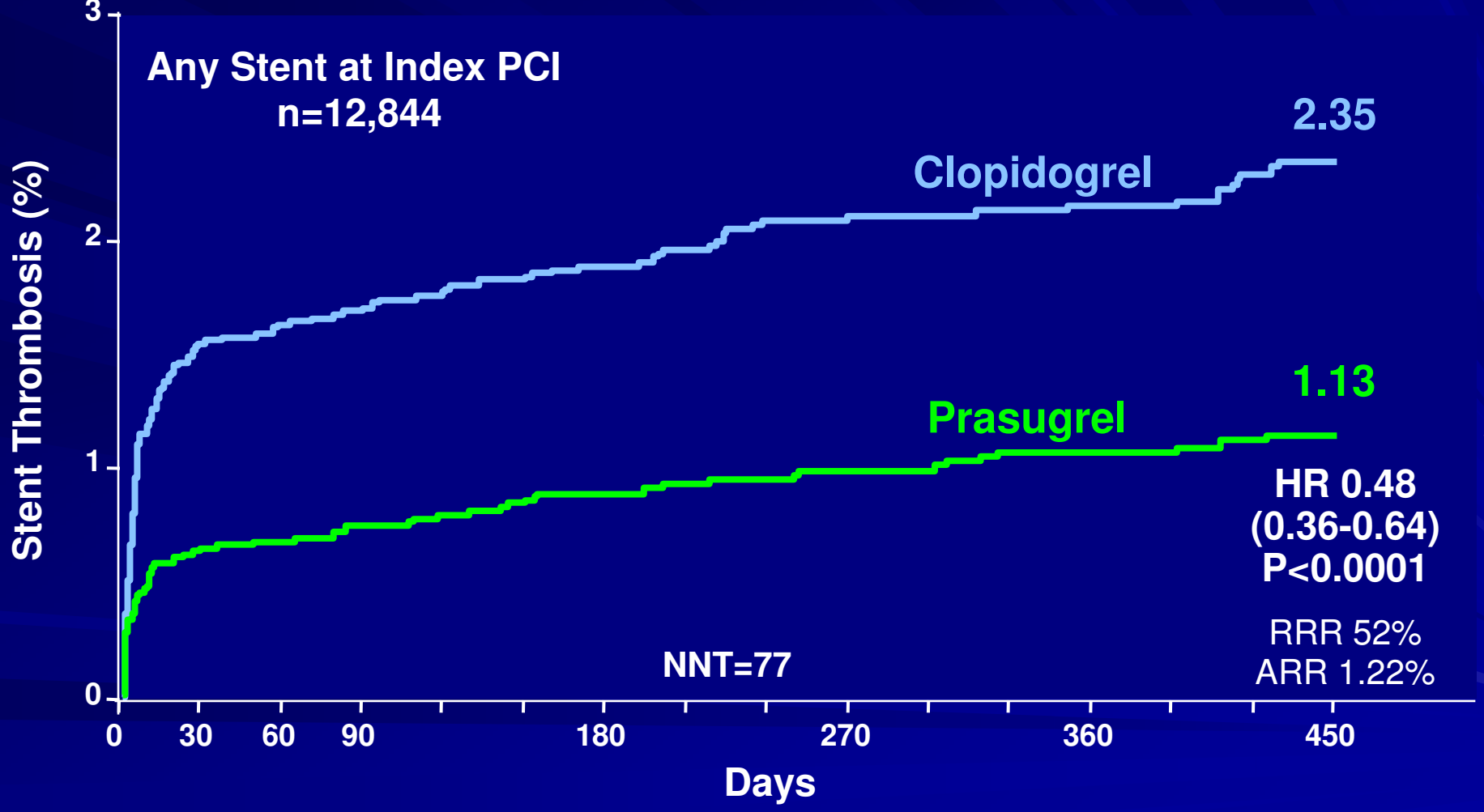
TRITON-TIMI 38: Rates of Key Study End Points (13,500 pts with ACS)



CABG=Coronary Artery Bypass Graft surgery; CV=Cardiovascular; MI=Myocardial Infarction; TIMI=Thrombolysis In Myocardial Infarction

Wiviott SD et al. *New Engl J Med* 2007;357:2001-2015

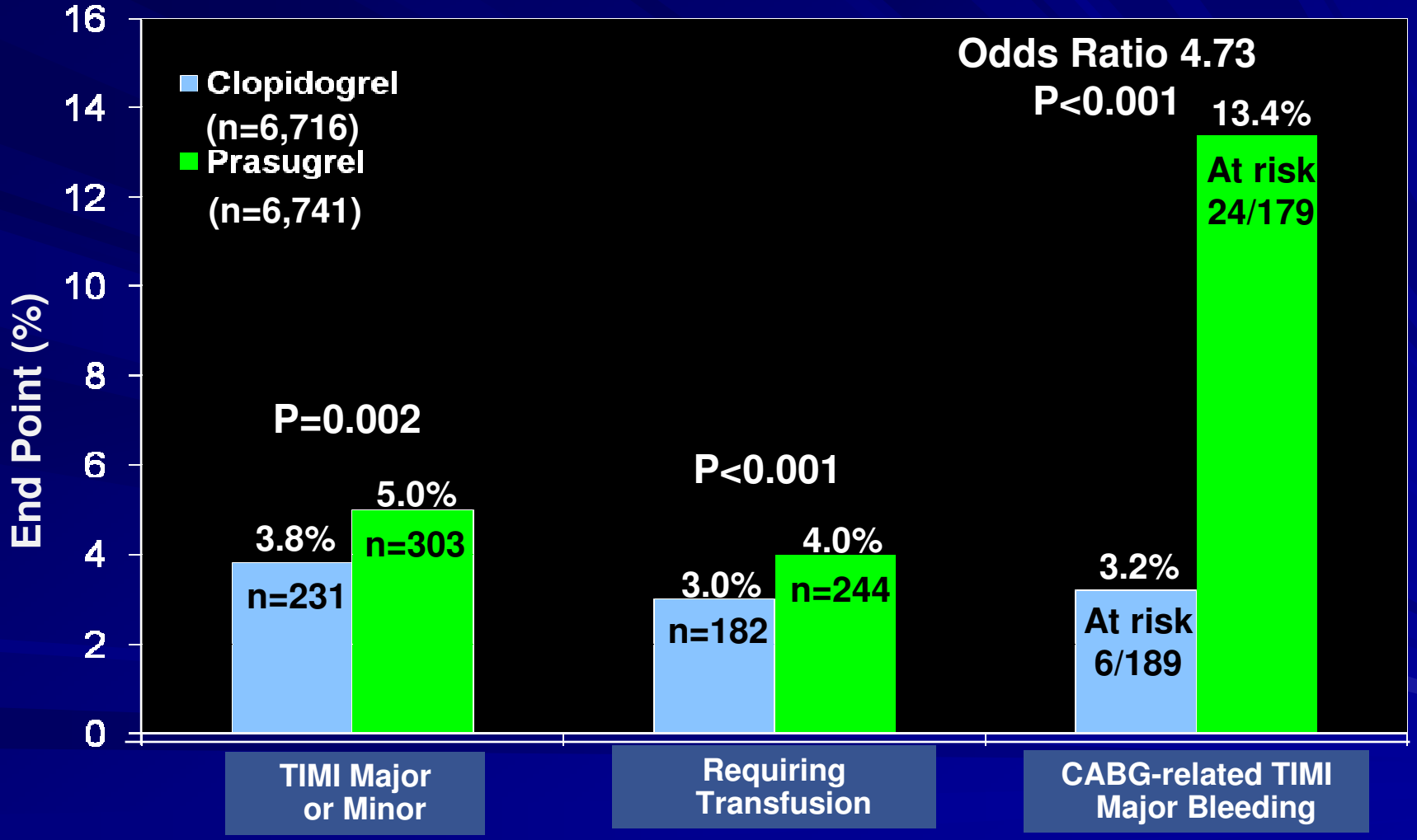
TRITON-TIMI 38: ARC Definite/Probable Stent Thrombosis:



ARC=Academic Research Consortium; ARR=Absolute Risk Reduction; HR=Hazard Ratio; NNT=Number Needed to Treat; PCI=Percutaneous Coronary Intervention; RRR=Relative Risk Reduction

Wiviott SD et al. *Lancet* 2008;371:1353-1363

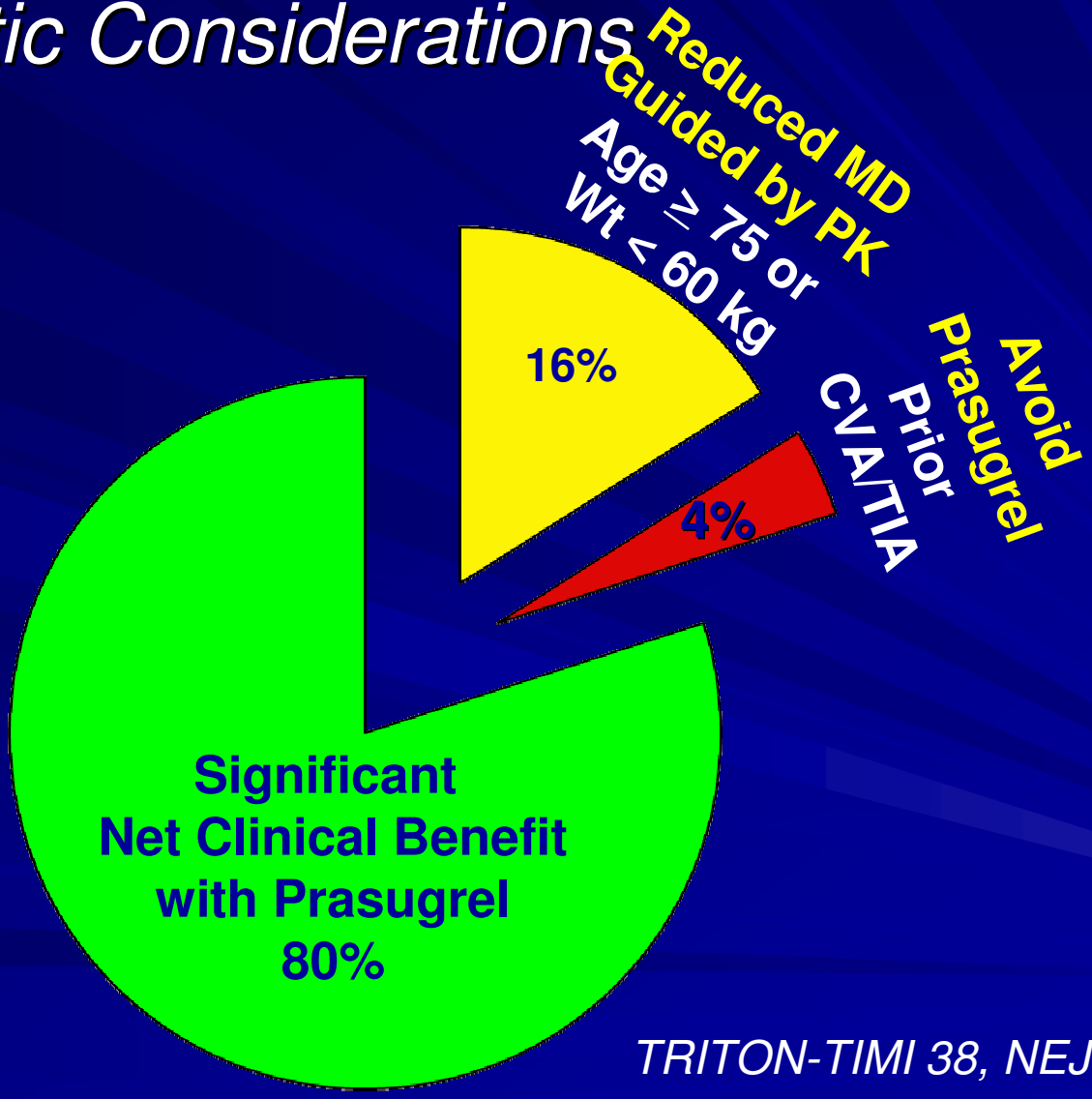
TRITON-TIMI 38: Other TIMI Bleeds at 15 Months (All ACS)



ACS=Acute Coronary Syndrome; CABG=Coronary Artery Bypass Graft surgery; HR=Hazard Ratio; TIMI=Thrombolysis In Myocardial Infarction

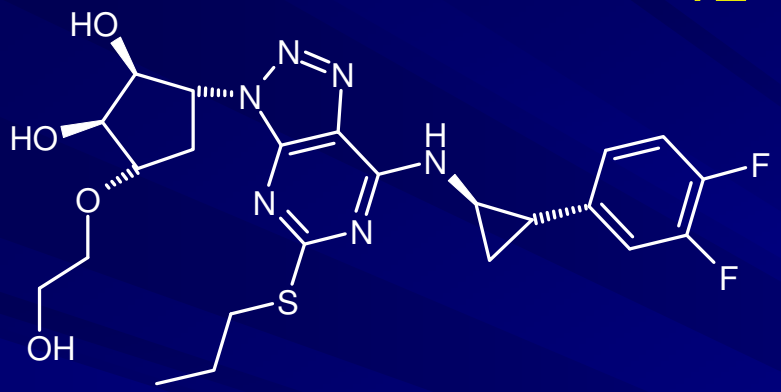
Wiviott SD et al. *New Engl J Med* 2007;357:2001-2015

Bleeding Risk Subgroups
Therapeutic Considerations



TRITON-TIMI 38, NEJM 2007

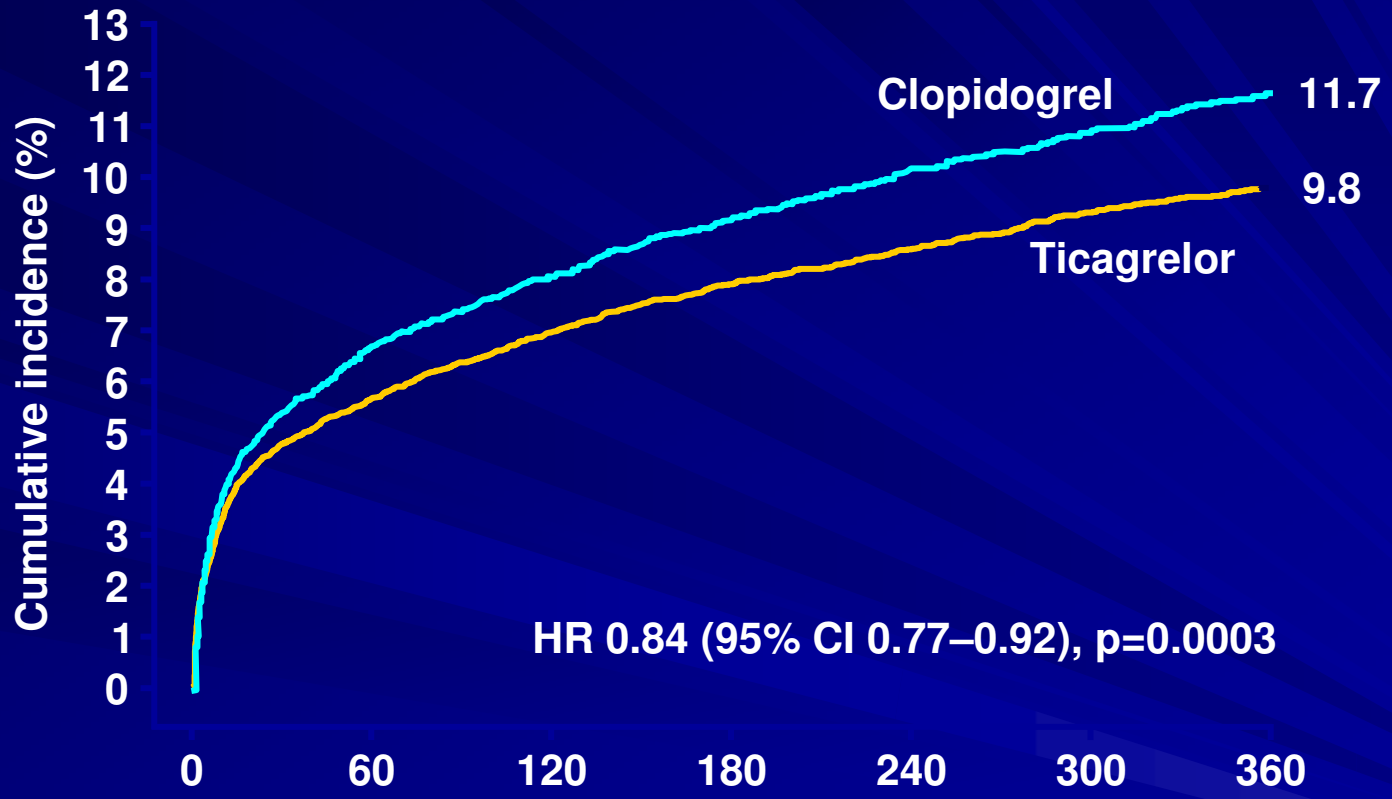
Ticagrelor (AZD 6140): an oral reversible $P2Y_{12}$ antagonist



Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- **Direct acting**
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor
  - Greater and more consistent inhibition of platelet aggregation versus clopidogrel
- **Reversibly bound**
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of all circulating platelets

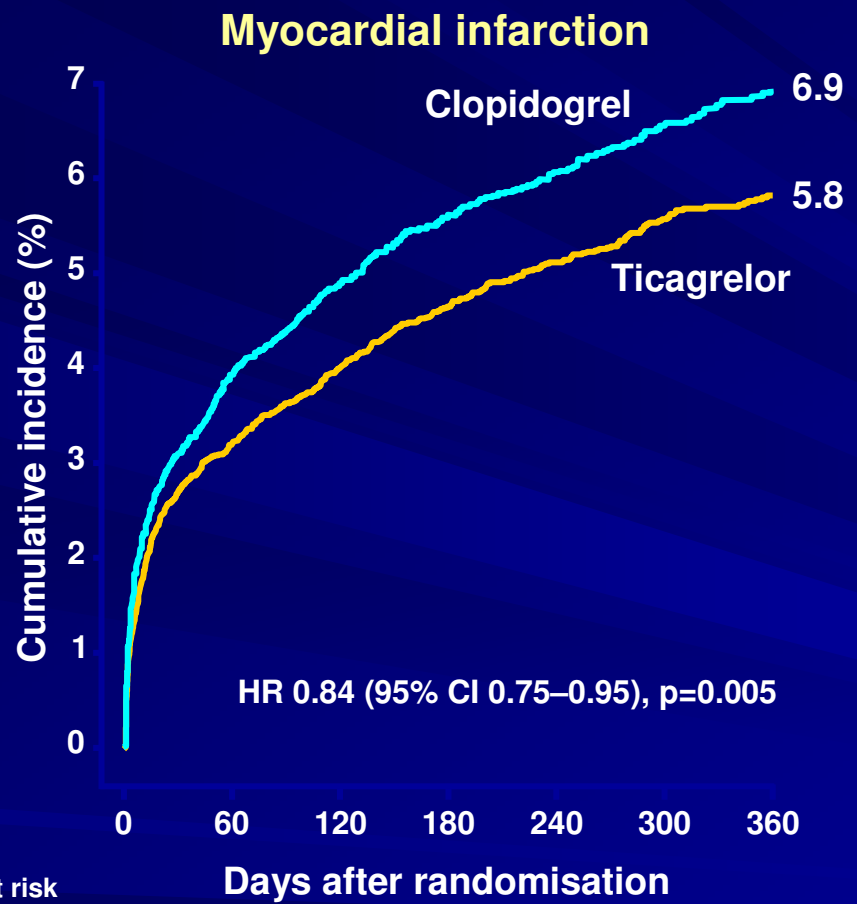
PLATO study primary efficacy event - CV death, MI or stroke (18,600 pts with ACS)

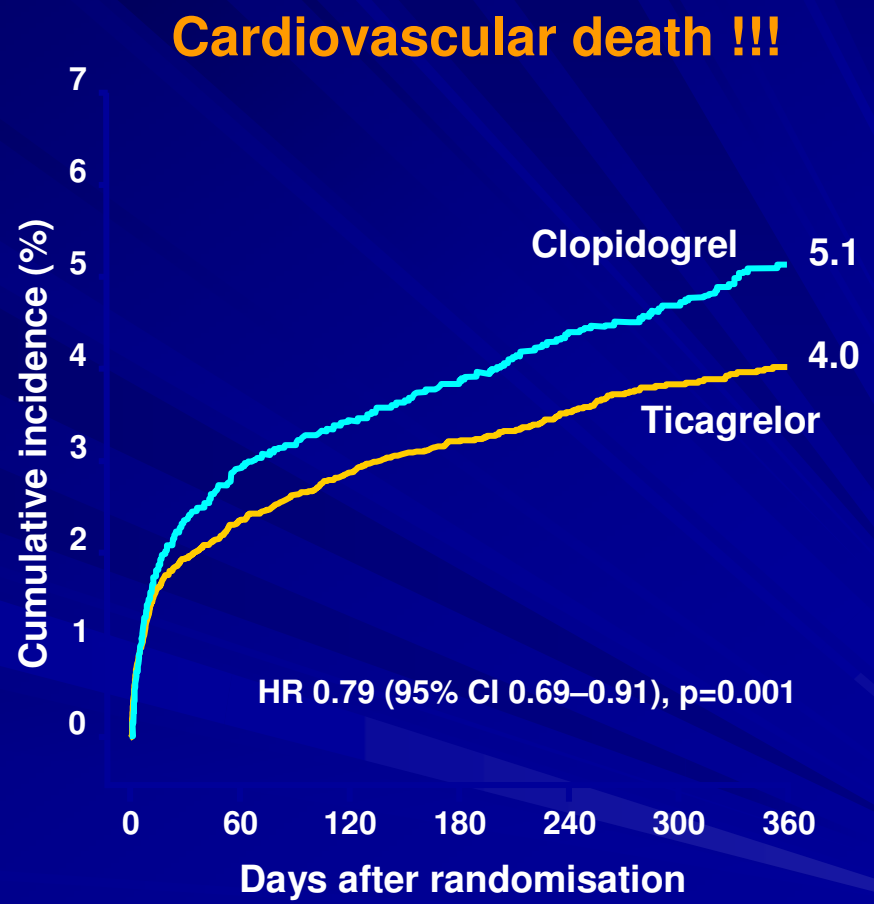


No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

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

K-M estimates of time to secondary efficacy endpoints



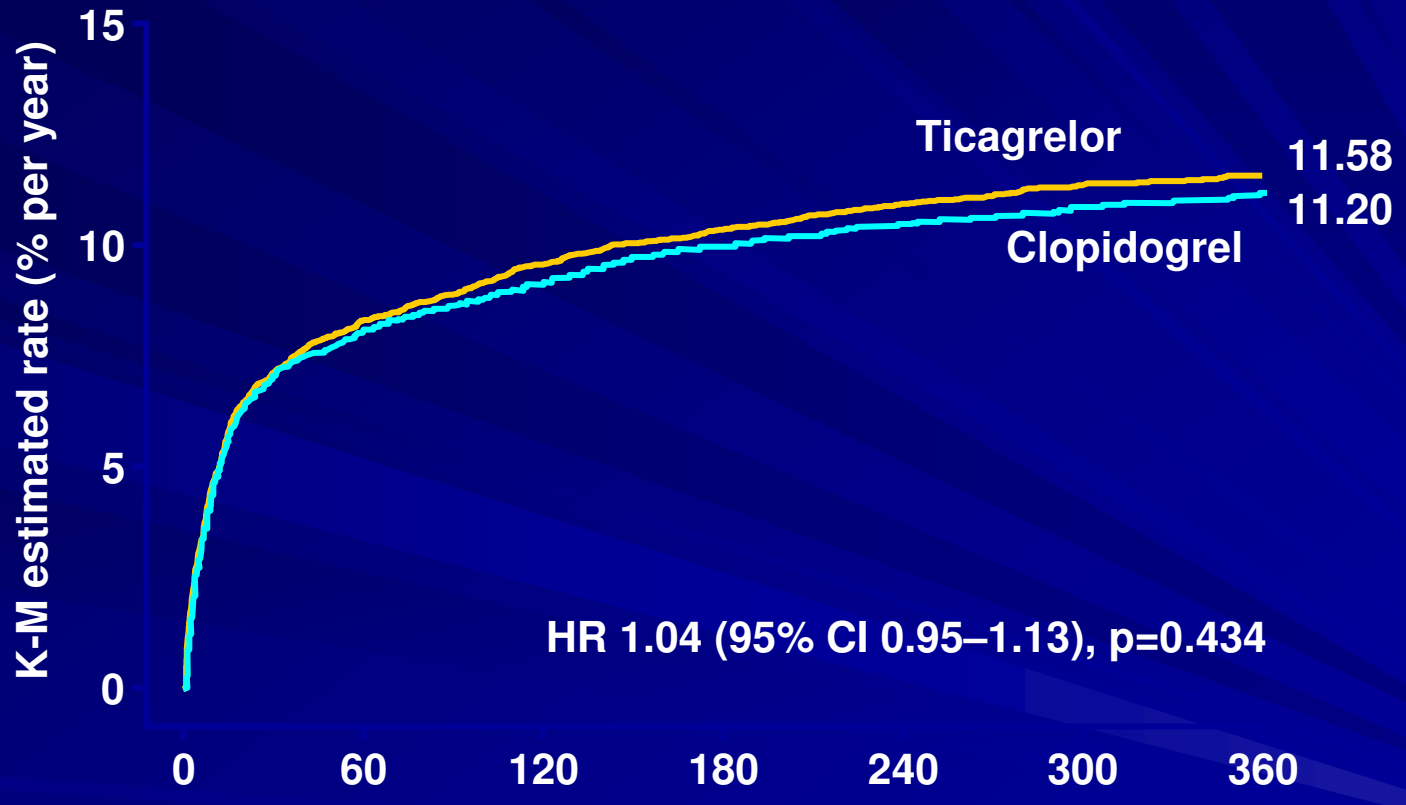


No. at risk

Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

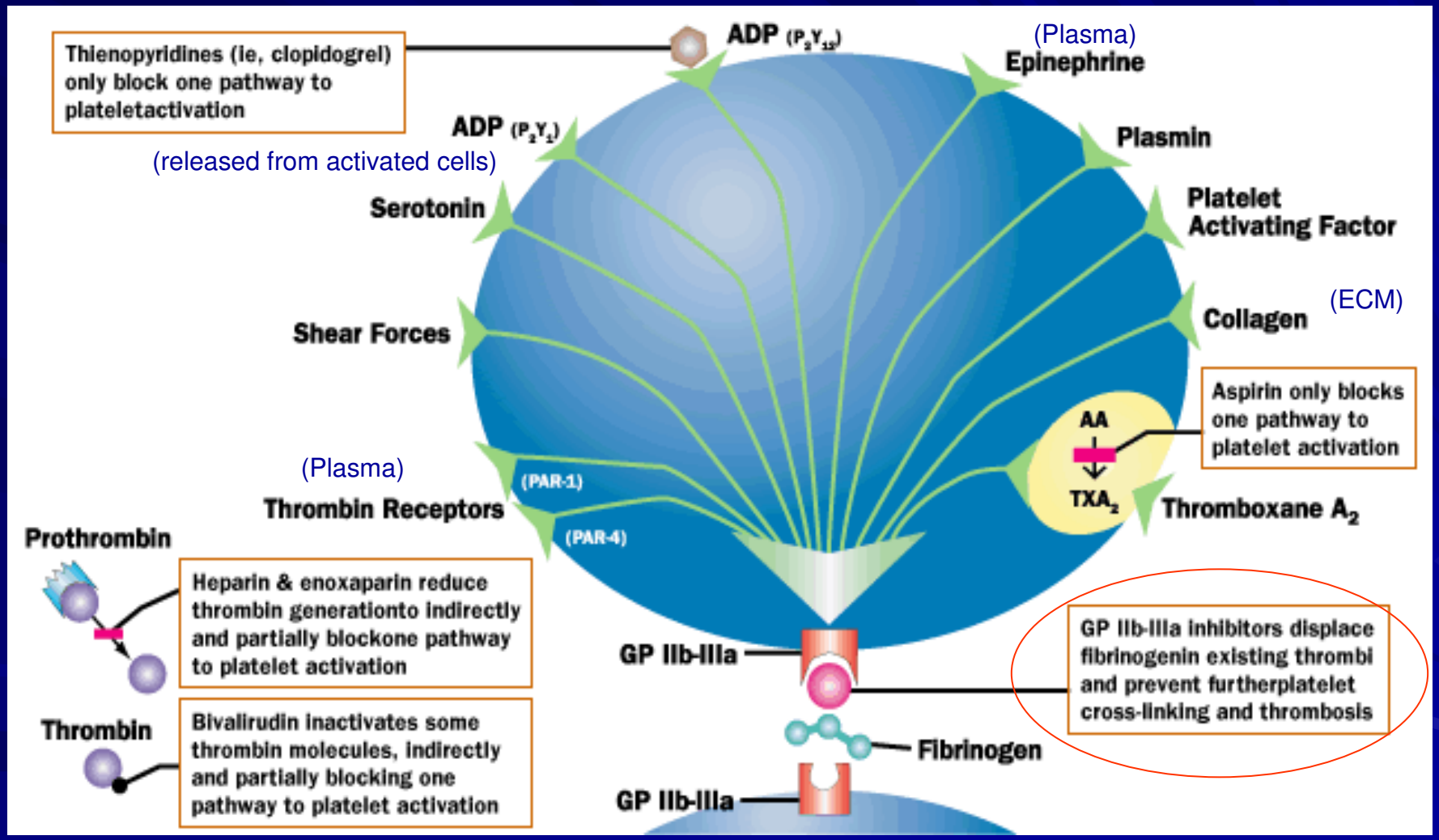
9,333	8,294	8,822	8,626	7119	5,482	4,419
9,291	8,865	8,780	8,589	7079	5,441	4,364

Major bleeding – primary safety event



No. at risk							
Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

Platelet Activation



GP IIb/IIIA Inhibitors

- **Abciximab (ReoPro®)** – the first inhibitor developed and approved for clinical use.

  Chimeric monoclonal antibody – 7E3, the murine constant region was replaced by its human counterpart

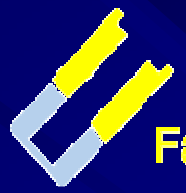
- **Eptifibatide (Integrilin®)** – synthetic cyclic hepta-peptide derived from a sequence found in the venom of the southeastern pygmy rattlesnake

- **Tirofiban (Aggrastat®)** – synthetic small molecule with structure similar to that of the RGD sequence of the snake venom echistatin

GP IIbIIIa inhibitors

Antibody

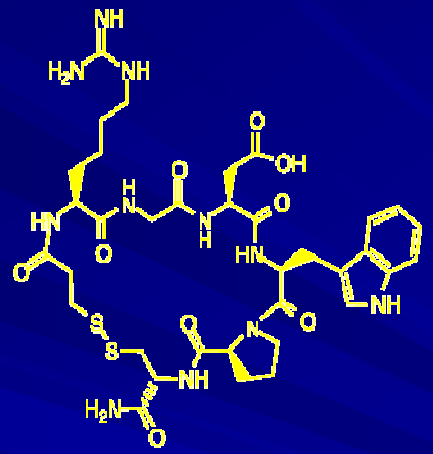
- abciximab



■ Murine variable region
■ Human constant region

Cyclic peptide

- eptifibatide



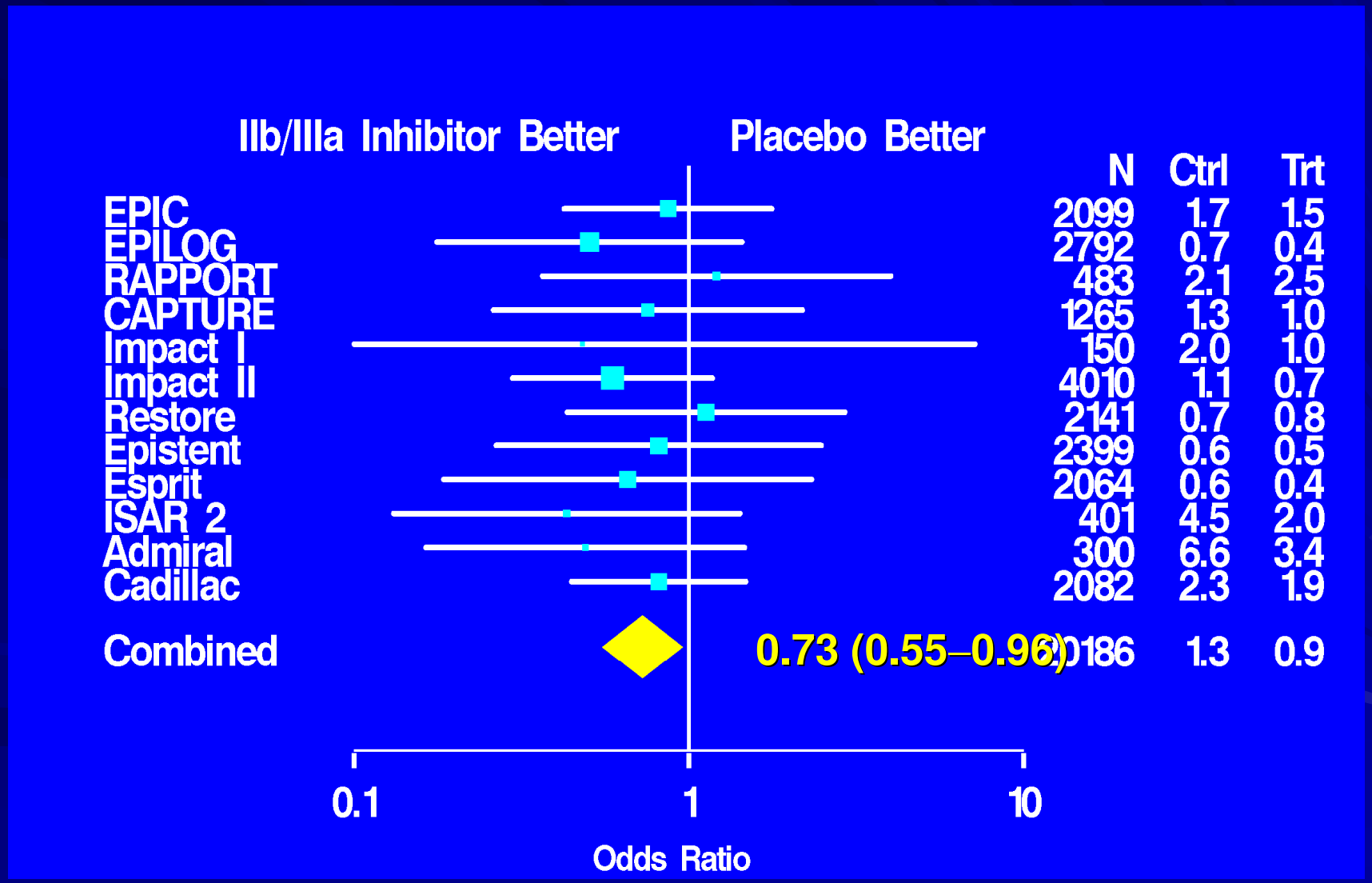
Nonpeptide

- tirofiban HCl
  (Aggrastat®, Merck)

Glycoprotein IIb/IIIa Receptor Antagonists

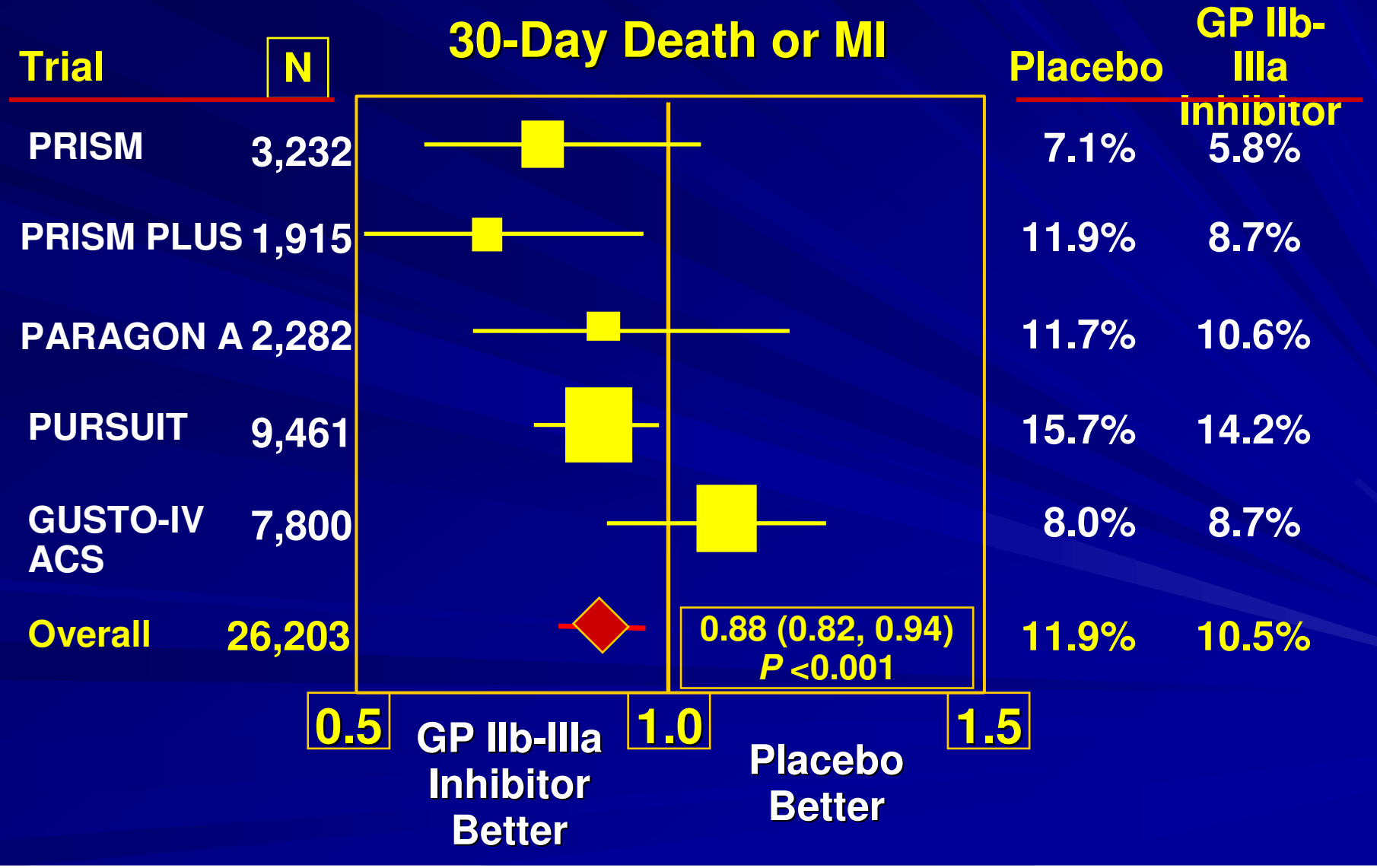
	Abciximab	Tirofiban	Eptifibatide
Pharma	Fab portion of chimeric monoclonal antibody	Synthetic non-peptide	Cyclic heptapeptide
Plasma ½ life	30 minutes	1.8 hours	2.5 hours
Specificity	Not specific	Highly specific	Highly specific
Dose	0.25 mcg/kg bolus followed by 0.125 mcg/kg/min drip (max 10 mcg/min) for 12-24 hours	0.4 mcg/kg/min for 30 minutes followed by 0.1 mcg/kg/min drip for 48-96 hours	180 mcg/kg bolus (x2) followed by 2.0 mcg/kg/min drip for 18-24 hours

PCI Trials - 30-Day Mortality

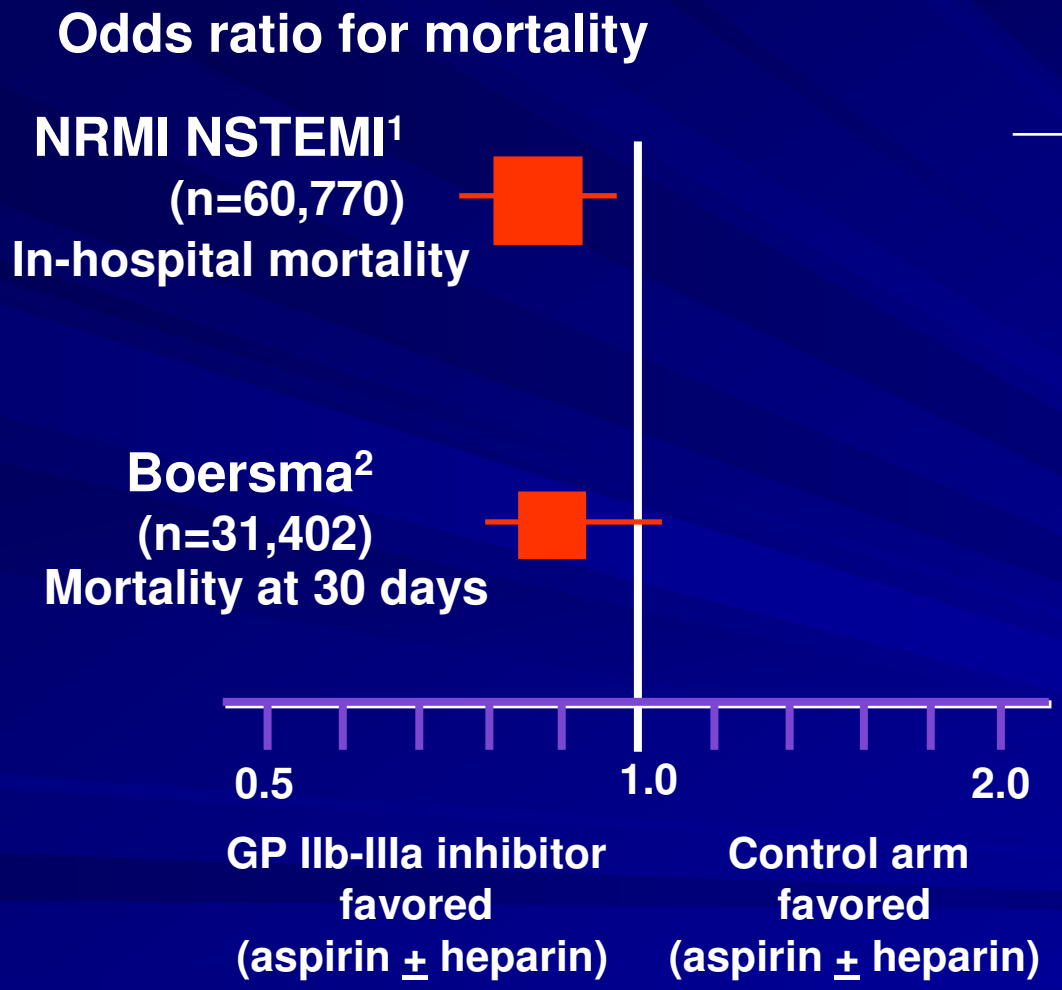


Am J Cardiol 2003;92:651-5

GP IIb/IIIa Inhibition in ACS



Meta-Analysis of Risk-Adjusted Mortality in GP IIb-IIIa Inhibitor NSTE ACS Trials

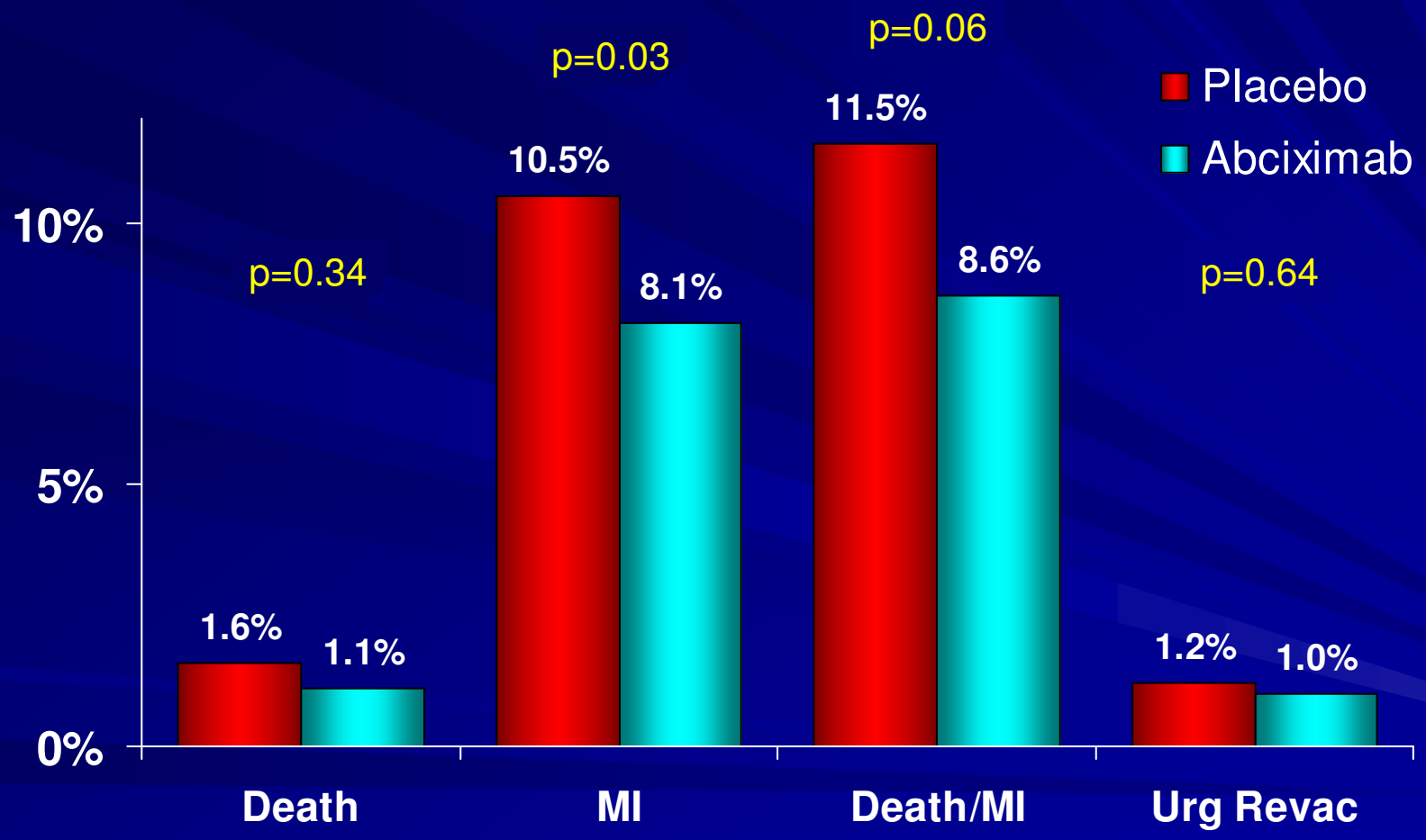


	Odds Ratio	95% CI
NRMI NSTEMI[1] (n=60,770) In-hospital mortality	0.88	0.79,0.97
Boersma[2] (n=31,402) Mortality at 30 days	0.91	0.81,1.03

NRMI=National Registry of Myocardial Infarction

[1]Peterson ED, et al. *J Am Coll Cardiol.* 2003;42(1):45-53.
[2]Boersma E, et al. *Lancet.* 2002;359:189-198.

ISAR-REACT 2
High-risk ACS Patients – 30 Days



JAMA 2006;295:1531-38

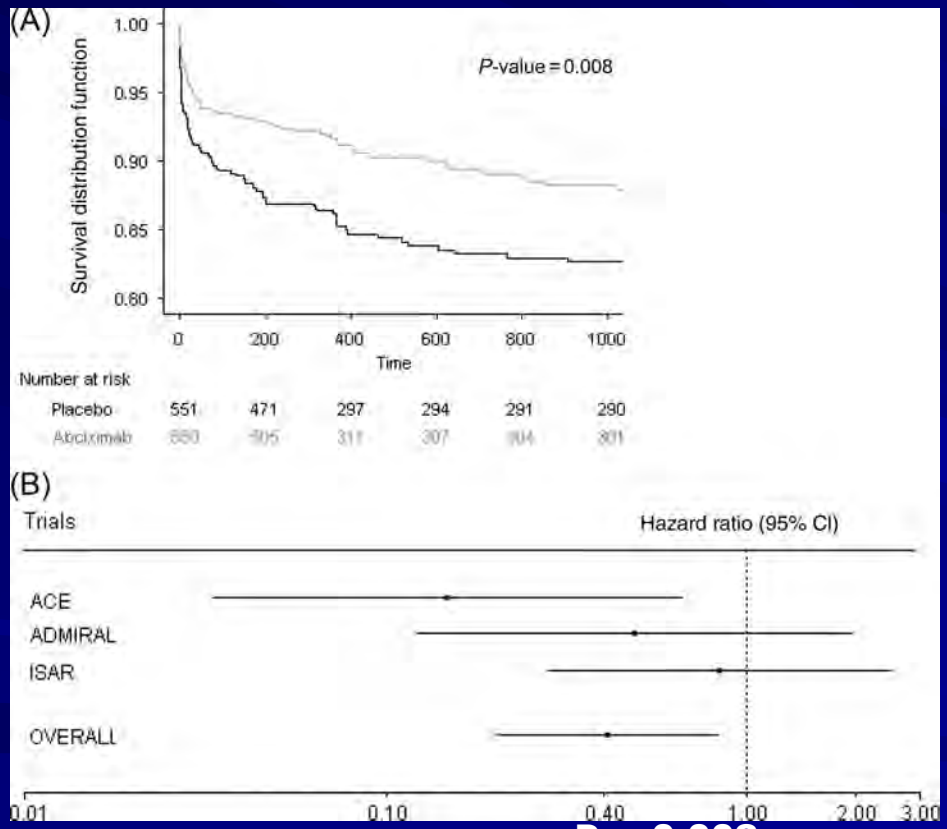
GP IIb/IIIA Inhibitors

- GP IIb/IIIa inhibitor “price”: increased risk of bleeding (mainly access site + GI, not intracranial hemorrhages)
- Increased risk of thrombocytopenia – 1-2% (mainly with abciximab)
- Two specific populations probably benefit most from GP IIb/IIIa administration

GP IIb/IIIa Inhibitors in STEMI

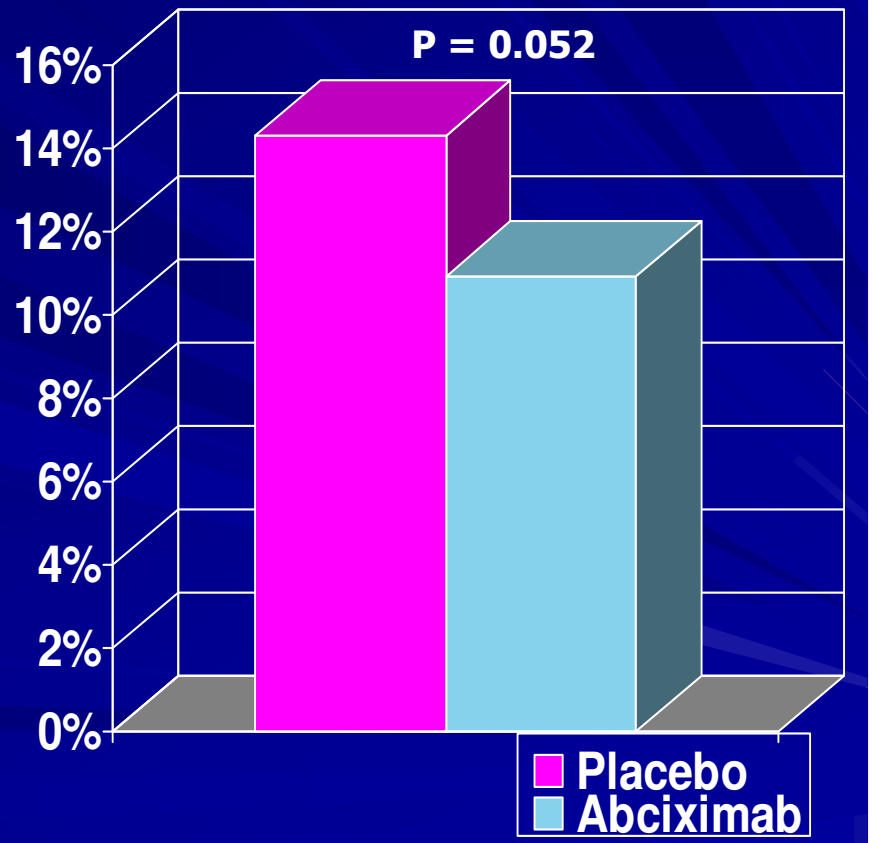
Trials of PCI with abcixiamb and *stenting* that included long-term follow-up

Death or re-infarction over 3 yrs of f/u



P = 0.008

3 year mortality



Montalescot, G. et al. Eur Heart J 2007 28:443-449

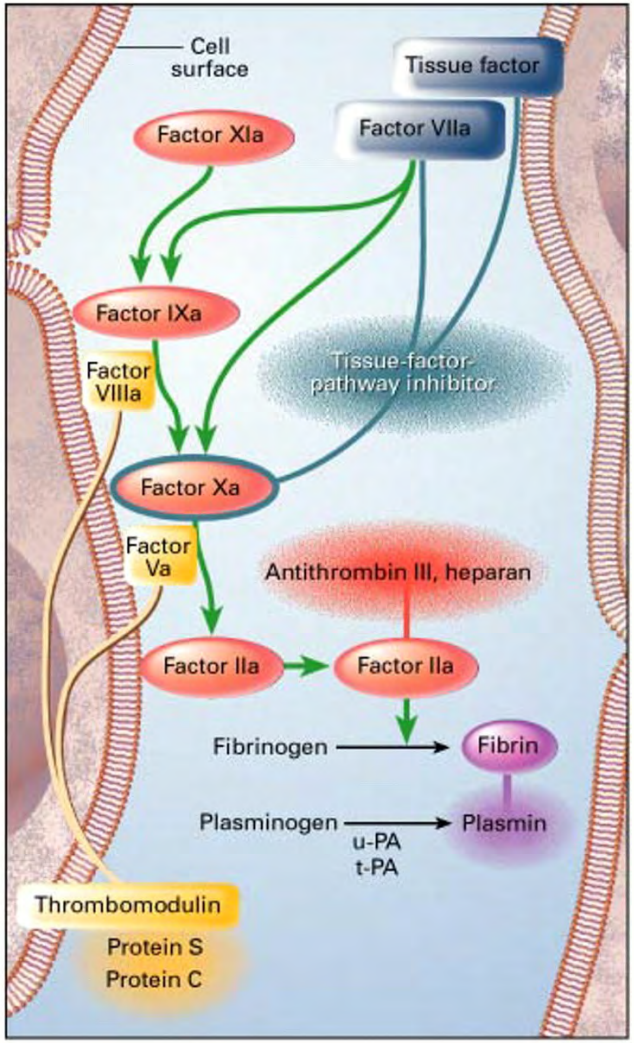
GP IIB/IIIA inhibitors and Diabetes

- Meta-analysis of non-STEMI ACS trials with GP IIb/IIIa inhib. (PRISM, PRISM-PLUS, PARAGON, PURSUIT, GUSTO-IV)
- 6,458 diabetic pts → significant **mortality** reduction at 30 dys: 6.2% vs. 4.6% (placebo vs. IIb/IIIa, P=0.007)
- 23,072 non diabetic pts → no survival benefit (3% vs. 3%)
- Main benefit in diabetics among those who underwent PCI (4% vs. 1.2%, P=0.002)

Roffi et al, Circulation 2001

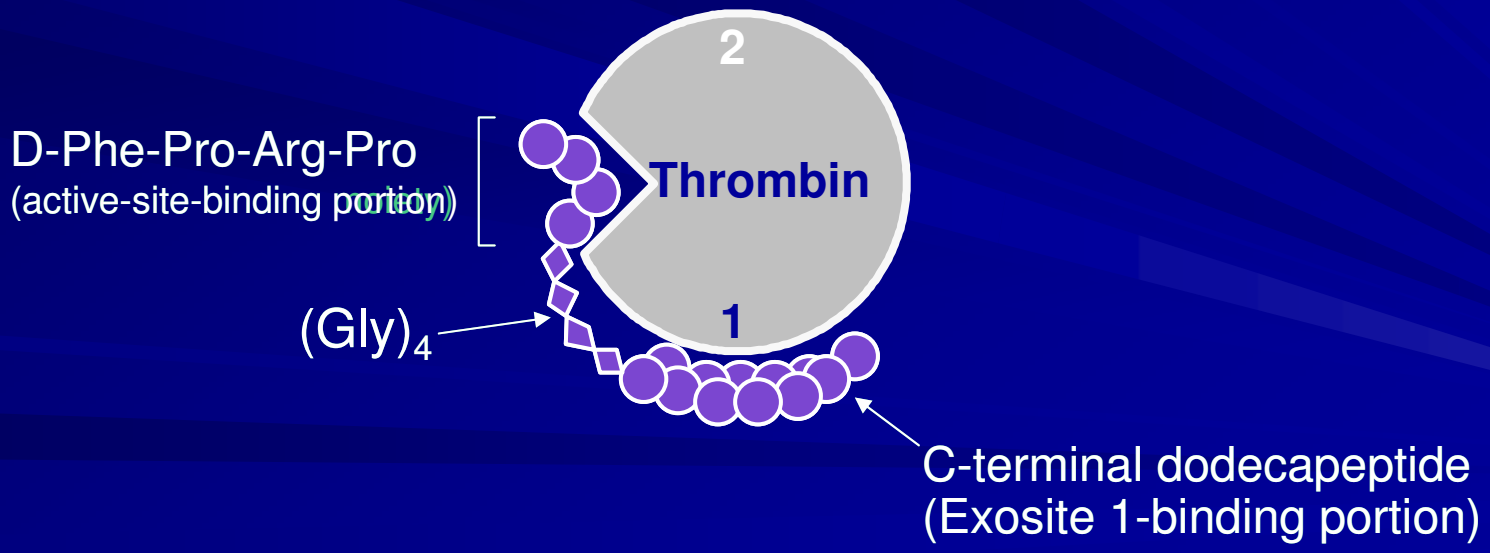
Bivalirudin - Angiomax

- Direct inhibitor of thrombin
- Very short half life (25 min)



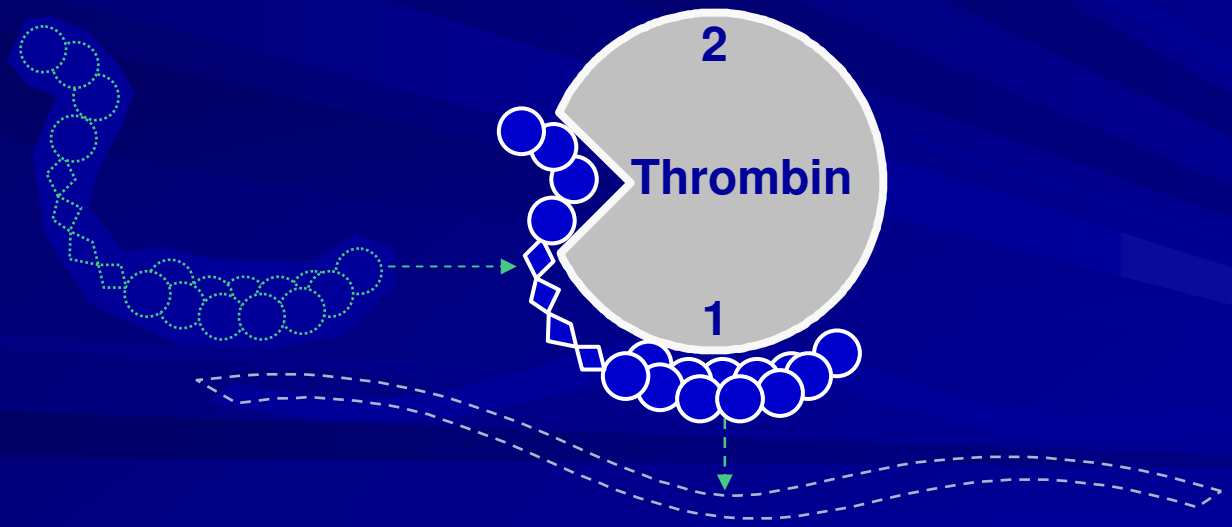
Bivalirudin

Bivalirudin – a direct thrombin inhibitor - binds bivalently and with high affinity to thrombin's active site



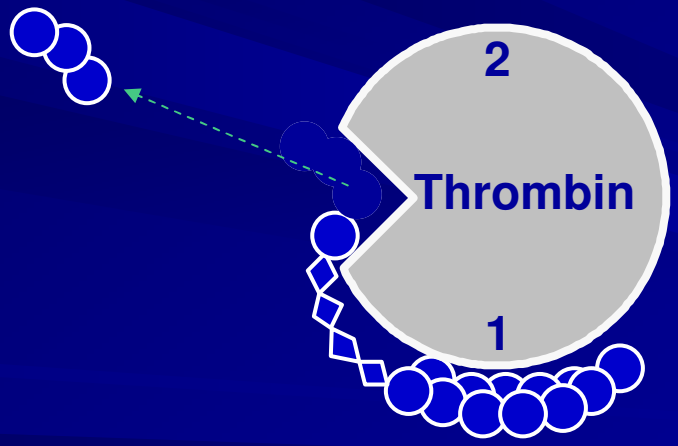
Bivalirudin

Bivalirudin can displace fibrin bound to thrombin—
Bivalirudin has high specificity for thrombin.



Bivalirudin

Bivalirudin is slowly cleaved by thrombin at the active site.



Bivalirudin

- Bivalirudin is cleared from plasma by a combination of renal mecahnisms and proteolytic cleavage
- Plasma half life = 25 minutes (norm renal funct)
- Mod. renal impairment, half life = 34 minutes (dose reduced)
- Almost immediate prolongation of ACT. aPTT
- Coagulation times return to normal after about 1 hour following drug d/c

ACUITY TRIAL

- 13,819 patients with ACS randomized to one of 3 antithrombotic regimens: heparin (or enoxaparin) + GP IIb/IIIa inhibitor, bivalirudin + GP IIb/IIIa inhibitor, or bivalirudin alone

- The primary end points were a composite ischemia end point (death, MI, or revasc. for ischemia), major bleeding.

Stone G et al, NEJM 2006

Ischemic Composite Endpoint

(Death, MI, unplanned revascularization for ischemia)

UFH/Enoxaparin + GPI vs. Bivalirudin + GPI vs. Bivalirudin Alone