Unment Needs and Alternatives to Clopidogrel in Patients with ACS Undergoing PCI

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Presenter Disclosure Information

Name: Dominick J Angiolillo

Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

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a) Consulting fee or honorarium from Bristol Myers Squibb, Sanofi-Aventis, Eli Lilly, Daiichi Sankyo, The Medicines Company, AstraZeneca, Merck, Evolva, Abbott Vascular and PLx Pharma;
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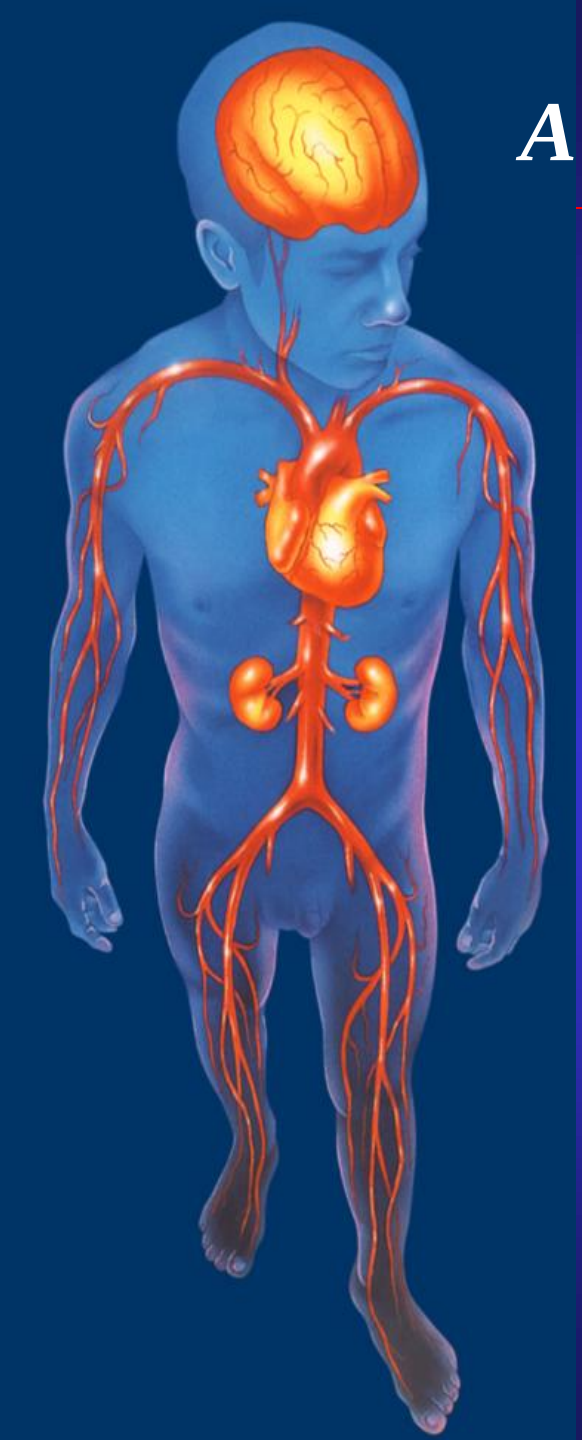
Basic Concepts



ATHEROSCLEROSIS

A Generalized and Progressive Process

Normal → Fatty streak → Fibrous plaque → Athero-sclerotic plaque ↔ Plaque rupture/ fissure

Increasing Age

Atherosclerosis

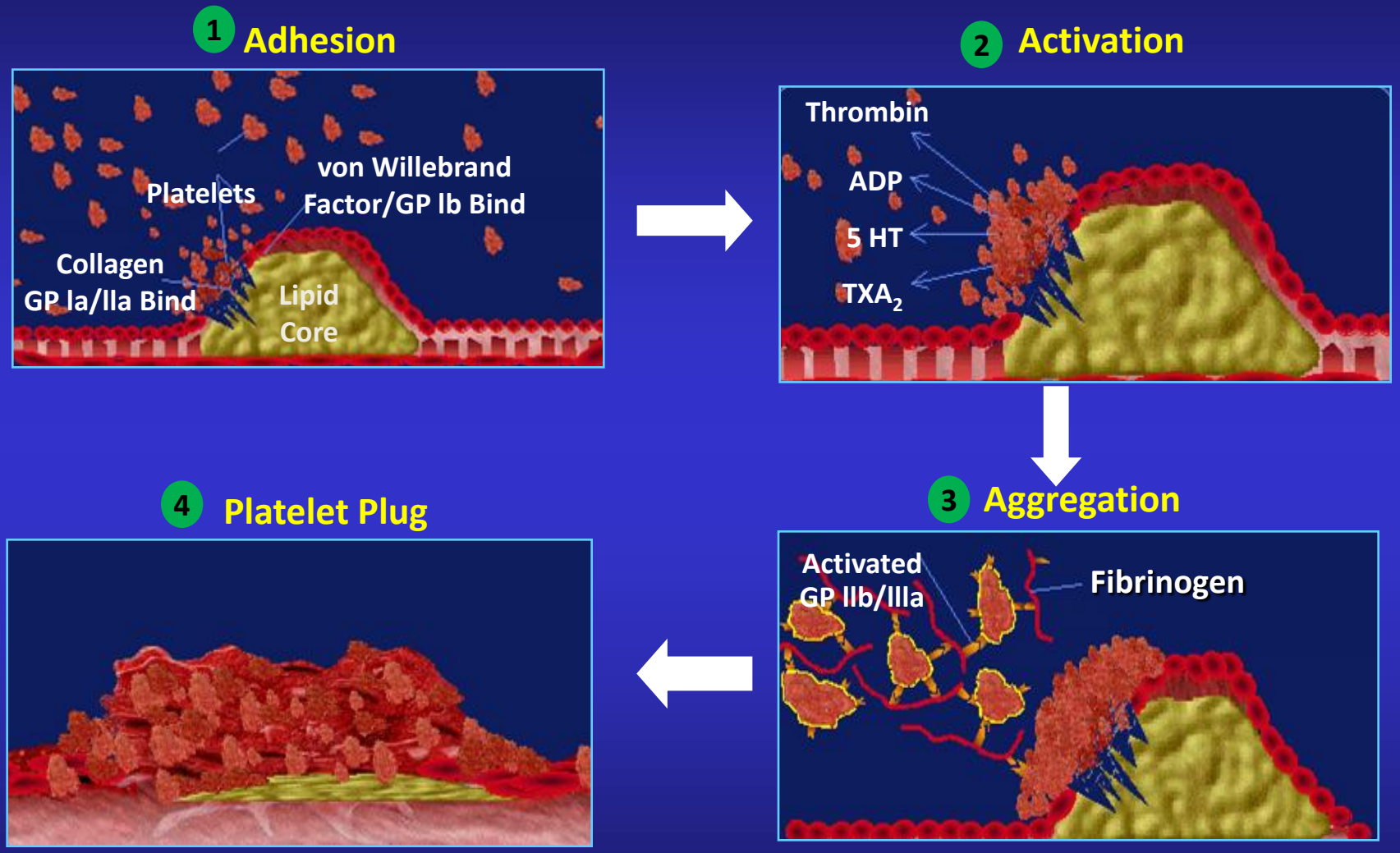
Thrombosis

Stable angina

Unstable angina
MI
Sudden Death

Heart Failure

Platelet Cascade in ACS



Schafer AI. *Am J Med*. 1996.

ANTITHROMBOTIC DRUGS USED IN ACS/PCI

I. ANTIPLATELET DRUGS

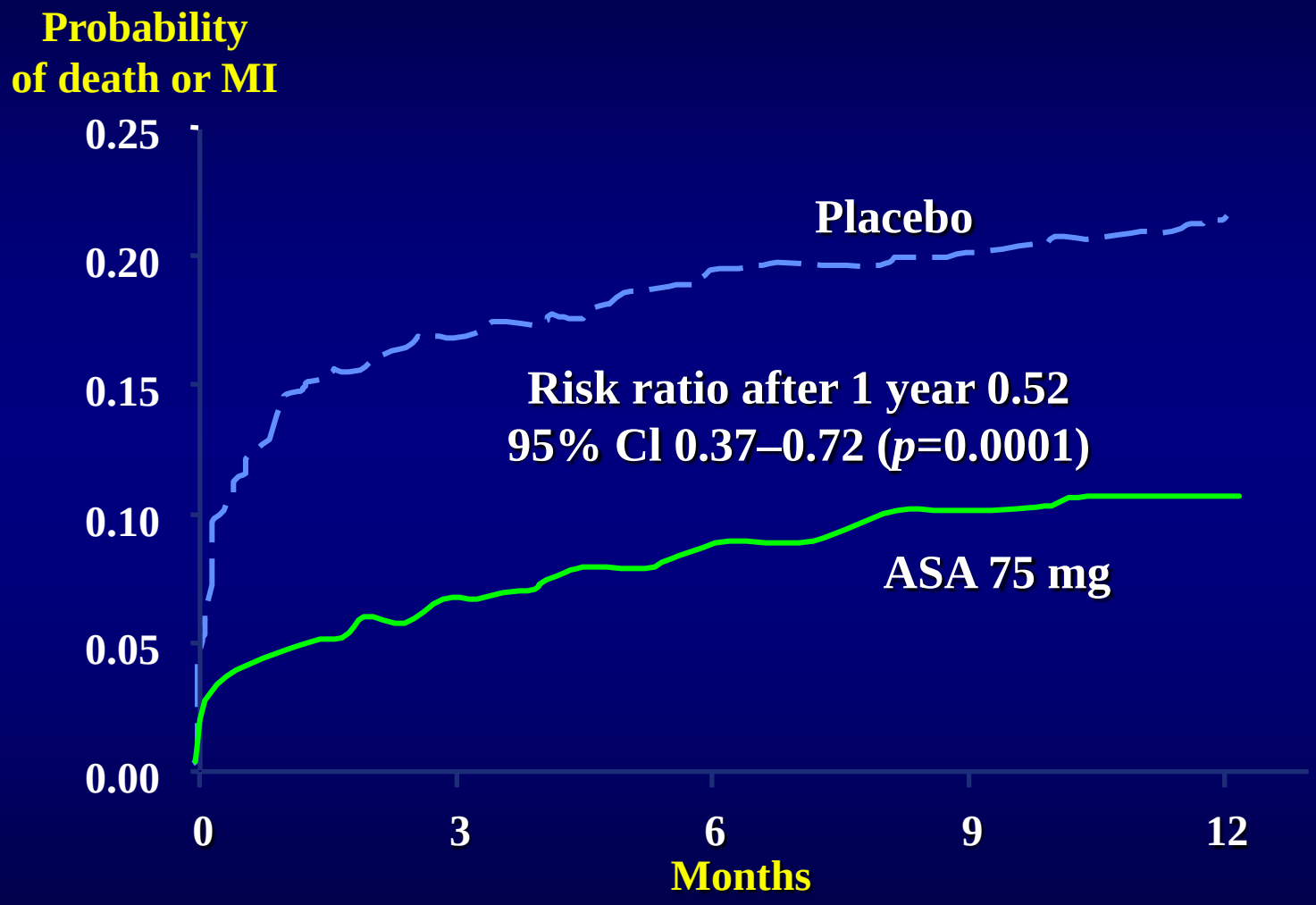
- COX-1 inhibitor (aspirin)
- $P2Y_{12}$ inhibitors (ticlopidine; clopidogrel; prasugrel; ticagrelor)
- Glycoprotein IIb/IIIa inhibitors (abciximab; eptifibatide; tirofiban)

II. ANTICOAGULANT DRUGS

- Anti-Factor II (anti-thrombins)
  - Indirect Thrombin Inhibitors (UFH & LMWH)
  - Direct Thrombin Inhibitors (Bivalirudin)
- Anti-Factor X
  - Fondaparinux

How did we get here?

Long-term Efficacy of ASA in Reducing Death or MI in Patients with Unstable Angina



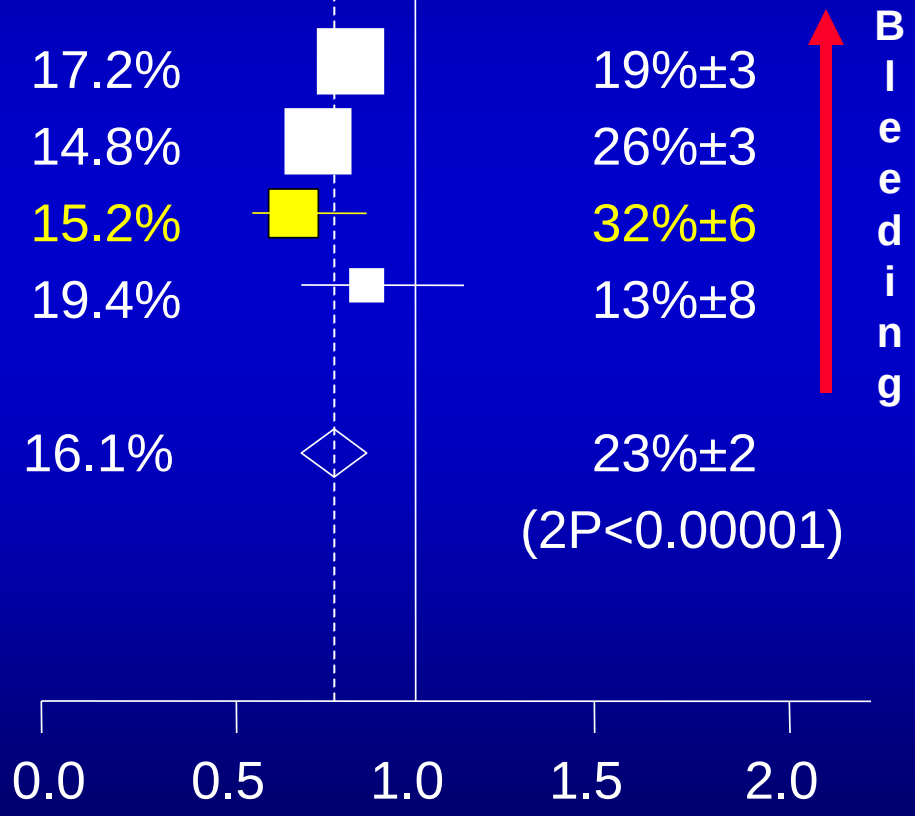
Wallentin LC et al *JACC* 1991;18:1587–1593

Antithrombotic Trialists' Collaboration

Different Doses of Aspirin vs Control

Daily Dose	Aspirin	Control	Reduction
Asp 500-1500	14.5%	17.2%	19%±3
Asp 160-325	11.5%	14.8%	26%±3
Asp 75-150	11.0%	15.2%	32%±6
Asp <75	17.3%	19.4%	13%±8
Any aspirin	12.9%	16.1%	23%±2

(2P<0.00001)



BMJ 2002;324:71-86

ASPIRIN: Take Home Points

Pro's

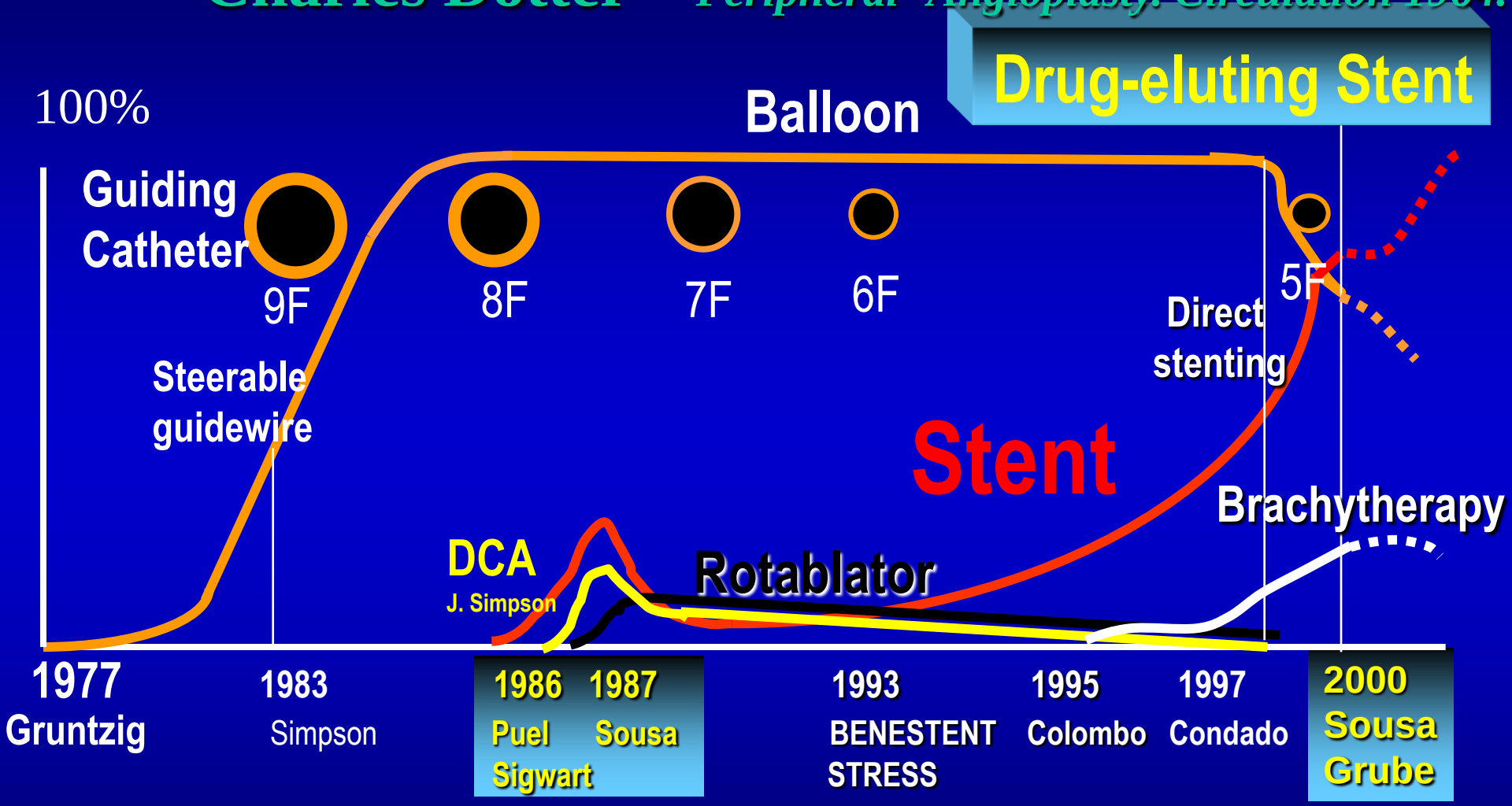
- Very effective
- Very inexpensive
- Very cost-effective

Con's

- Event rates still high
- Not good enough with emerging technology
- Need for more effective platelet inhibiting therapies

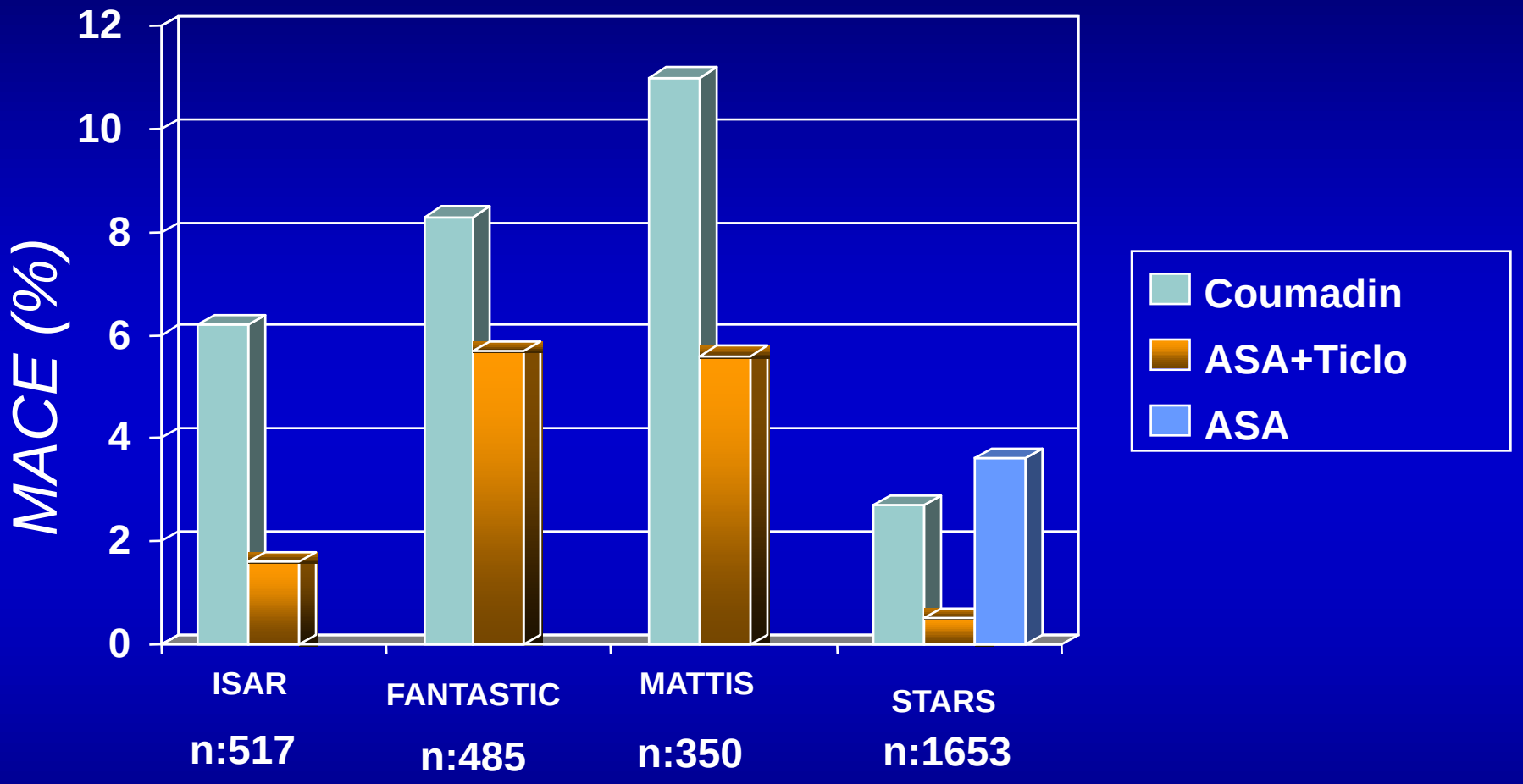
How did we get here?...

Charles Dotter – *Peripheral Angioplasty. Circulation 1964.*



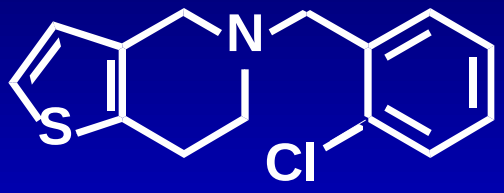
Modified from Michel Bertrand

Ticlopidine during PCI with use of Coronary Stents



- *Schomig et al, N Engl J Med 1996*
- *Urban et al, Circulation 1998*
- *Bertrand et al, Circulation 1998*
- *Leon et al, Circulation 1998*

The Thienopyridine Family



Ticlopidine

(1st generation)

$P2Y_{12}$ ADP receptor antagonism: antithrombotic treatment of choice for coronary stenting

Side effects: neutropenia, thrombocytopenia, rash, diarrhea, etc

Delayed time frame to achieve full antiplatelet effects

Solution to these problems:

Clopidogrel

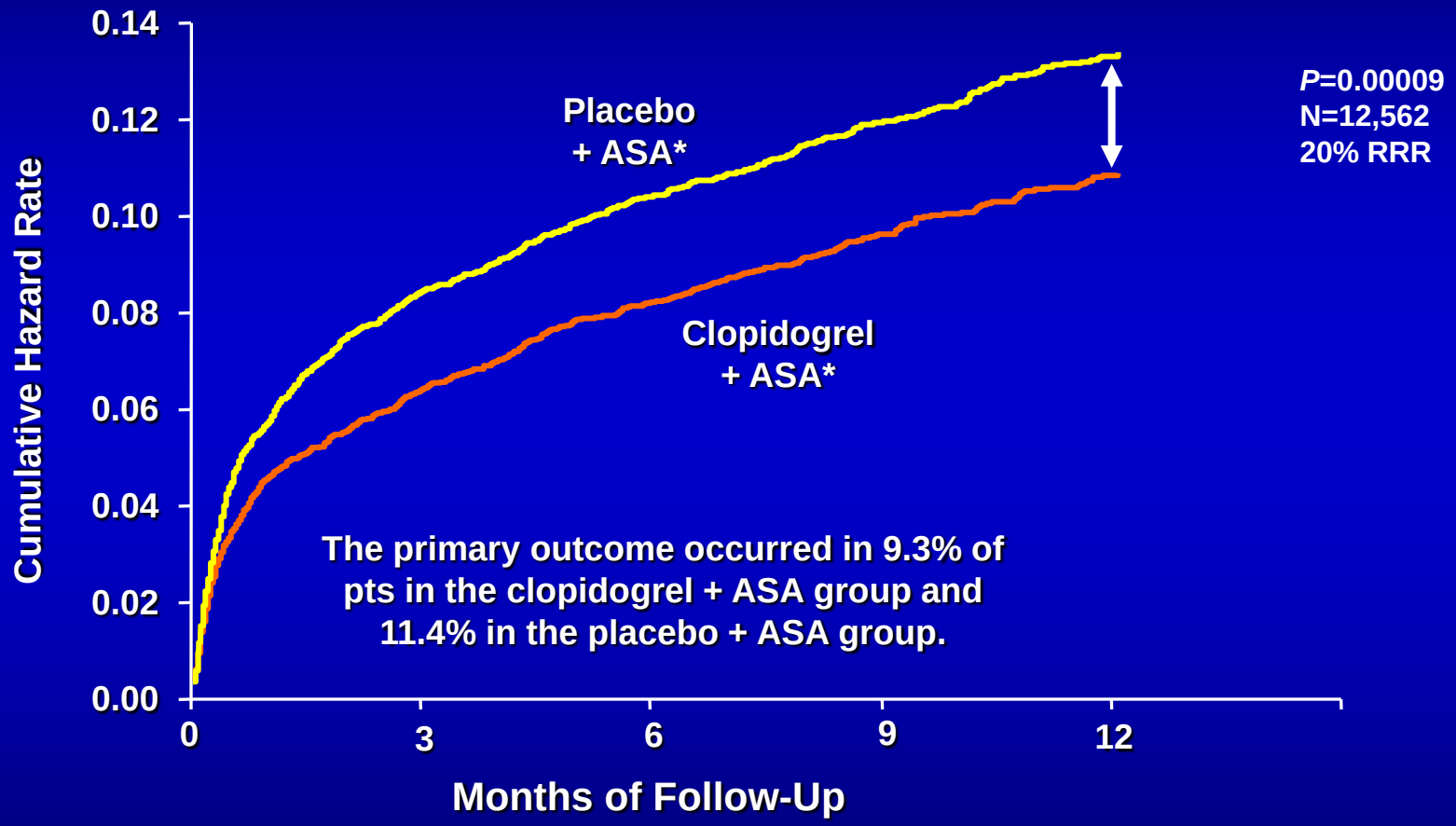
(2nd generation)

Better Safety profile - Fewer side effects
(CLASSICS trial. Bertrand NE *et al. Circulation* 2000; 102: 624–9).

Rapid onset of action with a loading dose
(Cadroy Y *et al. Circulation*. 2000;101:2823-28).

Better clinical outcomes
(Bhatt DL *et al. J Am Coll Cardiol* 2002; 39: 9–14.).

Primary Endpoint—MI/Stroke/CV Death



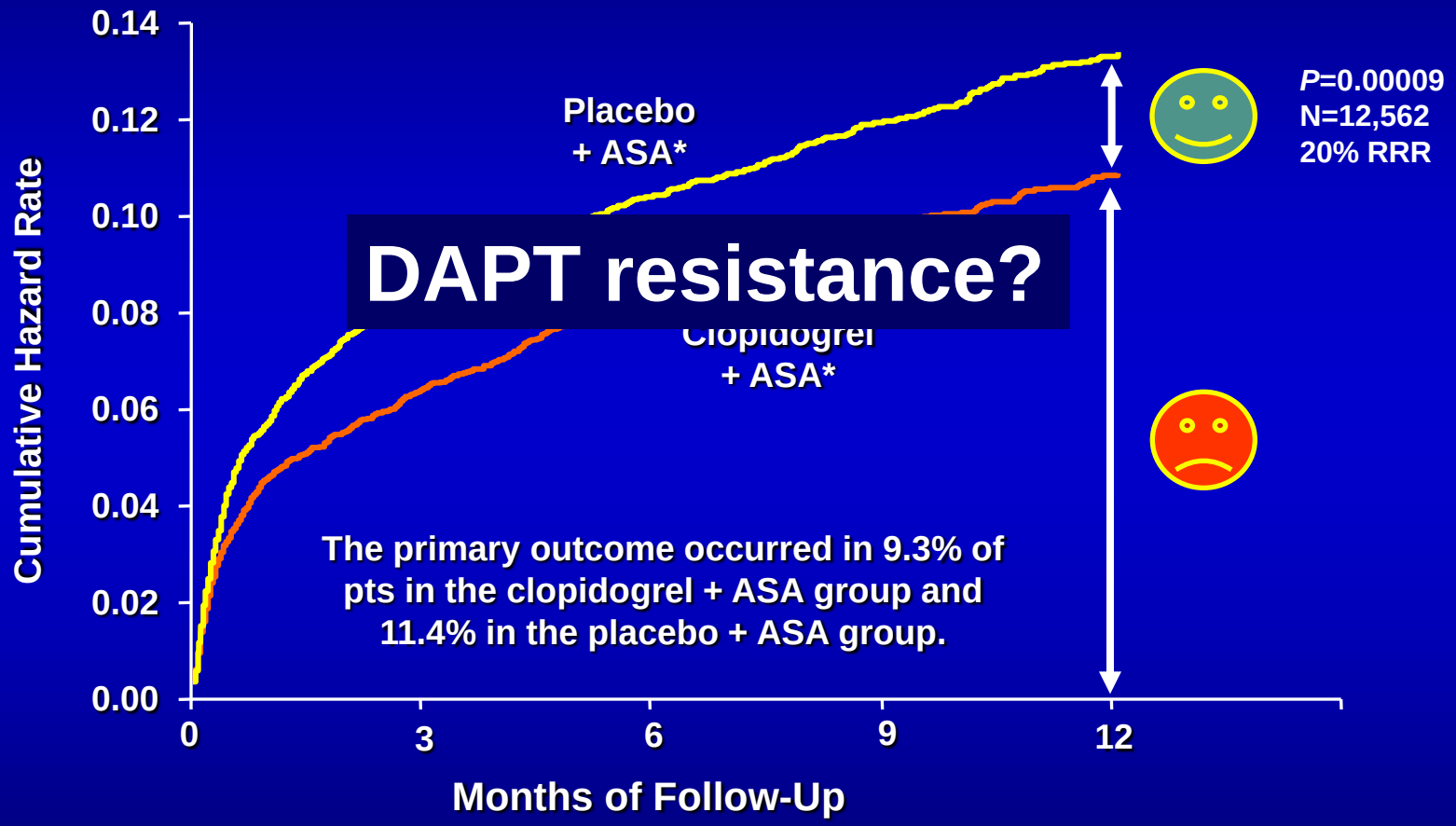
*Other standard therapies were used as appropriate.

Yusuf S et al. *N Engl J Med.* 2001;345:494-502.

Adjunctive Clopidogrel Therapy in ACS/PCI

UA/NSTEMI	PCI	Acute STEMI
CURE	CREDO	CLARITY TIMI 28
		COMMIT (CCS-2)
1 Year + Benefit	1 Year + Benefit	30 Days + Benefit
NEJM 2001	*JAMA 2002*	*NEJM 2005*
		Lancet 2005

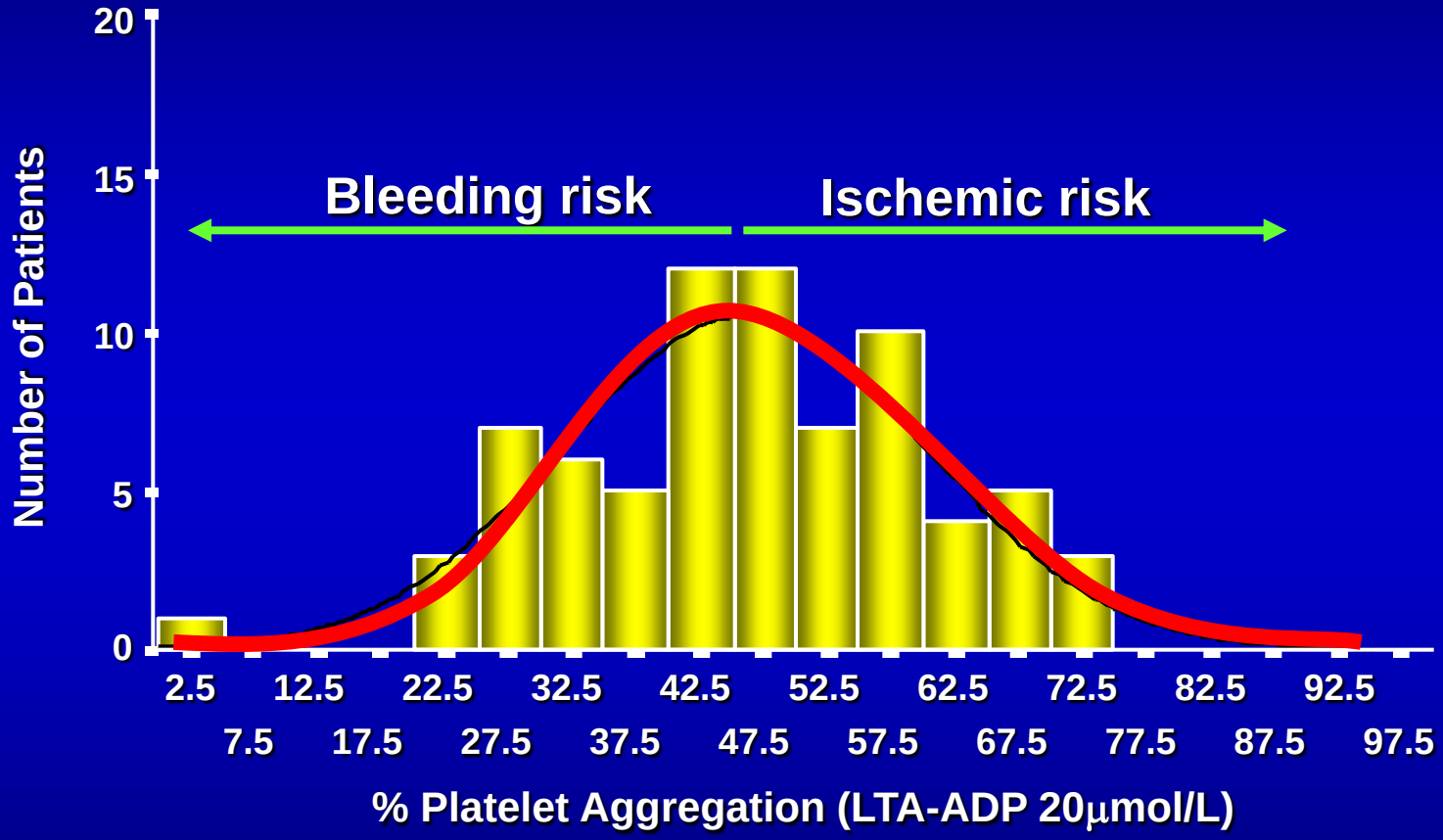
Primary Endpoint—MI/Stroke/CV Death



*Other standard therapies were used as appropriate.

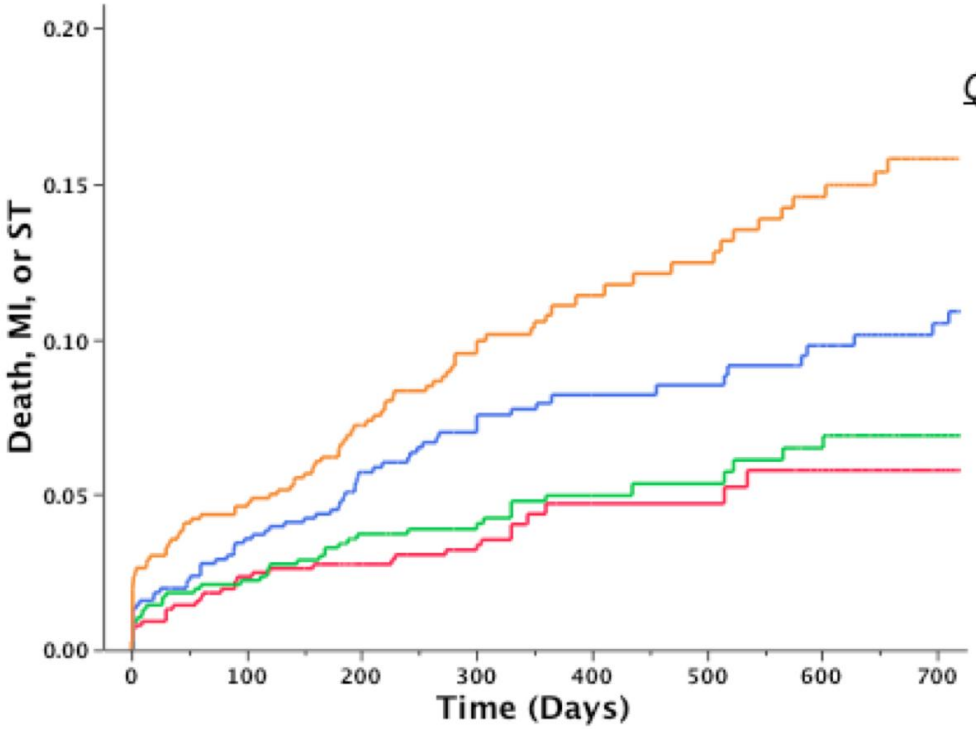
Yusuf S et al. *N Engl J Med.* 2001;345:494-502.

Individual Response Variability to Dual Antiplatelet Therapy in the *Steady State Phase* of Treatment



Adapted from Angiolillo DJ et al. *Am J Cardiol.* 2006;97:38-43.

On-Clopidogrel Platelet Reactivity & Ischemic Events Post-PCI: A Patient-Level Meta-Analysis



Quartile	Event Rate	P-value*
Q4	15.8%	<0.001
Q3	10.9%	0.02
Q2	6.9%	0.97
Q1	5.8%	–

No. at risk

Q1	765	639	179	169
Q2	761	611	249	237
Q3	757	595	294	271
Q4	758	588	252	224

Non-ACS pts with high reactivity : HR 2.47 (1.79–3.40), P<0.0001

Brar S, ten Berg J, Marcucci R, Price MJ et al, *J Am Coll Cardiol* 2011; 58:1945-1954

Genetic Factors

- Polymorphisms of CYP
- Polymorphisms of GPIa
- Polymorphisms of $P2Y_{12}$
- Polymorphisms of GPIIIa

FDA Box Warnings

Clopidogrel Response Variability

Clinical Factors

- Failure to prescribe/Poor compliance
- Under-dosing
- Poor absorption
- Drug-drug interactions
- Acute coronary syndrome
- Diabetes Mellitus/Insulin resistance
- Elevated body mass index

Cellular Factors

- Accelerated platelet turnover
- Reduced CYP3A metabolic activity
- Increased ADP exposure
- Up-regulation of the $P2Y_{12}$ pathway
- Up-regulation of the $P2Y_1$ pathway
- Up-regulation of P2Y–independent pathways (collagen, epinephrine, TXA_2, thrombin)

Angiolillo DJ et al. J Am Coll Cardiol 2007

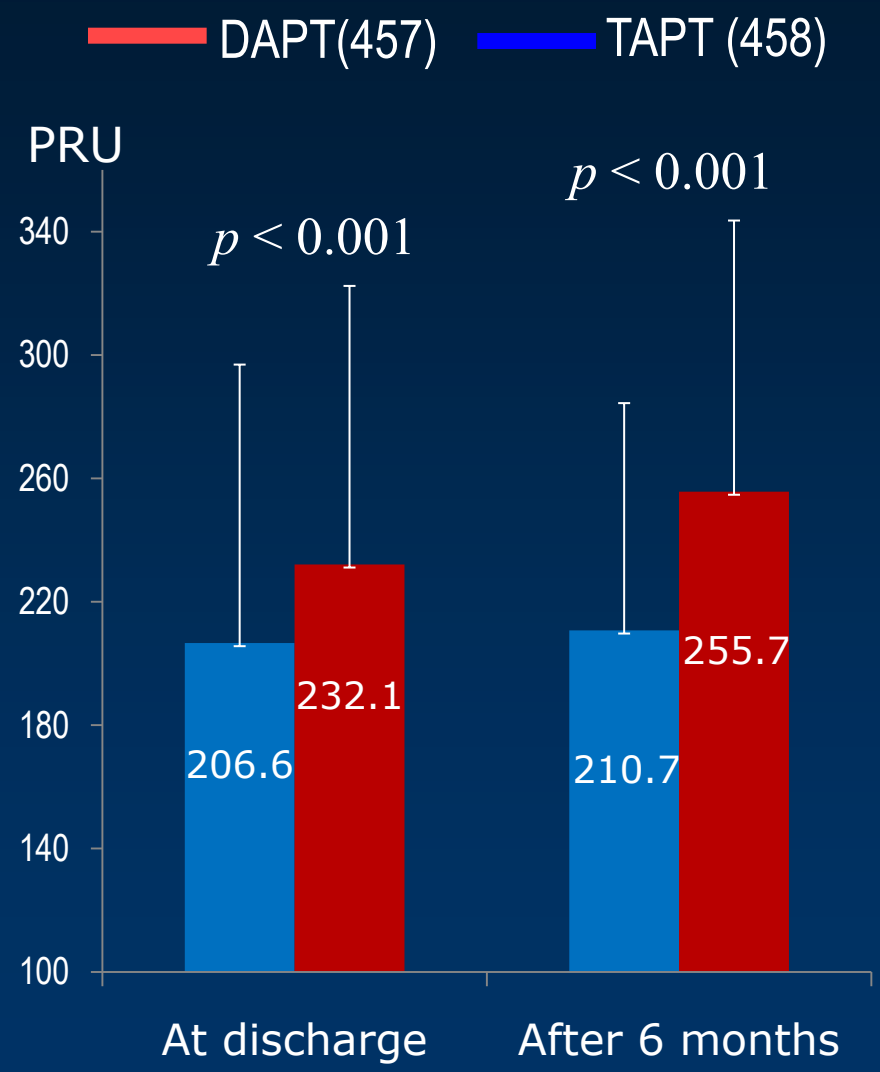
Optimizing Long-Term Anti-Platelet Drug Effects

- **Modifying dosage**
  (e.g. higher dose clopidogrel)
- **Adding other agents**
  (e.g. cilostazol, rivaroxiban -"triple therapy")
- **Using novel P2Y12 receptor antagonists**
  (e.g. prasugrel, ticagrelor)

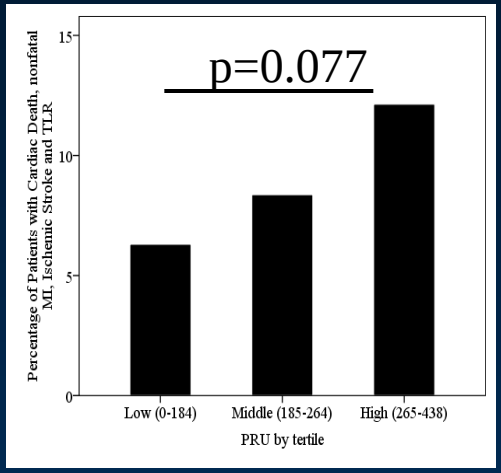
Clopidogrel: Double vs Standard Dose Primary Outcome and Components

	Standard	Double	HR	95% CI	P	Intn P
CV Death/MI/Stroke						
PCI (2N=17,232)	4.5	3.9	0.85	0.74-0.99	0.036	0.016
No PCI (2N=7855)	4.2	4.9	1.17	0.95-1.44	0.14	
Overall (2N=25,087)	4.4	4.2	0.95	0.84-1.07	0.370	
MI						
PCI (2N=17,232)	2.6	2.0	0.78	0.64-0.95	0.012	0.025
No PCI (2N=7855)	1.4	1.7	1.25	0.87-1.79	0.23	
Overall (2N=25,087)	2.2	1.9	0.86	0.73-1.03	0.097	
CV Death						
PCI (2N=17,232)	1.9	1.9	0.96	0.77-1.19	0.68	1.0
No PCI (2N=7855)	2.8	2.7	0.96	0.74-1.26	0.77	
Overall (2N=25,087)	2.2	2.1	0.96	0.81-1.14	0.628	
Stroke						
PCI (2N=17,232)	0.4	0.4	0.88	0.55-1.41	0.59	0.50
No PCI (2N=7855)	0.8	0.9	1.11	0.68-1.82	0.67	
Overall (2N=25,087)	0.5	0.5	0.99	0.70-1.39	0.950	

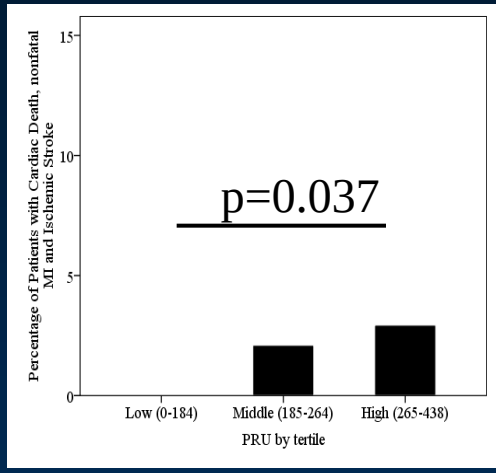
CILON-T: Randomized prospective trial of dual vs. triple antiplatelet therapy after DES implantation (KIM HS et al. ACC/i2 LBCT 2010)



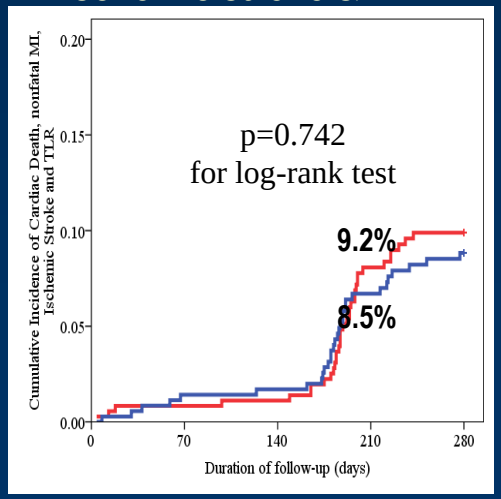
Composite of CD, nonfatal MI, ischemic stroke & TLR



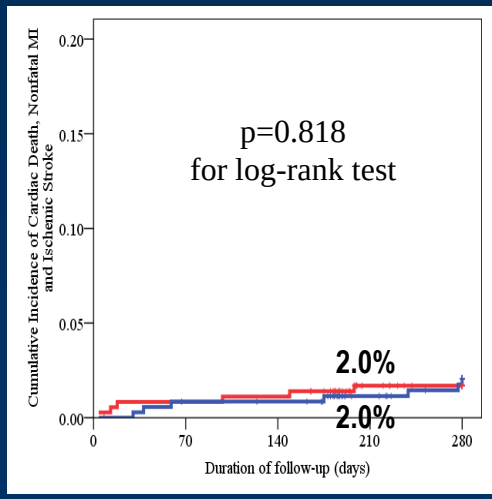
Composite of CD, nonfatal MI & ischemic stroke



Composite of CD, nonfatal MI, ischemic stroke & TLR



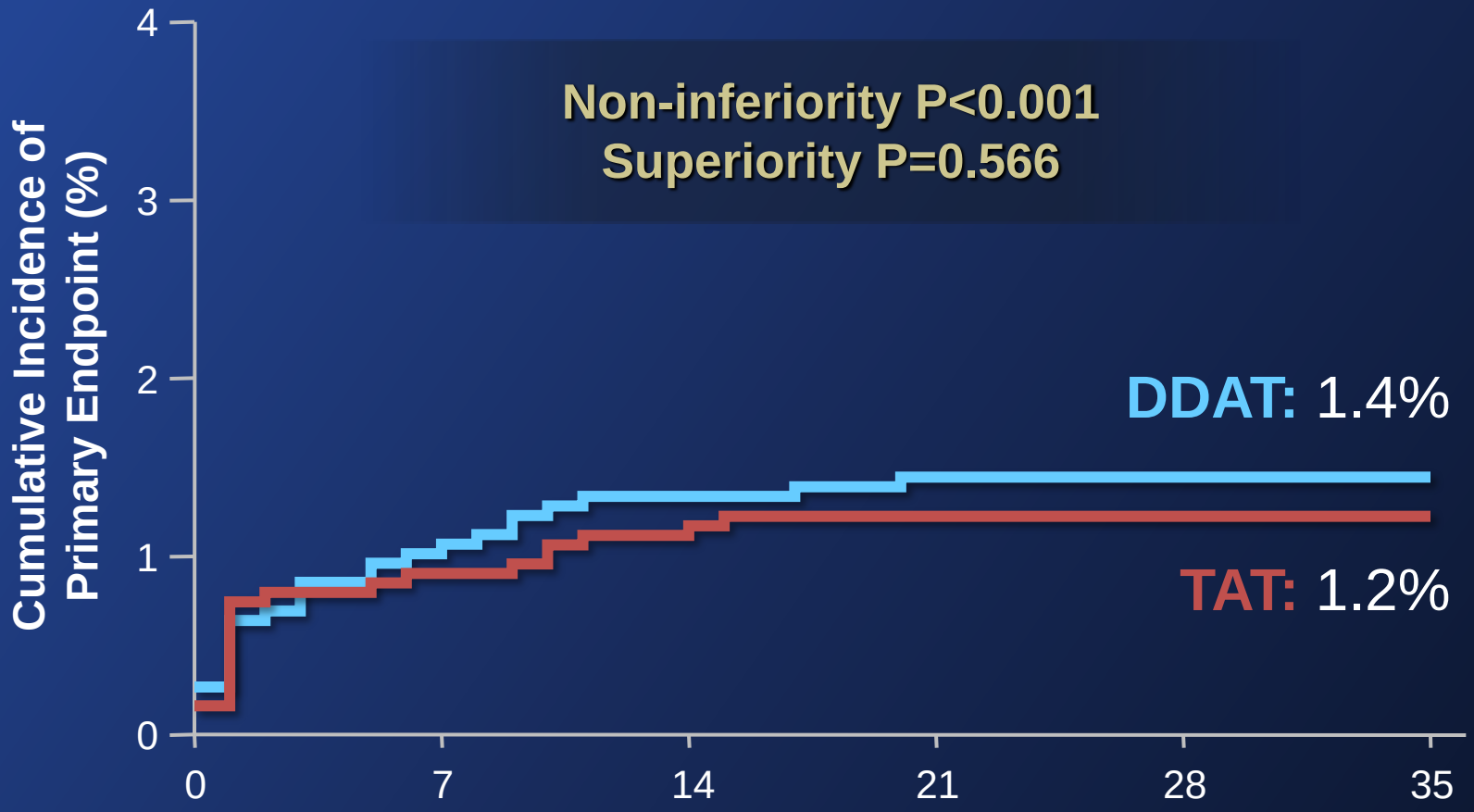
Composite of CD, nonfatal MI & ischemic stroke



Primary Endpoint

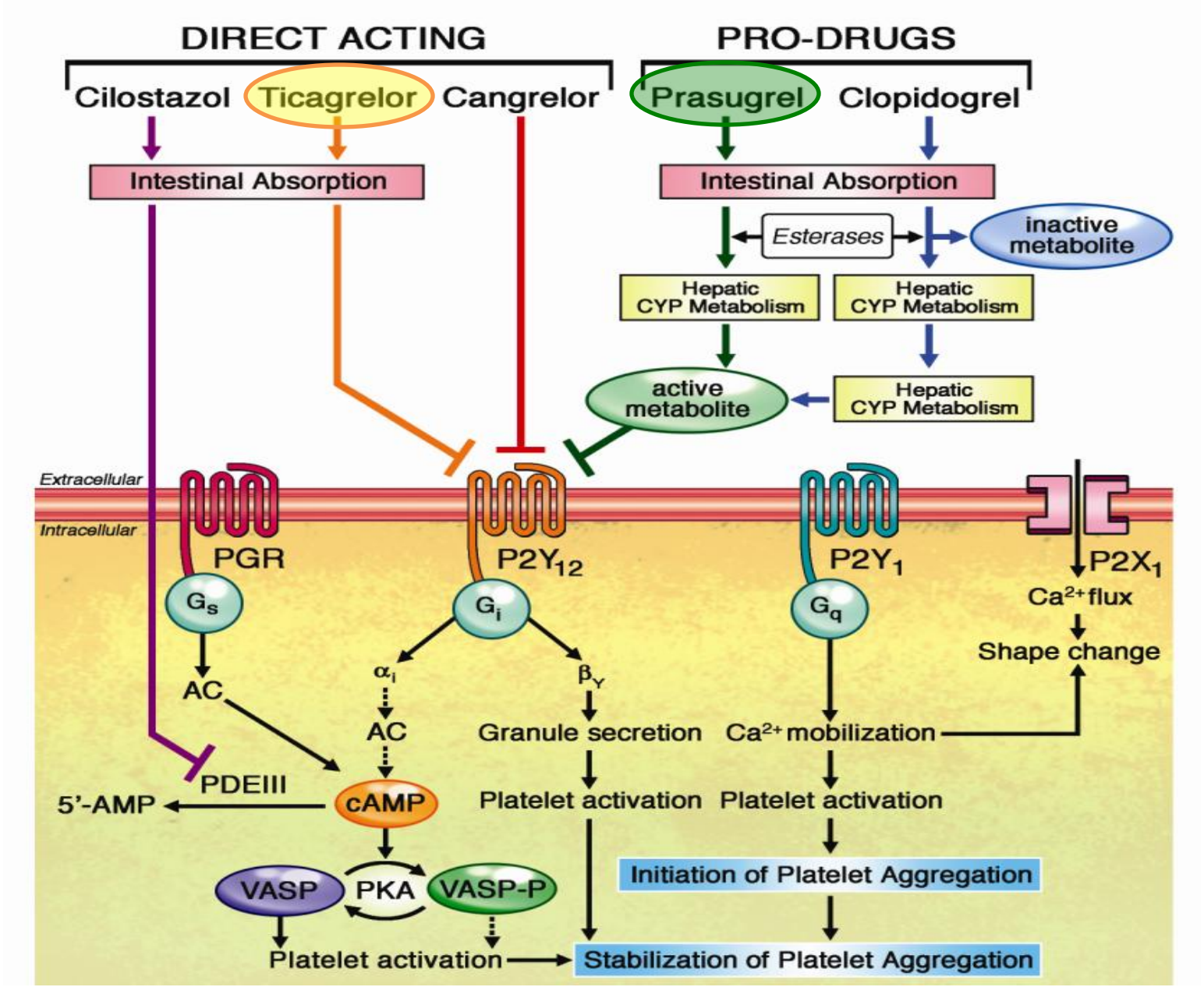
HOST ASSURE

Composite of Cardiac death, nonfatal MI, stroke, definite/probable ST, and PLATO major bleeding (KIM HS et al. ACC/i2 LBCT 2011)



No. at Risk						
TAT	1,879	1,855	1,845	1,832	1,763	1,538
DDAT	1,876	1,848	1,836	1,820	1,764	1,525

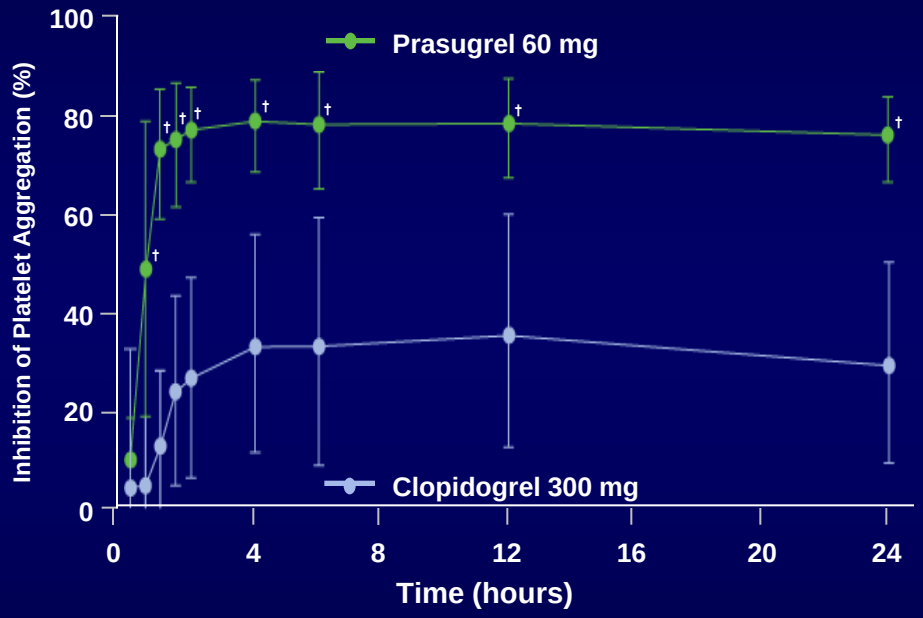
Strategies of ADP P2Y12 mediated platelet inhibition

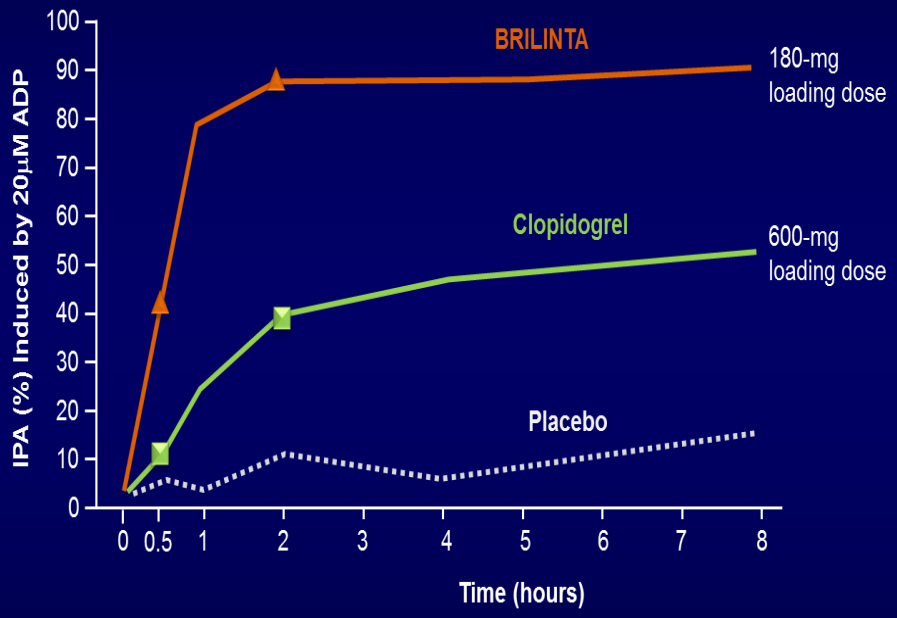


Angiolillo DJ et al. JACC Interv 2011

Inhibition of Platelet Aggregation (IPA)

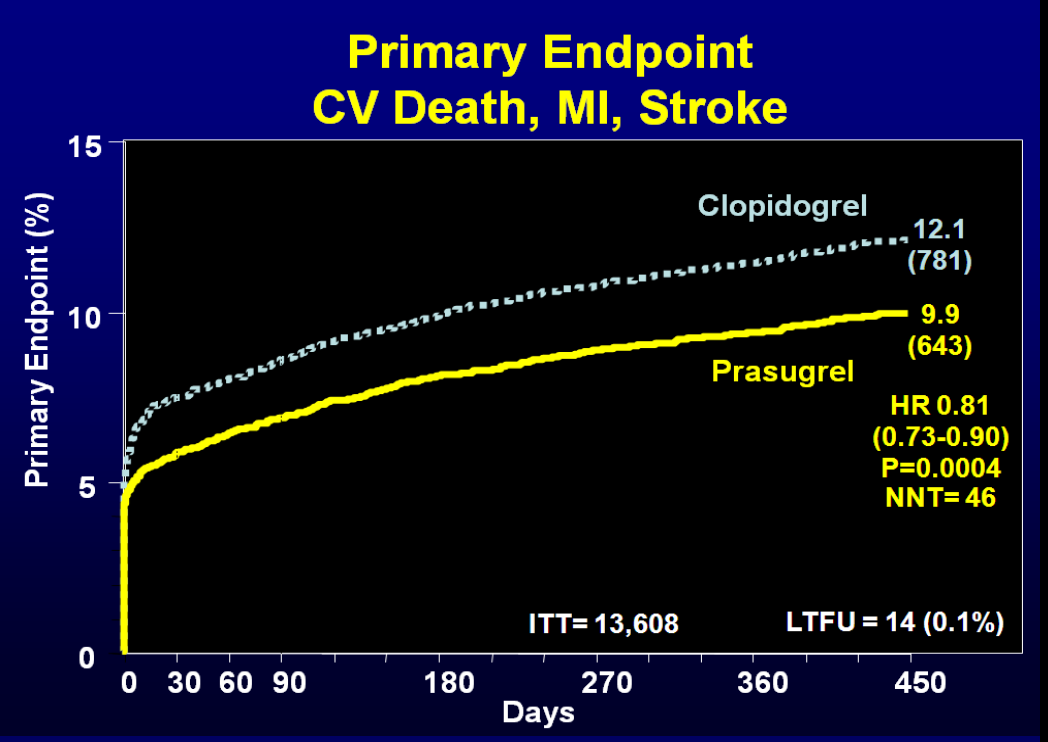
LTA - ADP (20 μmol/L)-induced

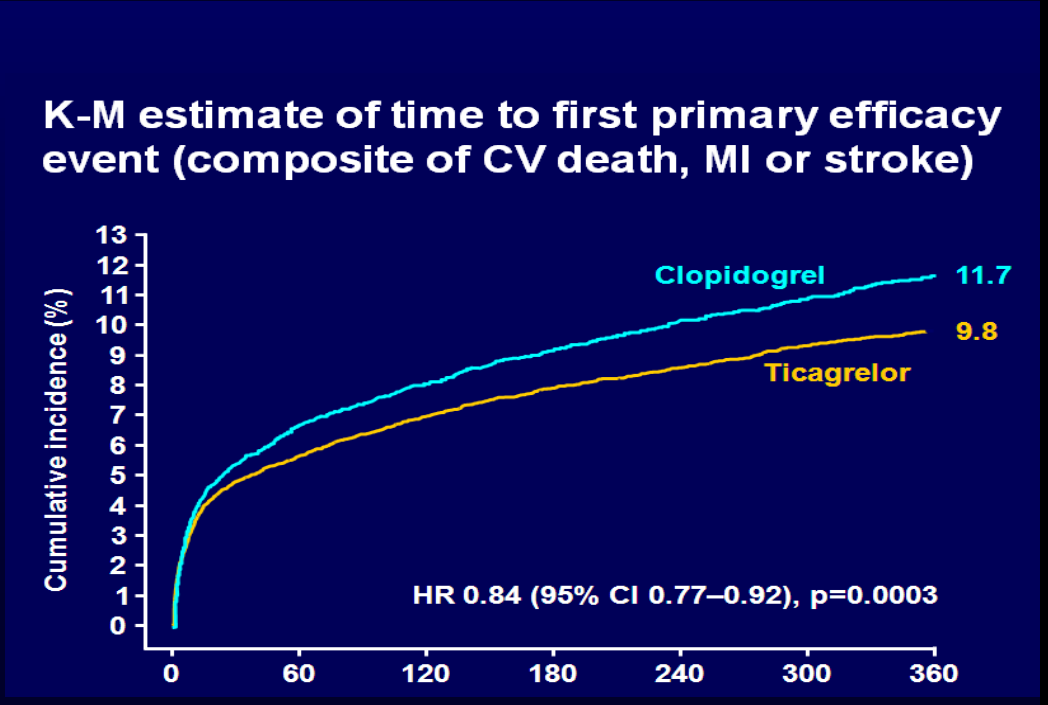




Rule of "3P's": More Prompt, Potent, and Predictable!

even compared with clopidogrel high LD (600-900mg) and MD (150mg)



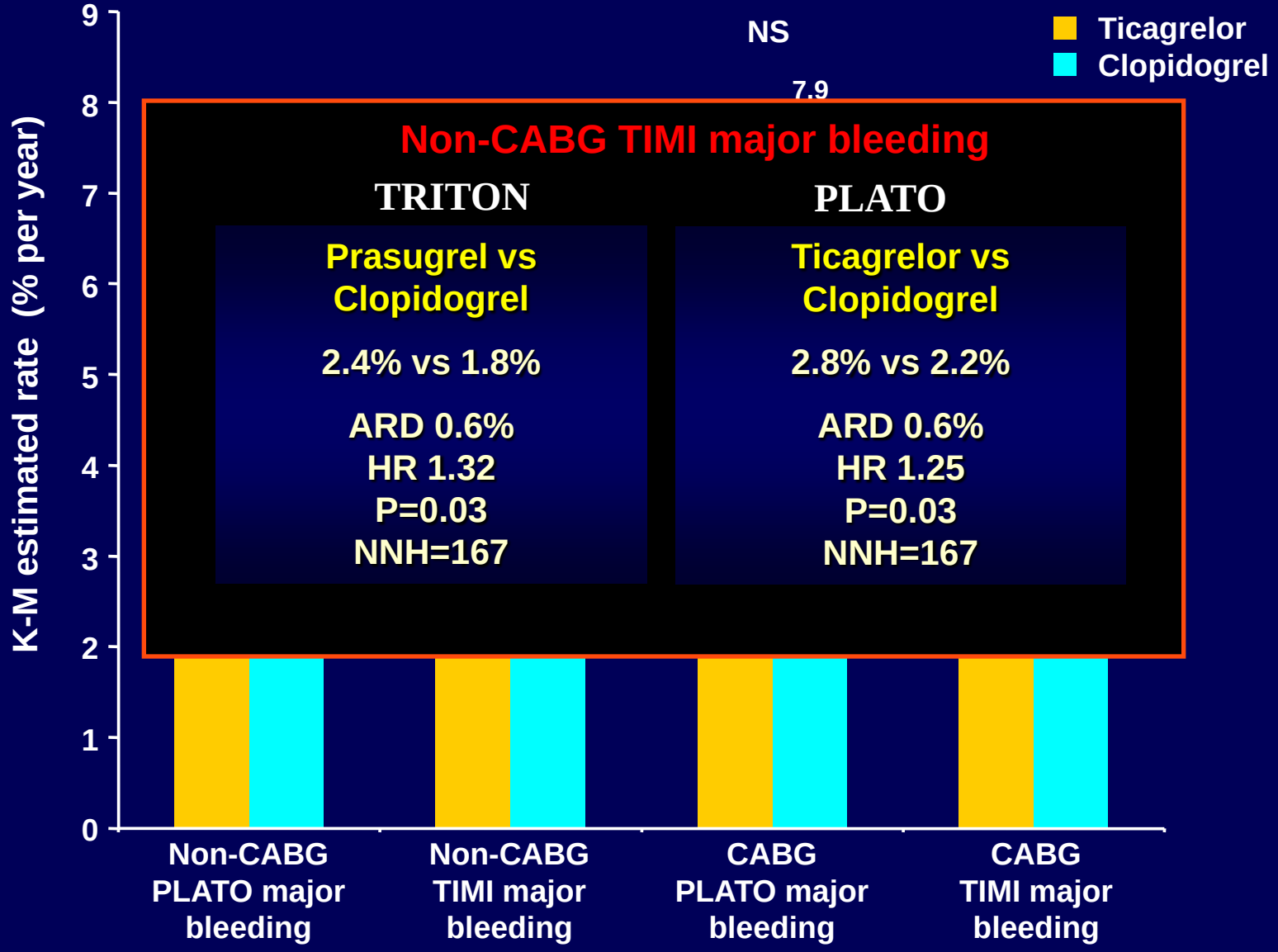


TRITON TIMI 38
(prasugrel vs clopidogrel)

PLATO
(ticagrelor vs clopidogrel)

Non-CABG and CABG-related major bleeding

PLATO



TRITON vs PLATO

Proof of concept: Higher IPA to Support ACS

Differences between trials

1. **Patient Population**
   TRITON: ACS undergoing PCI
   PLATO: Full spectrum ACS
2. **Pretreatment**
   TRITON: No pretreatment (except STEMI)
   PLATO: Pretreatment
3. **Clopidogrel Loading Dose**
   TRITON: 300mg
   PLATO: 300-600mg
4. **Duration of trial (median)**
   TRITON: 14.5 months
   PLATO: 9 months

ESC Guidelines for NSTE-ACS

Clopidogrel

Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A

New P2Y12 receptor antagonists

Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.[d]	I	B

Novel P2Y12 receptor antagonists: When *"NOT to Use"* or *"Use with Caution"*?

- **Prasugrel.**
  Contraindicated: high-risk bleeding; prior TIA/stroke; hypersensitivty

  Precautions: elderly, low-weight; CABG/surgery (7days).

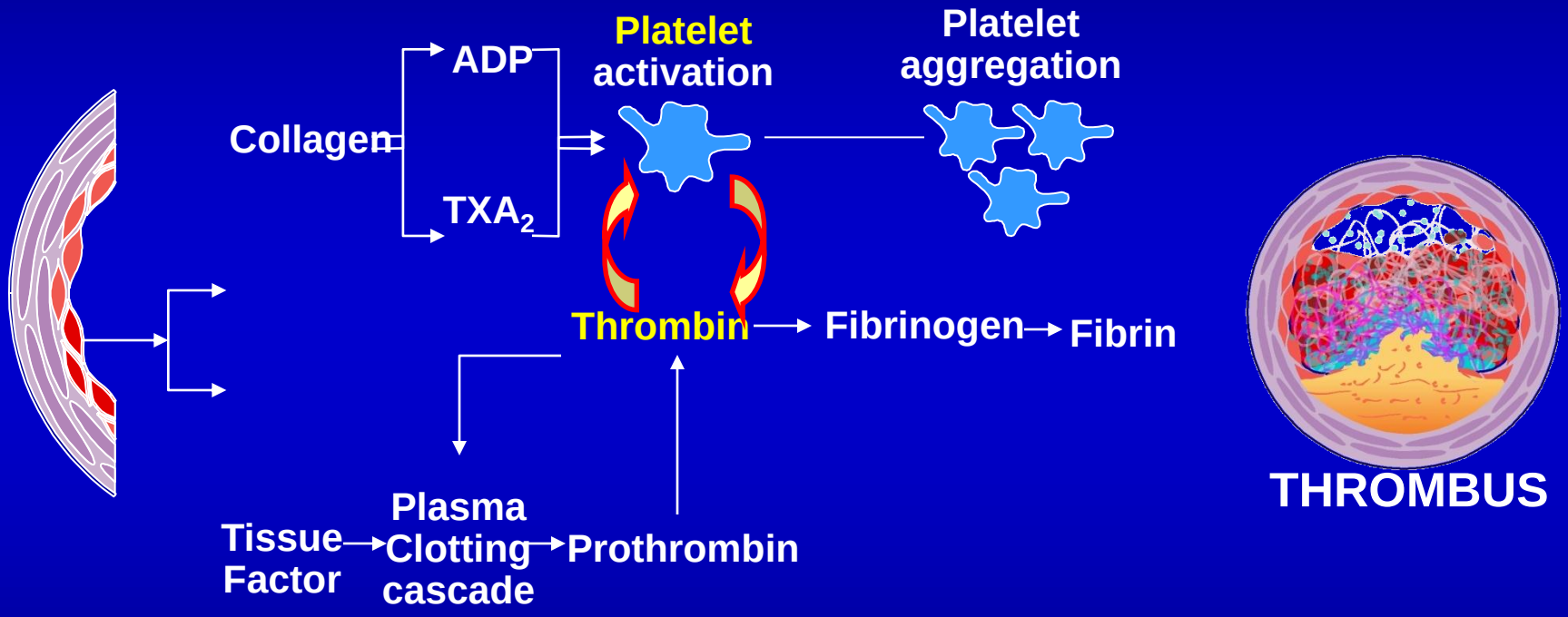
- **Ticagrelor.**
  Contraindicated: high-risk bleeding; prior hemorrhagic stroke; severe hepatic dysfunction; hypersensitivity

  Precautions: COPD/asthma, bradyarrythmia without pacemaker, compliance (b.i.d. administration), drug interactions (CYP 3A4 interfering agents); aspirin dose (<100mg), CABG/surgery (5-7days).

Is there still room for ischemic improvement?

Thrombus Formation

Two key elements: cellular (platelets) and plasmatic (coagulation factors)



How to Modulate Thrombin Effects

- Thrombin receptors on platelets
  - PAR-1 receptor antagonists (vorapaxar)
- Circulating (plasma) thrombin
  - Oral anticoagulants (anti-II and anti-X)

Oral Anticoagulants in ACS

What about factor IIa antagonists?

~~Ximelagatran~~ (ESTEEM)

~~Dabigatran~~ (stopped phase 2 REDEEM)

What about factor Xa antagonists?

~~Darexaban~~ (RUBY-1)

Rivaroxaban (ATLAS ACS 2)

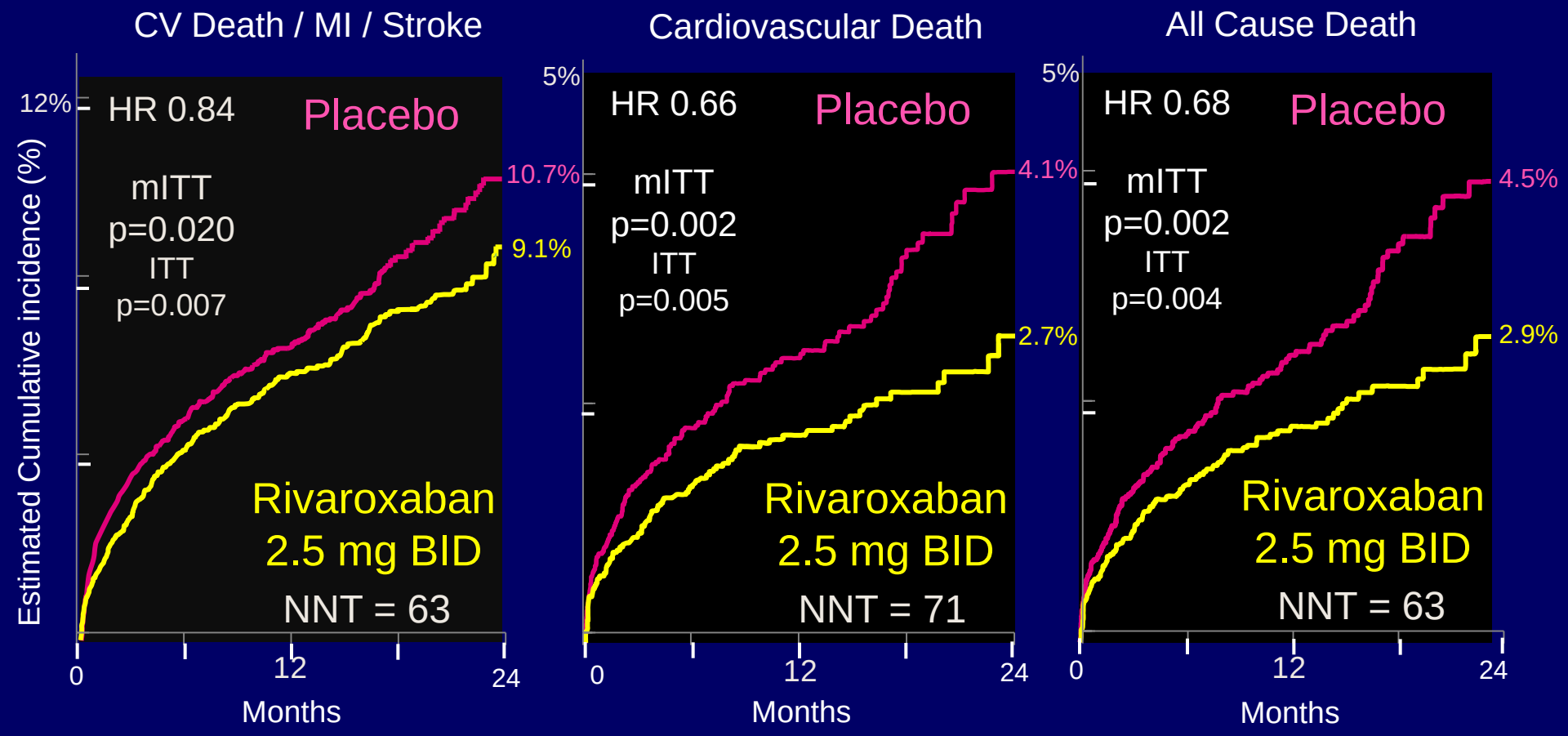
~~Apixaban~~ (APPRAISE 2)

Not Studied in ACS

Edoxaban (only Afib, phase III ongoing)

Betrixaban (only Afib, phase II completed)

Efficacy Endpoints: Very Low Dose 2.5 mg BID



Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM, *NEJM* 2012

Safety Endpoints

	Placebo	Rivaroxaban 2.5 mg BID	Rivaroxaban 5 mg BID
Non-CABG TIMI Major	0.6%	1.8% (P<0.001)	2.4% (P<0.001)
ICH	0.2%	0.4% (P=0.04)	0.7% (P=0.005)
Fatal	0.2%	0.1% (P=NS)	0.4% (P=NS)
Fatal ICH	0.1%	0.1% (P=NS)	0.2% (P=NS)

2-yr KM event rates

Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM, *NEJM* 2012

Antithrombotic Therapies

Antithrombotic Therapy

COMPARATOR	TRITON TIMI 38	PLATO	ATLAS ACS 2 TIMI 51
Aspirin	Aspirin	Aspirin	Aspirin
+	+	+	+
Clopidogrel Standard Dose	Prasugrel	Ticagrelor	Clopidogrel Standard Dose
			+
			Rivaroxaban (Very Low Dose 2.5 mg BID)*

CV Endpoints

* Not approved for ACS in US

Is there a winner?