Antiplatelet Options: The Changing Landscape

Alternative and Next Antiplatelet Therapy Beyond ADP Blocker

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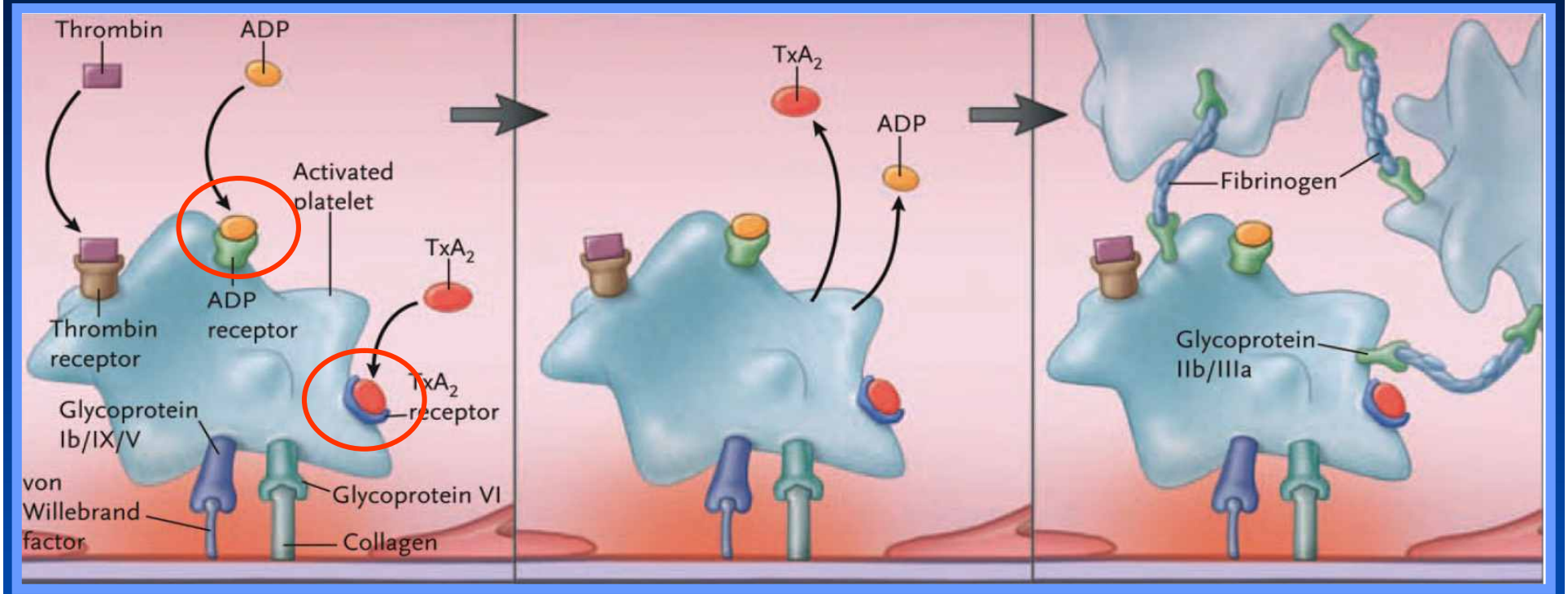
Disclosures

Duk-Woo Park, MD, PhD

I have no real or apparent conflicts of interest to report

Dual antiplatelet therapy in the setting of ACS or PCI



- DAT with aspirin and clopidogrel have complementary mechanisms of action and are the current standard of care in patients with CAD.
- Over the 10 years, physicians have had few new antiplatelet options available to them for the treatment of acute and chronic CAD.

Limitations of clopiodogrel

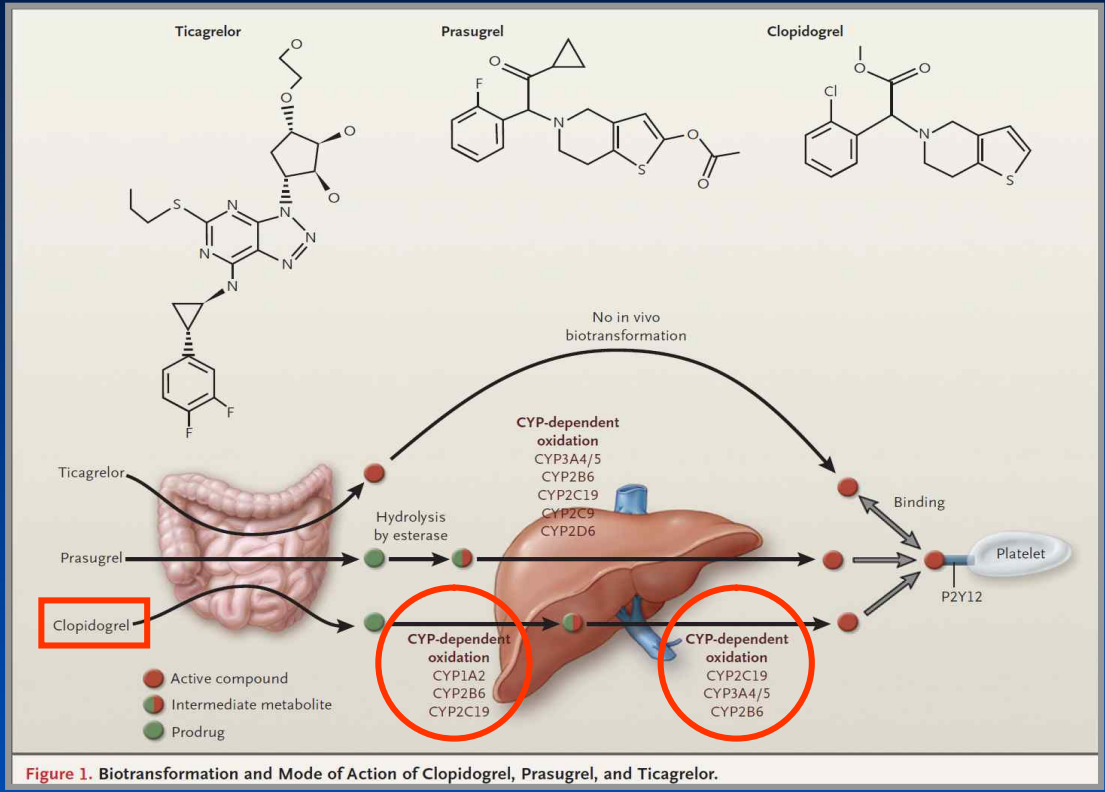


Figure 1. Biotransformation and Mode of Action of Clopidogrel, Prasugrel, and Ticagrelor.

- Clopidogrel require two separate steps for activation.

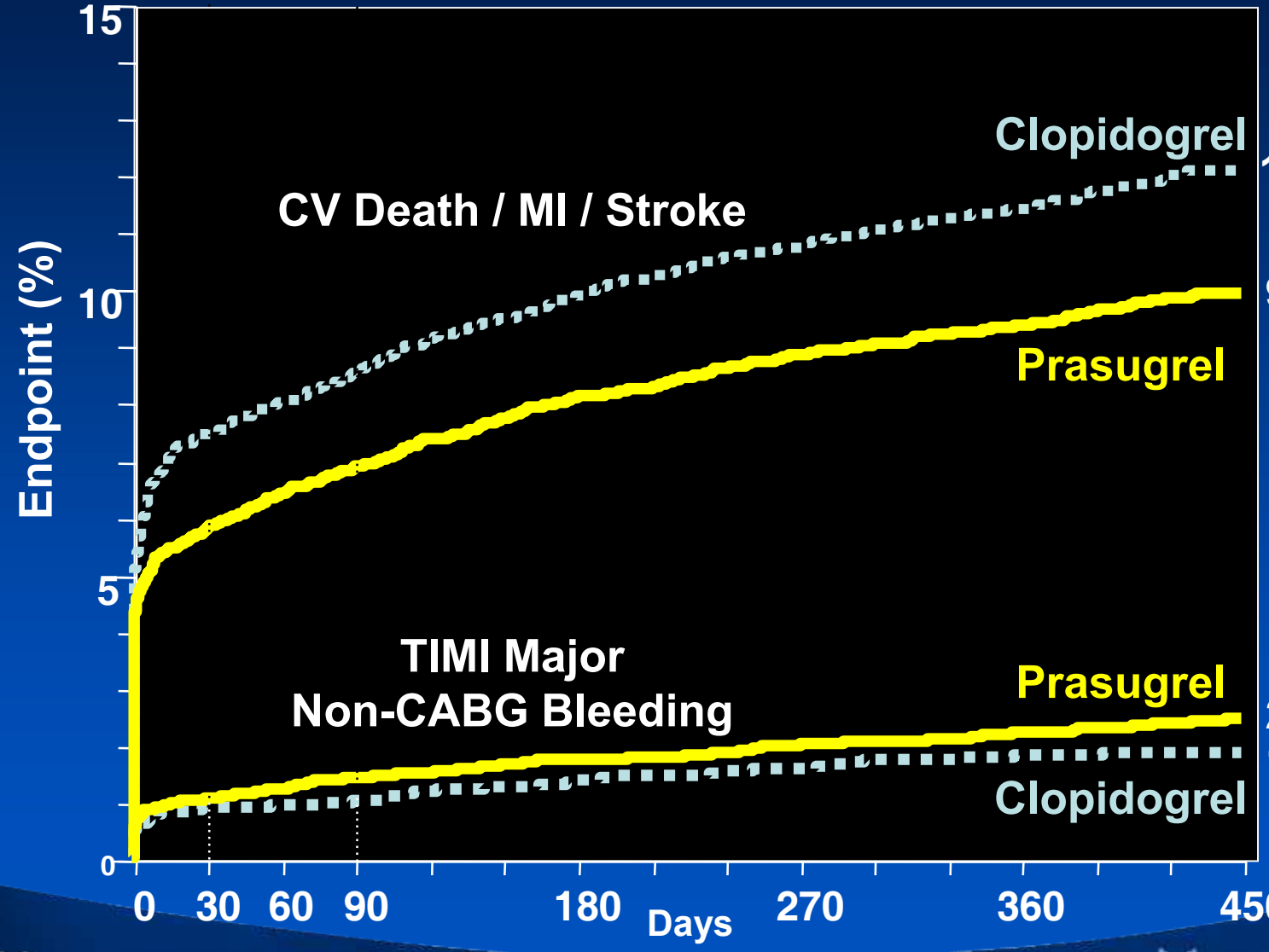
(1) Rapidity and predictability/variability of effect
(2) Several drug-drug interactions
(3) Vulnerable to genetic polymorphism

New P2Y12 antagonists

ADP blocker	Type	Action	Phase III Trial	Dose	Action time
Clopidogrel (oral)	Thienopyridine Hepatic conversion	Irreversible binding	CURE CREDO PCI-CURE	300-600 mg LD 75 mg QD MD	15-20% 300mg: 8-24hr 600mg: 2-6hr 75mg QD: 5-7days
Prasugrel (oral)	Thienopyridine Hepatic conversion	Irreversible binding	TRITON-TIMI38	60 mg LD 15 mg QD MD	70% < 1hr
Ticagrelor (oral)	Cyclopentyltri-azolopyrimidine Direct inhibition	Competitive binding	PLATO	90 mg bid	95% <1h, peak 2-3h
Cangrelor (i.v.)	ATP analogue Direct inhibition	Competitive binding	CHAMPION	4 mcg/kg/min	95% Few minutes
Elinogrel (i.v. and oral)	Novel Thienopyridine	Competitive binding	Planning	10-60 mg	95% Few minutes

Prasugrel Lowers Events, but Increase Bleeding versus Clopidogrel in ACS

TRÎTON TIMI-38



↓138 events
HR 0.81
(0.73-0.90)
P=0.0004
NNT = 46

↑35 events
HR 1.32
(1.03-1.68)
P=0.03
NNH = 167

Wiviott et al. N Eng J Med. 2007;357:200

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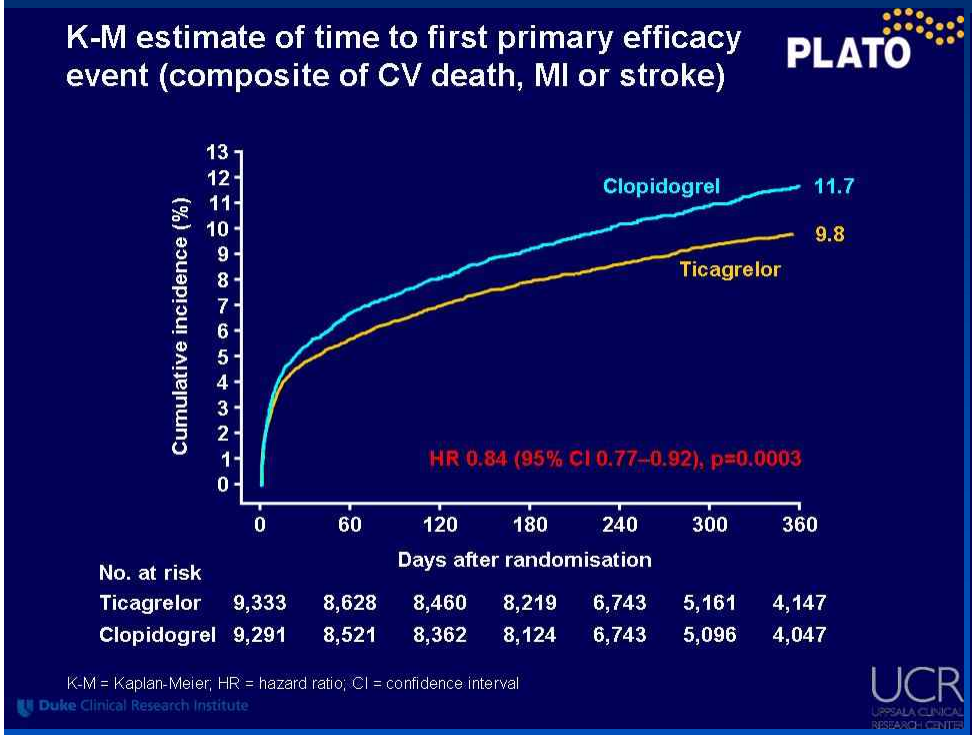
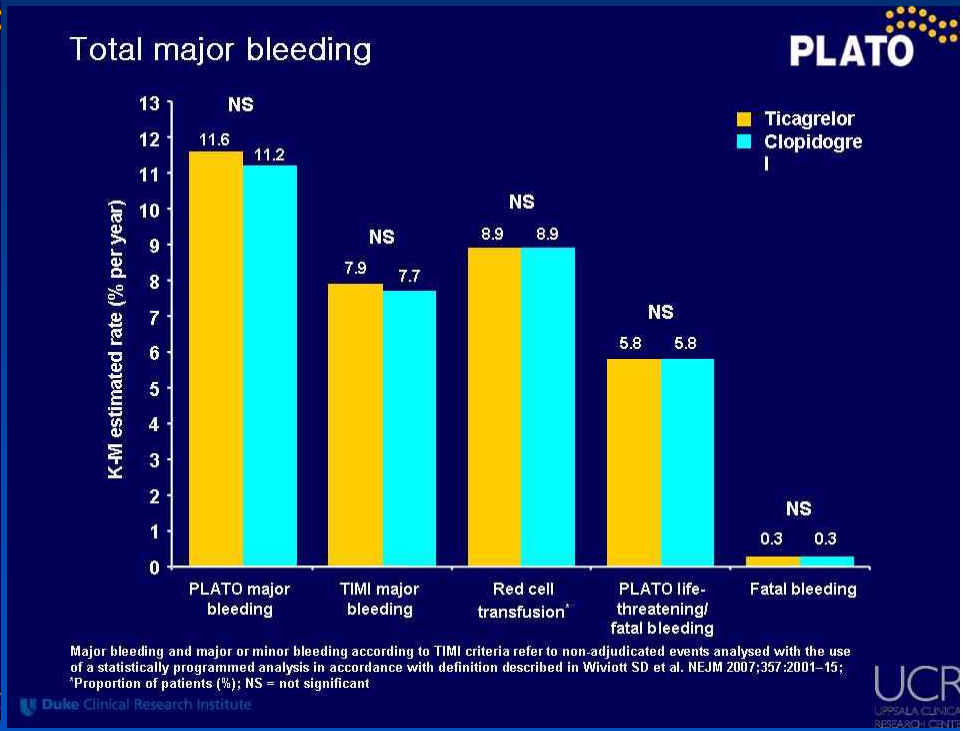
Ticagrelor Lowers Events, and Have a Similar Risk of Major Bleeding versus Clopidogrel in ACS.

Efficacy Outcomes



Safety Outcomes



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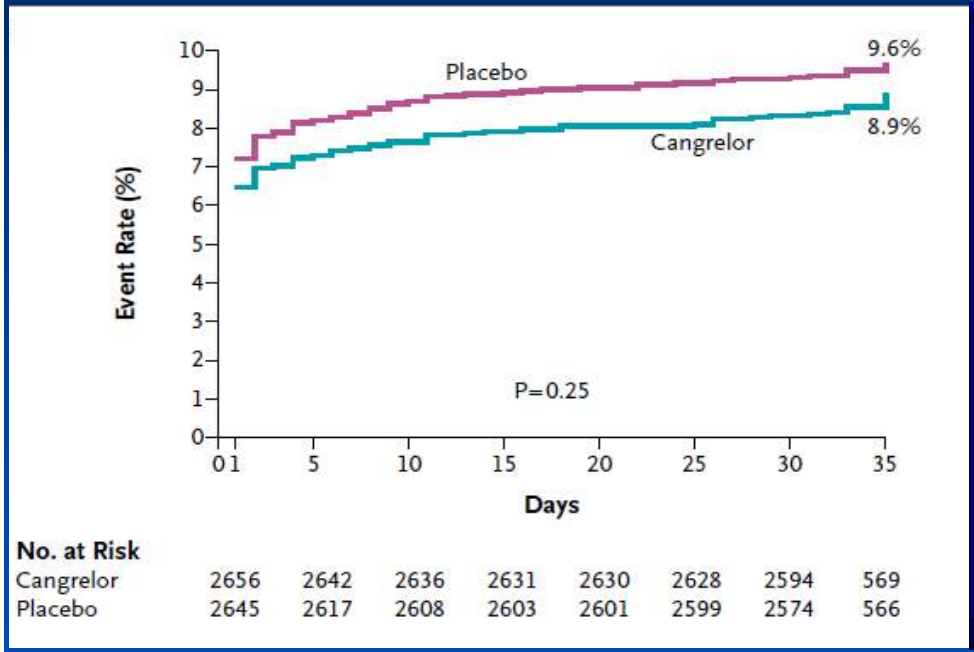
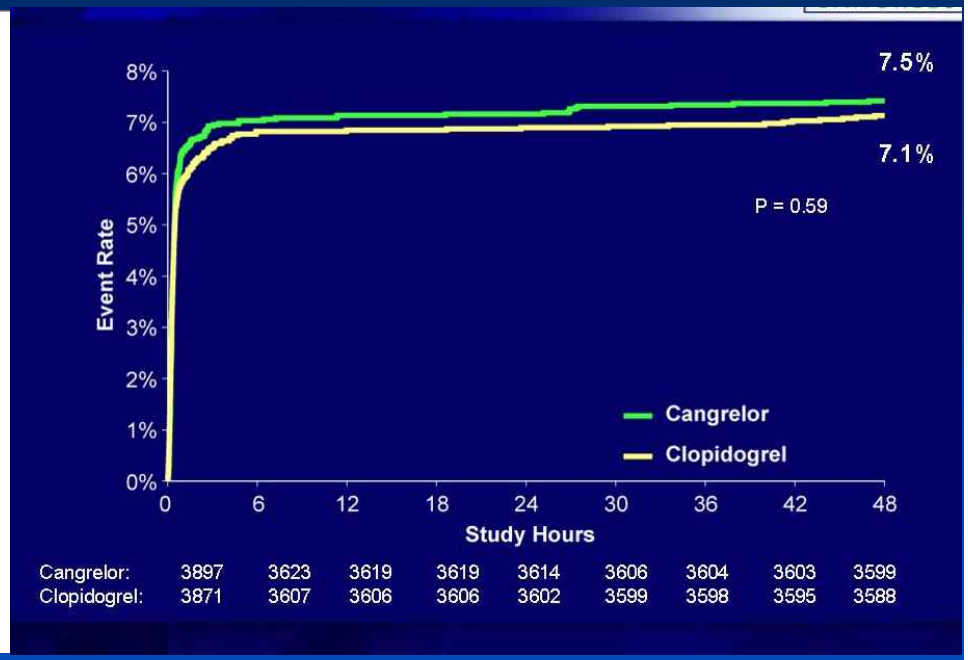
Wallentin et al. N Engl J Med. 2009;361:1045-57

Rapid-acting, reversible, i.v., ADP blocker (Cangrelor) in ACS and PCI settings

Primary Endpoint: 48-hr Death/MI/IDR





Cangrelor was not superior to 600 mg clopidogrel in ACS and PCI setting.

Bhatt et al. N Engl J Med. 2009;361:2330-41

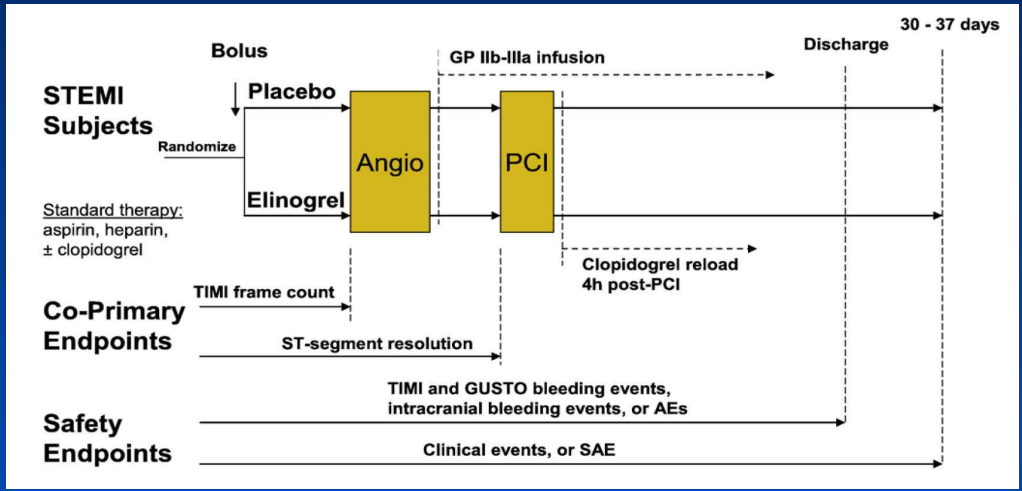
Harrington et al. N Engl J Med. 2009;361:2318-2

Elinogrel (PRT060128);

a novel, direct-acting, reversible, IV or oral P2Y12 antagonist

ERASE-MI

A pilot, phase IIA, dose-escalation RCT to evaluate the safety and tolerability of escalating doses (10, 20, 40, and 60 mg) of elinogrel iv bolus before the start of the diagnostic angiogram preceding primary PCI.



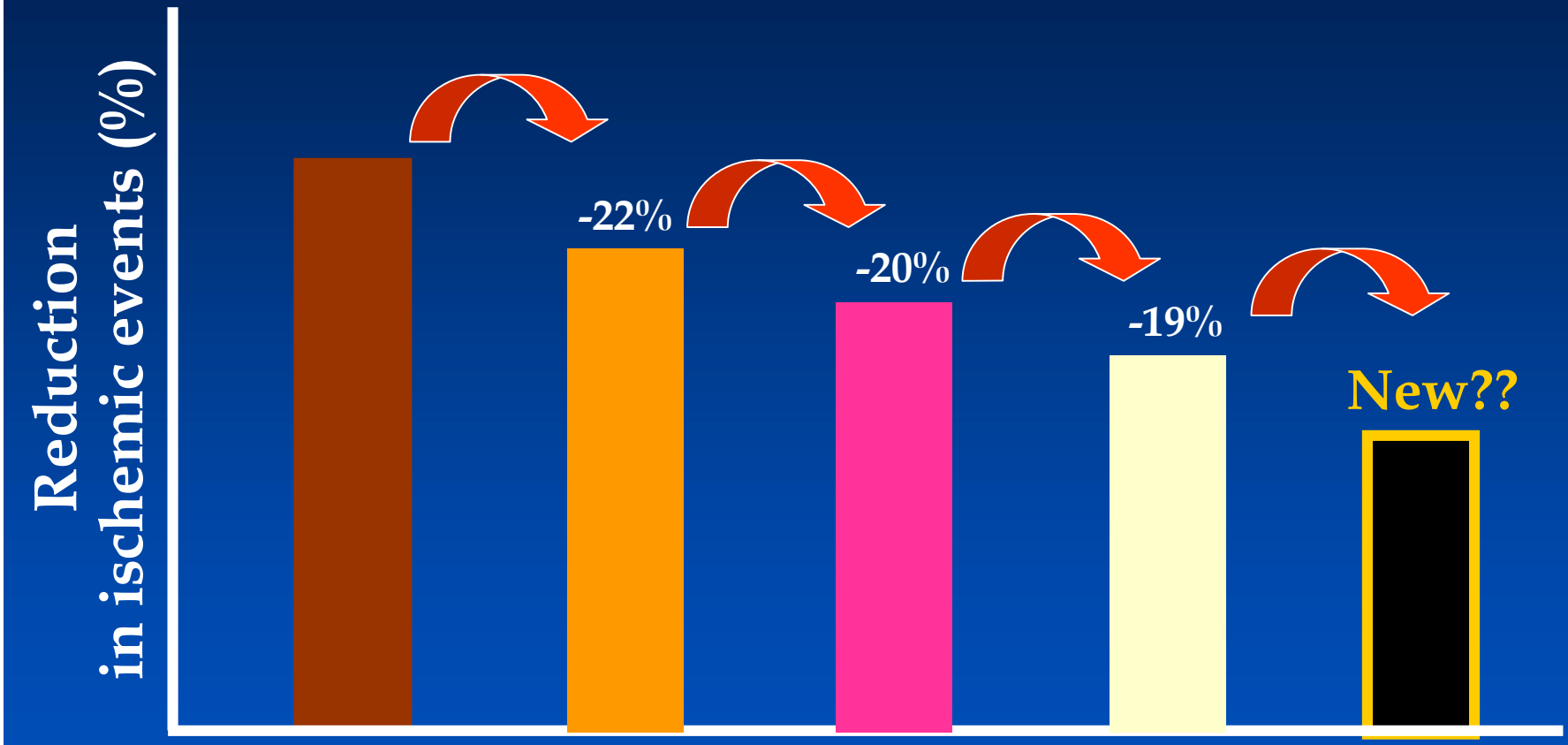
INNOVATE-PCI

A nonurgent PCI trial to compare both IV and oral dosing of elinogrel with clopidogrel.

Phase III (PRT128A2301)

To compare both IV and oral dosing of ellinogrel with clopidogrel in approximately **19,000** ACS (NSTEMI and STEMI) patients, alike TRITON-TIMI 38 or PLATO trial

Evolution of Anti-platelet Therapy Significantly Improves Outcomes

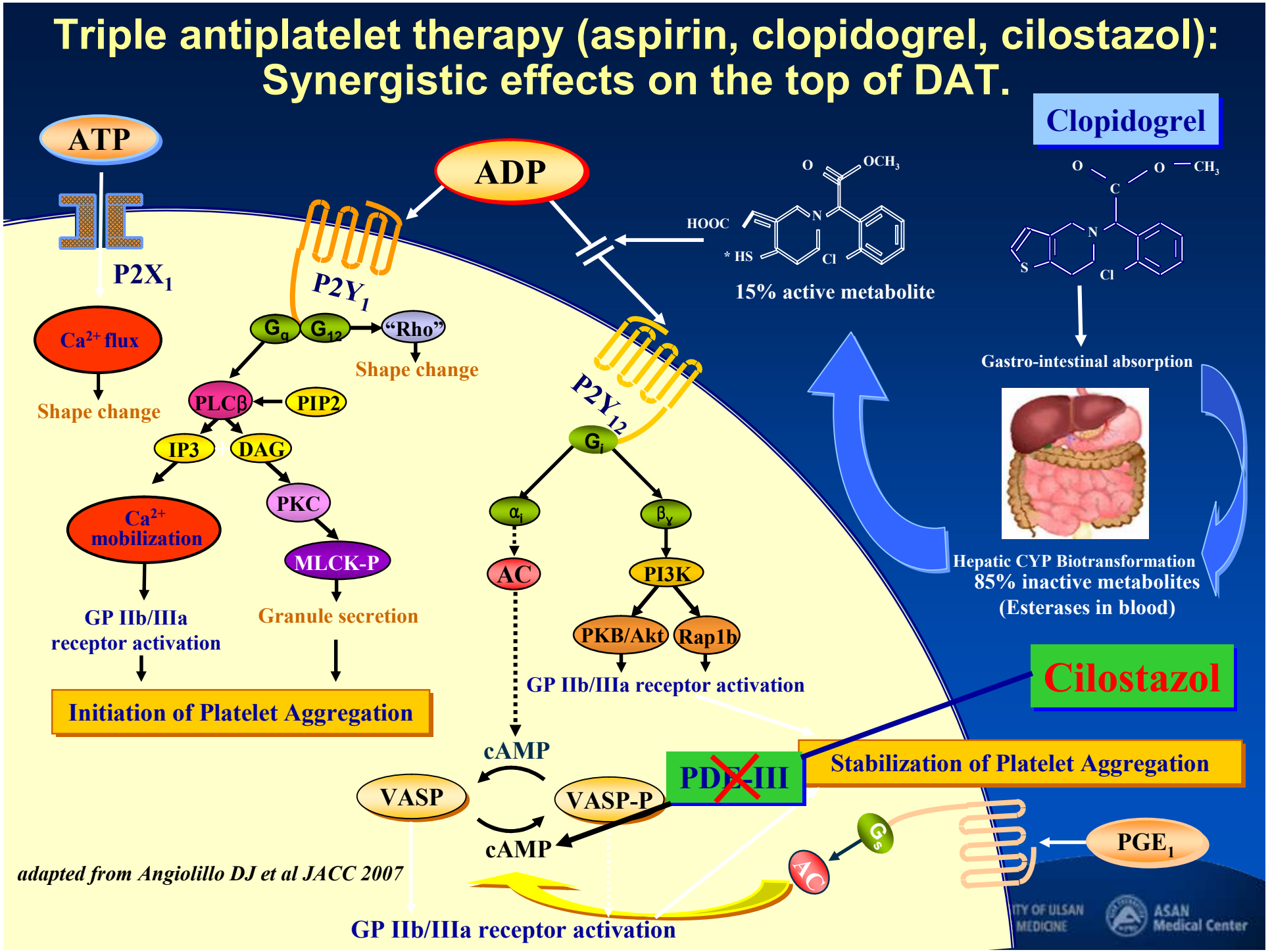


Before
New Antiplatelet Therapy....

What Is Good
Alternative or Additive Antiplatelet Therapy
in Current Practice
In addition to DAT ??

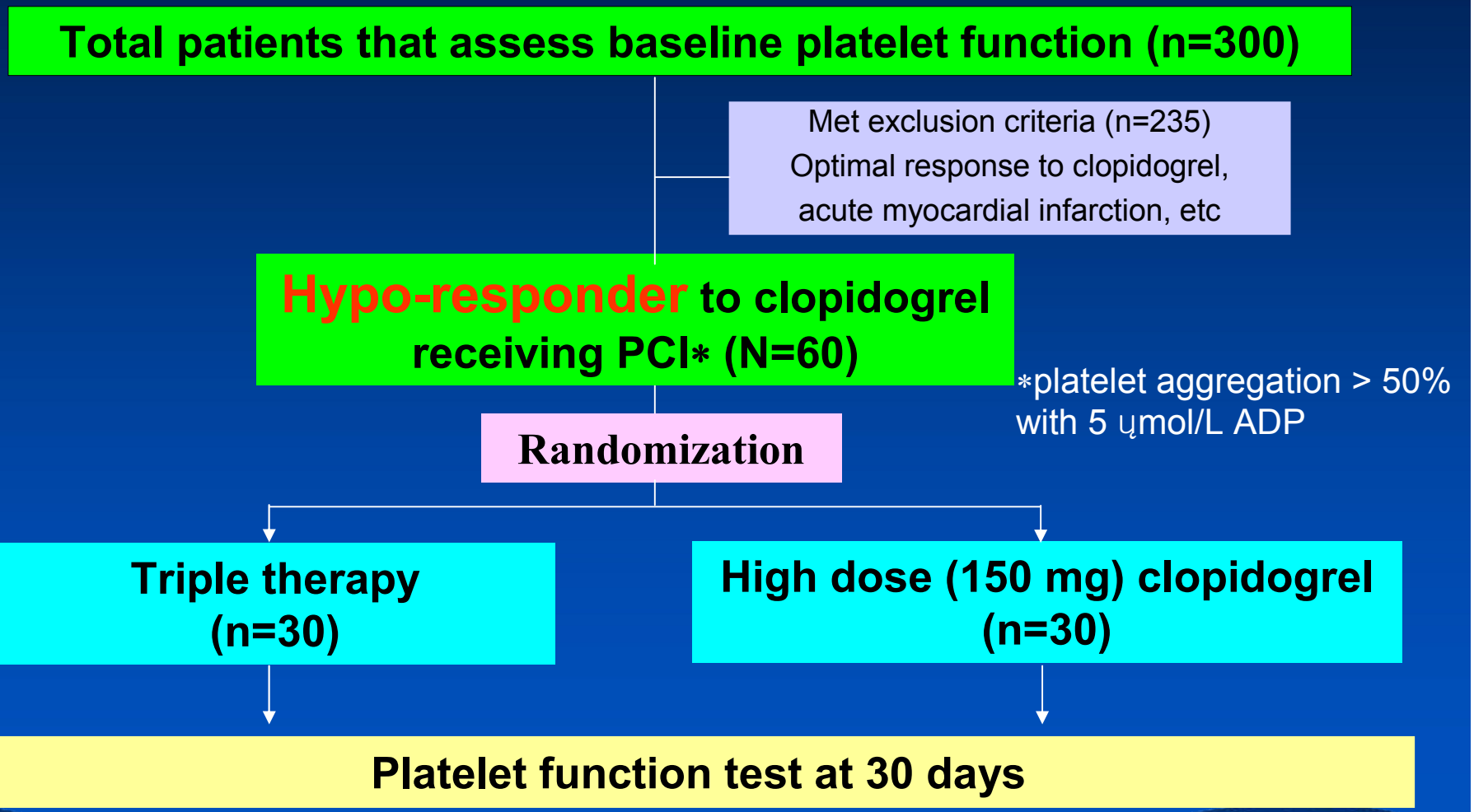
Cilostazol

Triple antiplatelet therapy (aspirin, clopidogrel, cilostazol): Synergistic effects on the top of DAT.



Asan Medical Center and
Gyeongsang National University Hospital experience

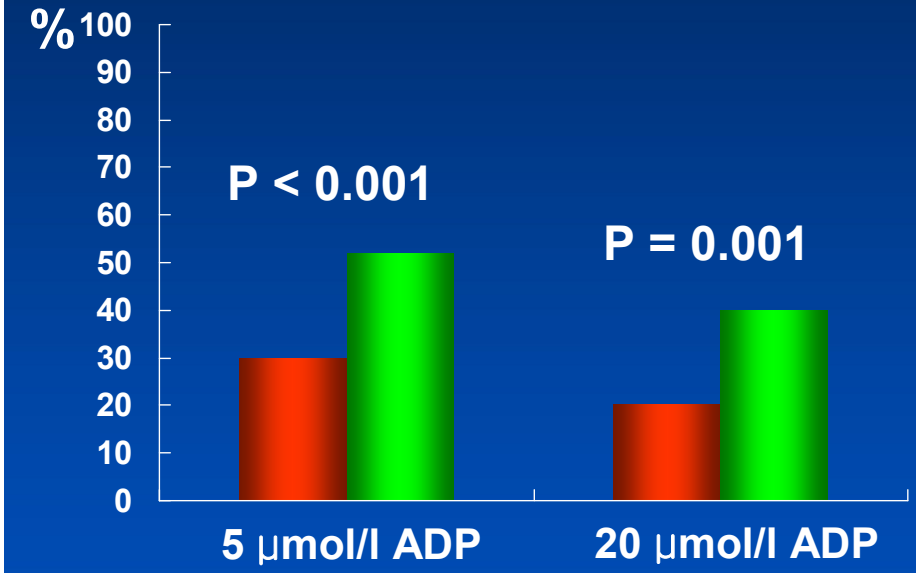
ACCEL-RESISTANCE study



J Am Coll Cardiol 2009;53:1101-9

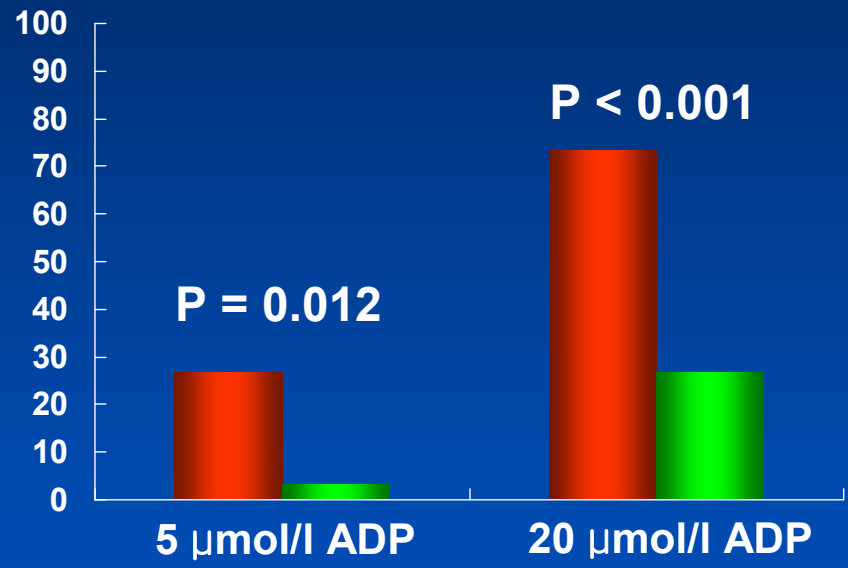
Primary Outcome: 1-months Platelet Function Assay

Inhibition of maximal platelet aggregation



Rate of clopidogrel hyporesponsiveness;

(ADP-induced maximal platelet aggregation > 50)



High dose clopidogrel (n=30)

Triple group (n=30)

J Am Coll Cardiol 2009;53:1101-9

Efficacy of cilostazol in reducing death, MI, or Stent thrombosis in PCI or ACS patients.

- DECREASE Registry
  ; Routine PCI patients with DES
- KAMIR Registry
  ; STEMI patients with primary PCI
- Chinese-ACS RCT
  ; ACS-PCI RCT

DECREASE Registry

AMC data

3099 Real-world patients receiving DES;
1443 triple vs. 1656 dual group.

12Mo-Outcomes	Crude		IPTW		Propensity-matched (965 pairs)	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Cardiac events						
Death	0.925 (0.521 -1.644)	0.7907	0.762 (0.401-1.448)	0.4062	0.644(0.300-1.381)	0.2584
MI	0.381 (0.138-1.048)	0.0617	0.233 (0.077-0.703)	0.0097	0.298 (0.082-1.086)	0.0665
Stent thrombosis	0.286 (0.081-1.013)	0.0524	0.136 (0.035-0.521)	0.0036	0.124 (0.016-0.996)	0.0496
Death/MI	0.761 (0.464-1.251)	0.2817	0.591 (0.3364-1.037)	0.0665	0.556 (0.287-1.075)	0.0811
Bleeding						
Major bleeding	0.850 (0.477-1.516)	0.5830	0.969 (0.443-2.119)	0.9372	0.683 (0.343-1.360)	0.2781
Minor bleeding	1.039 (0.757-1.426)	0.8125	1.062 (0.734-1.537)	0.7504	1.045 (0.703-1.555)	0.8267

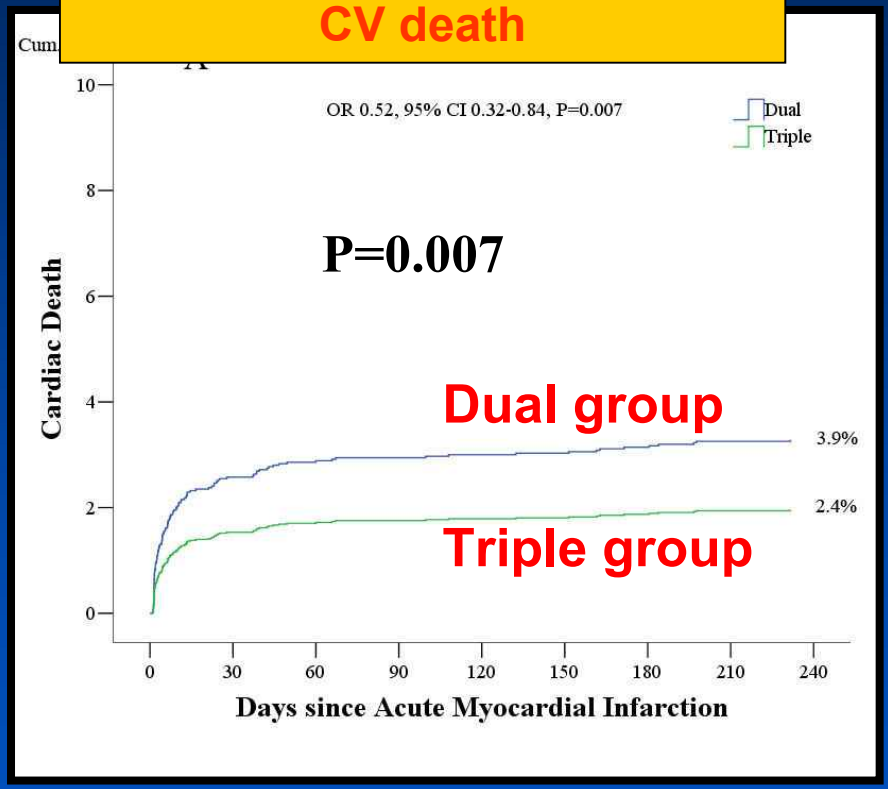
HR for the triple group vs. the dual group.

Jeong et al. Am Heart J. 2010;159:284-291

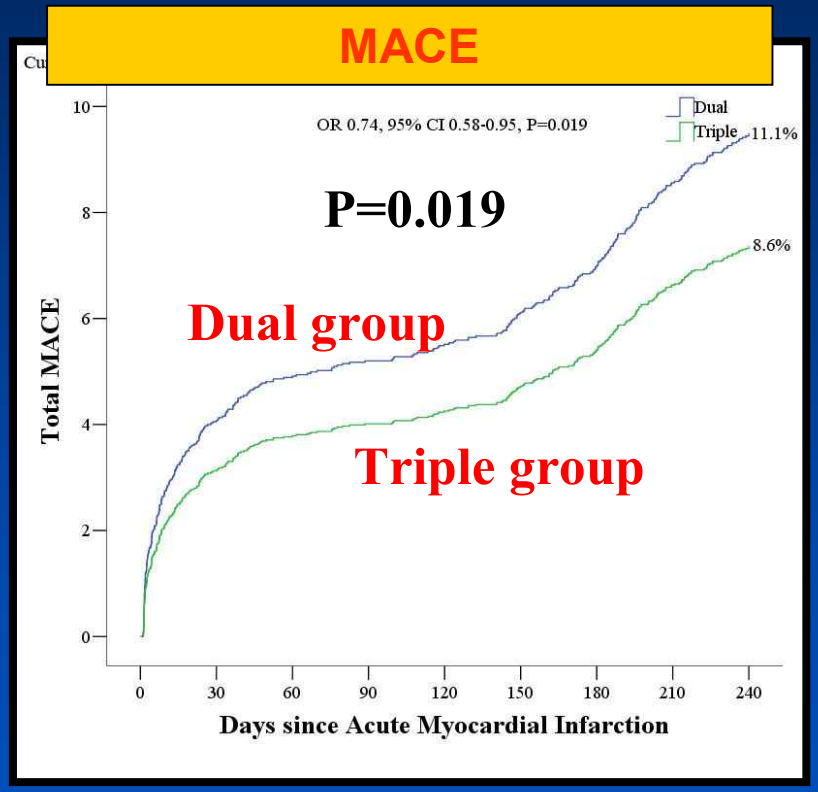
KAMIR Registry

4203 STEMI with primary PCI;
1634 triple vs. 2569 dual group.

CV death



MACE



*MACE: death/MI/repeat revascularization

Chinese-ACS RCT

1,212 ACS were randomly assigned to dual (n = 608) vs. triple-Tx. with a 6-month course of cilostazol (n = 604) after successful PCI

The primary end point (MACCE) :
composite of cardiac death, nonfatal MI, stroke, or TVR at 1 year

	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

Efficacy of cilostazol in reducing restenosis in patient receiving stent implantation.

EuroIntervention

10 RCT (2,809 patients) comparing triple vs. dual after BMS or DES implantation

Efficacy of Cilostazol in reducing restenosis in patients undergoing contemporary stent based PCI: a meta-analysis of randomised controlled trials

Umesh Tamhane[1], MD; Pascal Meier[1], MD; Stanley Chetcuti[1], MD, FACC; Kang-Yin Chen[2], MD, PhD; Seung-Woon Rha[3], MD, PhD, FACC, FAHA; Michael P. Grossman[1], MD, FACC; Hitinder Gurm[1]*, MD, FACC

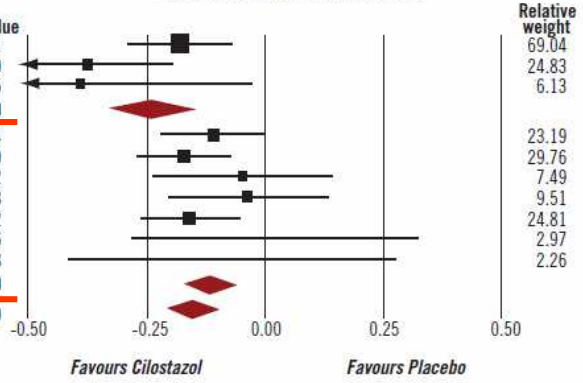
1. University of Michigan Cardiovascular Medicine, VA Ann Arbor Health Care System, Ann Arbor, MI, USA; 2. Second Hospital of Tianjin Medical University, Cardiovascular Center, Tianjin, China; 3. Cardiovascular Center, Korea University Guro Hospital, Seoul, Republic of Korea

Angiographic Outcomes

Late Loss

Figure 2. The Forest plot of mean difference of late loss. Sizes of data markers are proportional to the weight of each study in the meta-analysis. Horizontal bars=95% CI.

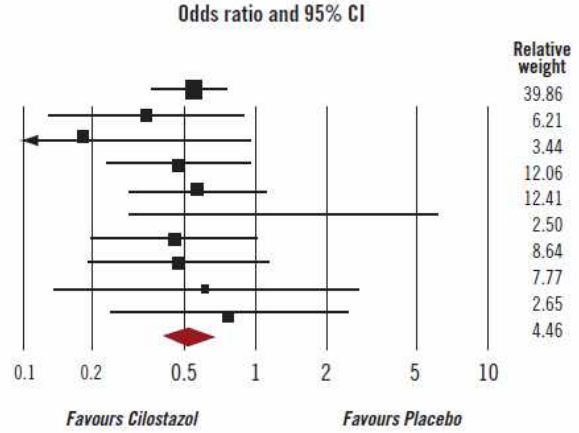
Study name	Stent type	Year	Difference in means	Standard error	Number of Patients Cilostazol	Number of Patients Control	Lower limit	Upper limit	p-Value	Relative weight
CREST	BMS	2005	-0.180	0.055	259	267	-0.288	-0.072	0.001	69.04
CHEN YD et al	BMS	2006	-0.370	0.092	52	54	-0.550	-0.190	0.000	24.83
Min PK et al	BMS	2007	-0.390	0.185	35	30	-0.752	0.028	0.035	6.13
Late loss reduction in BMS subgroup			**-0.240**	**0.046**			**-0.330**	**-0.150**	**0.000**	
DECLARE-DIABETES	DES	2008	-0.110	0.054	163	167	-0.217	-0.003	0.044	23.19
DECLARE–Long	DES	2007	-0.170	0.048	210	205	-0.264	-0.076	0.000	29.76
Kim DH et al	DES	2008	-0.050	0.096	55	54	-0.238	0.138	0.602	7.49
CIDES	DES	2008	-0.040	0.085	113	124	-0.207	0.127	0.638	9.51
Lond-DES II	DES	2008	-0.160	0.053	168	164	-0.263	-0.057	0.002	24.81
Hong SJ et al	DES	2008	0.020	0.152	39	41	-0.278	0.318	0.896	2.97
Jeong JW et al	DES	2008	-0.070	0.175	23	30	-0.412	0.272	0.688	2.26
Late loss reduction in DES subgroup			**-0.124**	**0.026**			**-0.176**	**-0.073**	**0.000**	
Overall late loss reduction			-0.153	0.023			-0.198	-0.108	0.000	



Restenosis

Figure 3. The Forest plot of odds ratios of binary angiographic restenosis. Sizes of data markers are proportional to the weight of each study in the meta-analysis. Horizontal bars=95% CI.

Study name	Stent type	Year	Odds ratio	Lower limit	Upper limit	p-Value	Restenosis / Total Cilostazol	Restenosis / Total Control	Relative weight
CREST	BMS	2005	0.537	0.364	0.791	0.002	57 / 259	92 / 267	39.86
CHEN YD et al	BMS	2006	0.339	0.127	0.904	0.031	7 / 52	17 / 54	6.21
Min PK et al	BMS	2007	0.355	0.095	1.327	0.124	4 / 35	8 / 30	3.44
DECLARE-DIABETES	DES	2008	0.470	0.232	0.951	0.036	13 / 163	26 / 167	12.06
DECLARE–Long	DES	2007	0.565	0.282	1.132	0.107	14 / 210	23 / 205	12.41
Kim DH et al	DES	2008	1.333	0.284	6.260	0.715	4 / 55	3 / 54	2.50
CIDES	DES	2008	0.450	0.196	1.034	0.060	9 / 113	20 / 124	8.64
Lond-DES II	DES	2008	0.463	0.192	1.112	0.085	8 / 168	16 / 164	7.77
Hong SJ et al	DES	2008	0.600	0.133	2.700	0.506	3 / 39	5 / 41	2.65
Jeong JW et al	DES	2008	0.756	0.237	2.405	0.635	7 / 23	11 / 30	4.46
Combined OR			0.517	0.405	0.660	0.000			

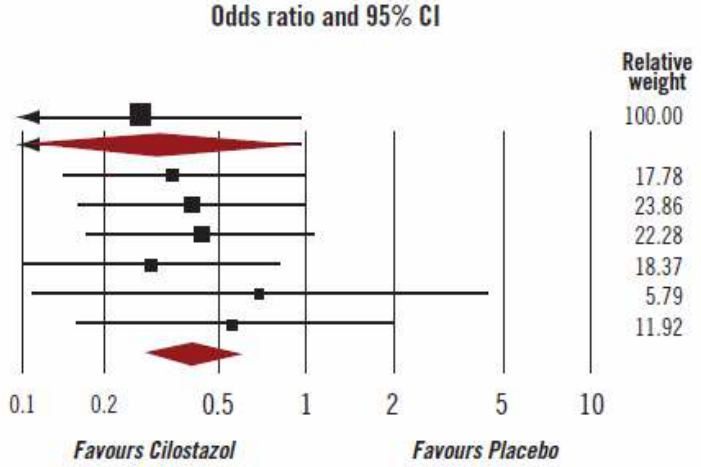


Clinical Outcomes

Target-lesion Revascularization

Figure 5. The Forest plot of odds ratios of target lesion revascularisation stratified by type of stent. Sizes of data markers are proportional to the weight of each study in the meta-analysis. Horizontal bars=95% CI.

Study name	Stent type	Year	Statistics for each study				TLR / Total		Relative weight
			Odds ratio	Lower limit	Upper limit	p-Value	Cilostazol	Control	
CHEN YD et al	BMS	2006	0.263	0.069	1.010	0.052	3 / 60	10 / 60	100.00
			0.263	0.069	1.010	0.052			
DECLARE-DIABETES	DES	2008	0.341	0.120	0.964	0.043	5 / 200	14 / 200	17.78
DECLARE–Long	DES	2007	0.395	0.161	0.970	0.043	7 / 250	17 / 250	23.86
CIDES	DES	2008	0.432	0.170	1.094	0.077	7 / 141	15 / 139	22.28
Lond-DES II	DES	2008	0.286	0.103	0.796	0.017	7 / 206	16 / 200	18.37
Hong SJ et al	DES	2008	0.677	0.109	4.194	0.675	2 / 64	3 / 66	5.79
Jeong JW et al	DES	2008	0.548	0.154	1.952	0.353	4 / 46	8 / 54	11.92
			0.397	0.256	0.615	0.000			

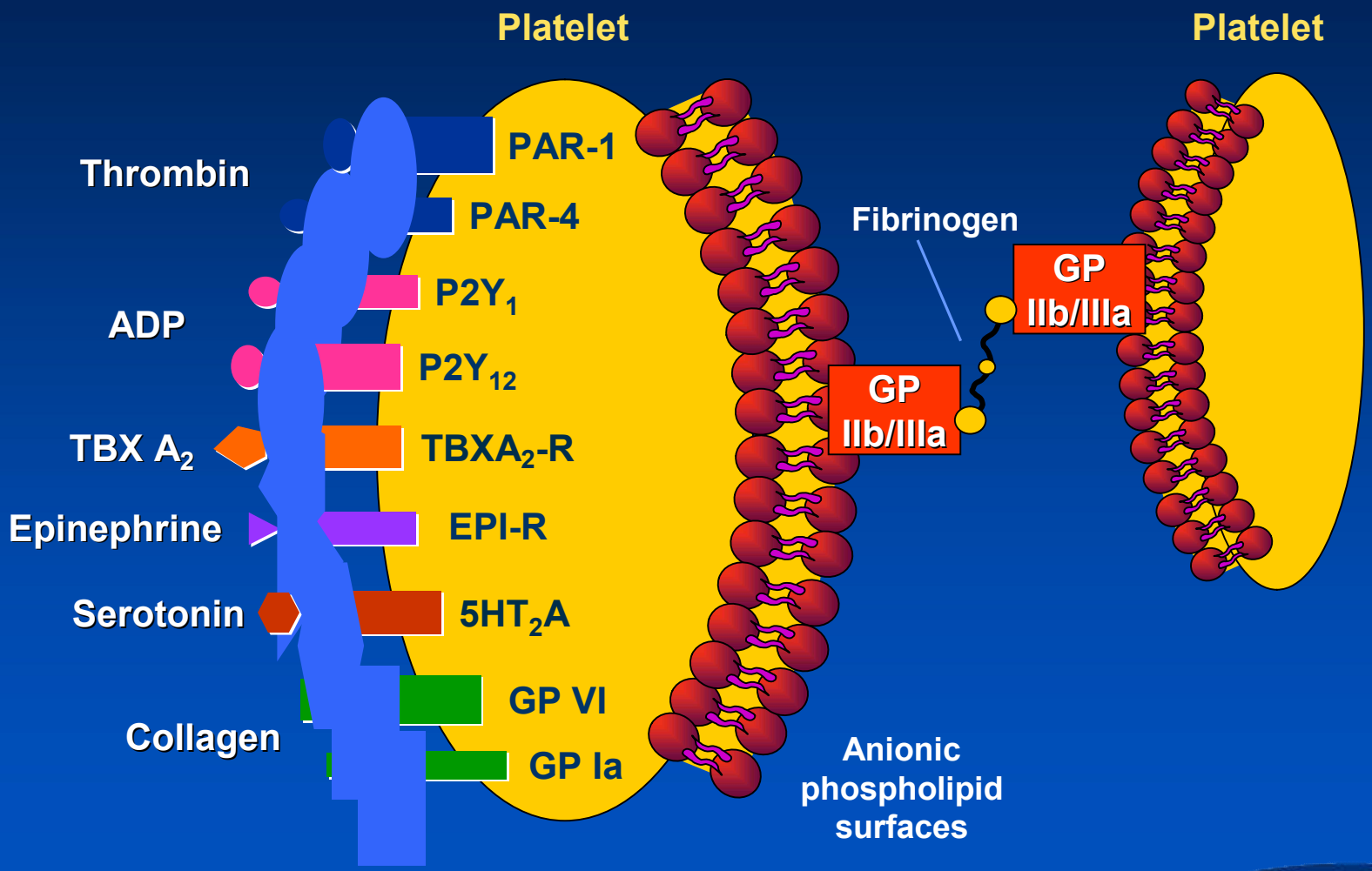


Cilostazol

Summary

- Triple antiplatelet therapy (DAT plus cilostazol) significantly reduce hard clinical endpoints (MI or stent thrombosis) in broad range of ACS and PCI patients.
- Cilostzol in addition to DAT is associated with a reduction in angiographic or clinical restenosis in patients undergoing stent-based PCI.
- **Finally, this inexpensive drug for at least 6 months may be particularly beneficial in patients who are at high risk of ischemic events or restenosis.**

Platelet Receptors: Where are new antiplatelet targets?



New Antiplatelet Agents Beyond ADP Blockers Under Development and Testing

Antiplatelet	Administration	Mechanism of action	Trials
ARC 1779	Intravenous	**vWF antagonist (A1 domain)**	Phase I trials
SCH 530348 E 555	Oral	**Thrombin receptor (PAR-1) antagonist**	Phase III trials Phase II trials
Terutorban	Oral	**Thromboxan receptor antagonists**	Phase III trials
NCX 4016	Oral	**New type COX-1 inhibitor**	Phase II trials

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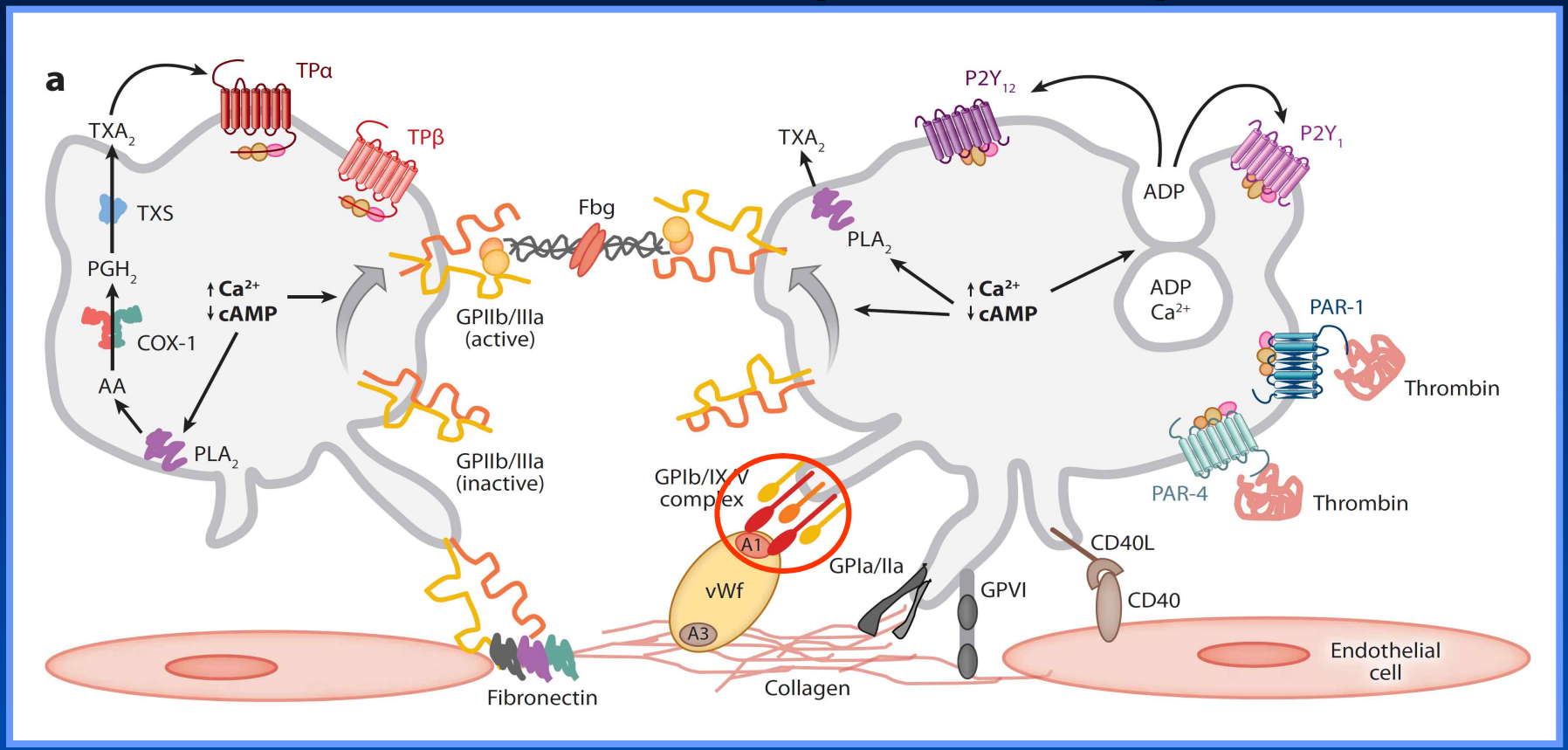
ARC 1779 (apatmer)

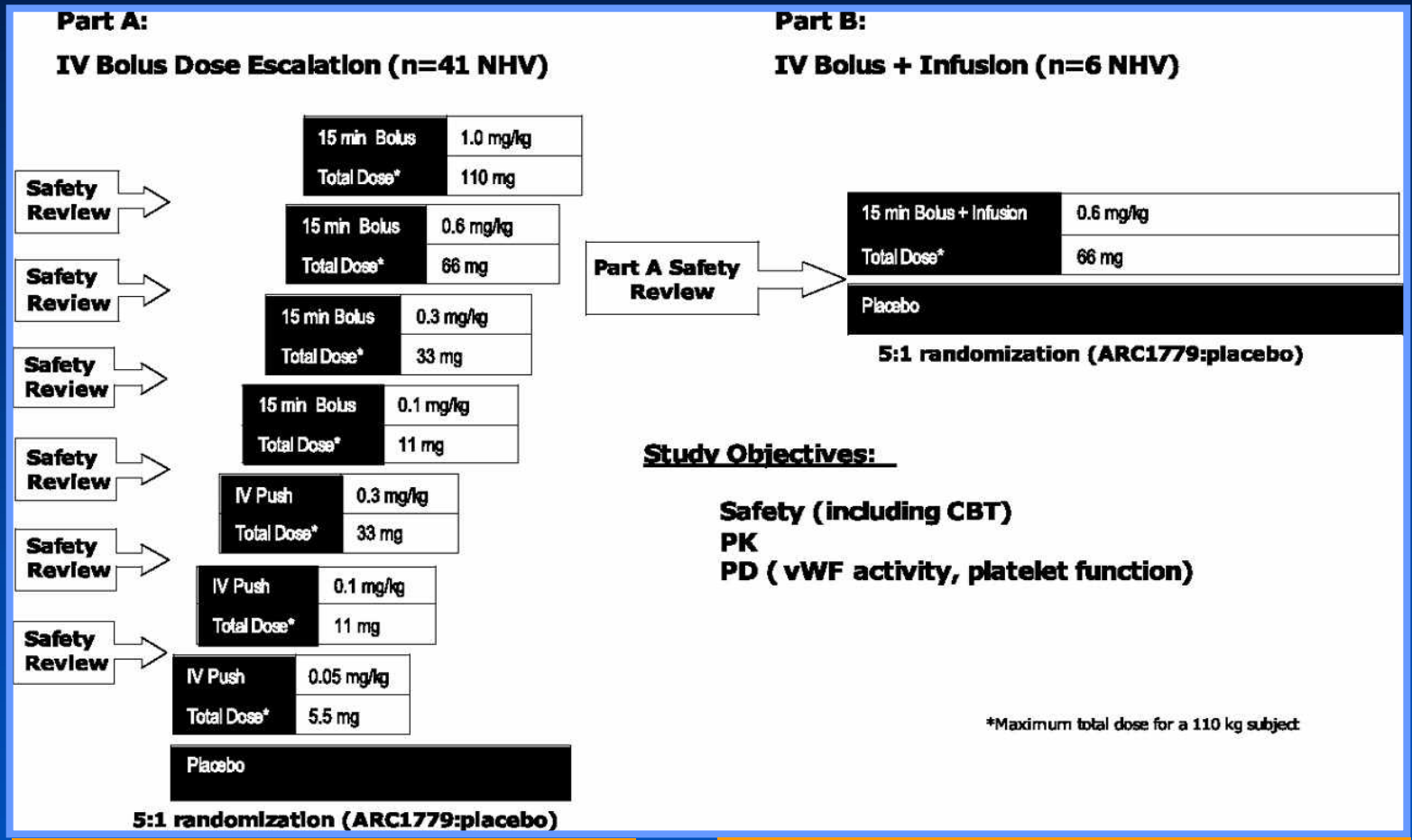


- ARC-1779 inhibit the binding of vWf to the GPIb receptor on platelets (the first stage of thrombus formation).

➔ i.v. formulation with a rapid onset and offset of action.

➔ ARC-1779 has potential therapeutic benefit in ACS and in vWF-related platelet disorders.

Phase I dose escalation trial of ARC 1779 in 47 healthy volunteers

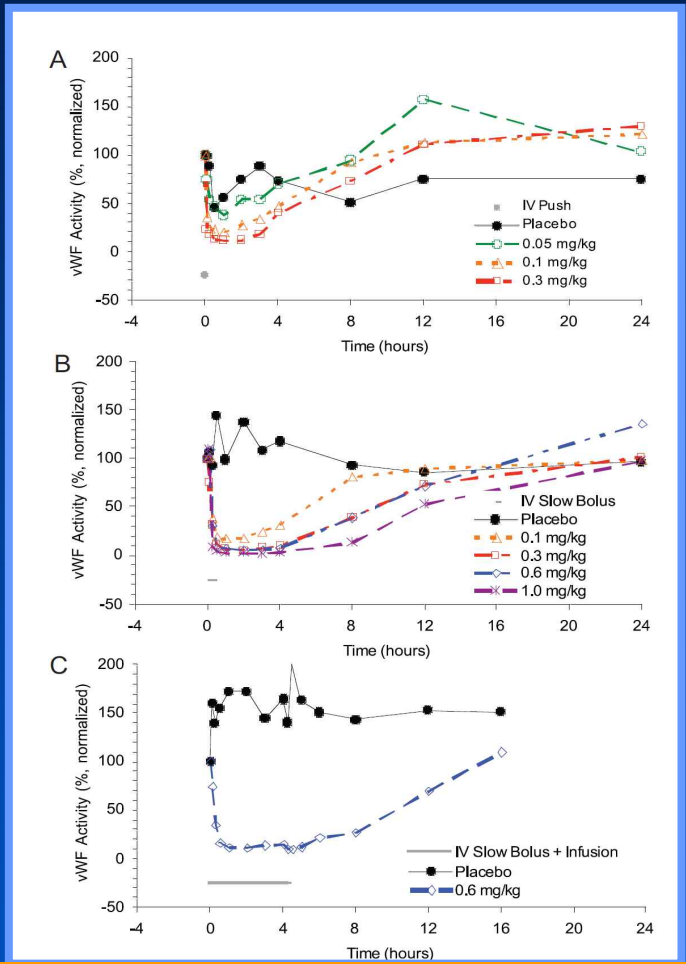


Dose-escalation arm (part A)

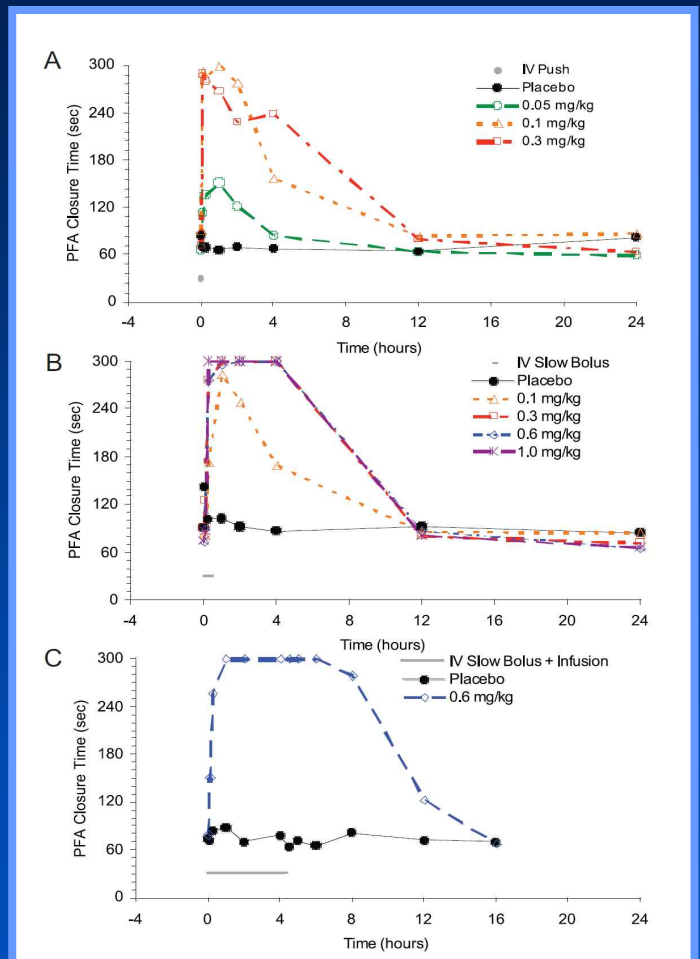
Bolus plus infusion arm (part B)

Gilbert et al. Circulation. 2007;116:2678-2686

Phase I dose escalation trial of ARC 1779 in 47 healthy volunteers



vWF activity-time profiles



PFA-100 closure time profiles

Gilbert et al. Circulation. 2007;116:2678-2686

Phase II, Study of ARC1779 in Patients With Acute Myocardial Infarction Undergoing PCI (vITAL-1)

Study of ARC1779 in Patients With Acute Myocardial Infarction Undergoing PCI (vITAL-1)

This study has been terminated.

First Received: July 24, 2007 Last Updated: January 8, 2009 History of Changes

Sponsor:	Archemix Corp.
Information provided by:	Archemix Corp.
ClinicalTrials.gov Identifier:	NCT00507338

Arms	Assigned Interventions
ARC1779 low dose: Experimental 0.1 mg/kg	Procedure: PCI early PCI for NSTEMI; primary PCI for STEMI
ARC1779 mid dose: Experimental 0.3 mg/kg	Procedure: PCI early PCI for NSTEMI; primary PCI for STEMI
ARC1779 high dose: Experimental 1.0 mg/kg	Procedure: PCI early PCI for NSTEMI; primary PCI for STEMI
abciximab: Active Comparator labeled regimen for primary PCI	Procedure: PCI early PCI for NSTEMI; primary PCI for STEMI

Estimated enrollment: 300 patients

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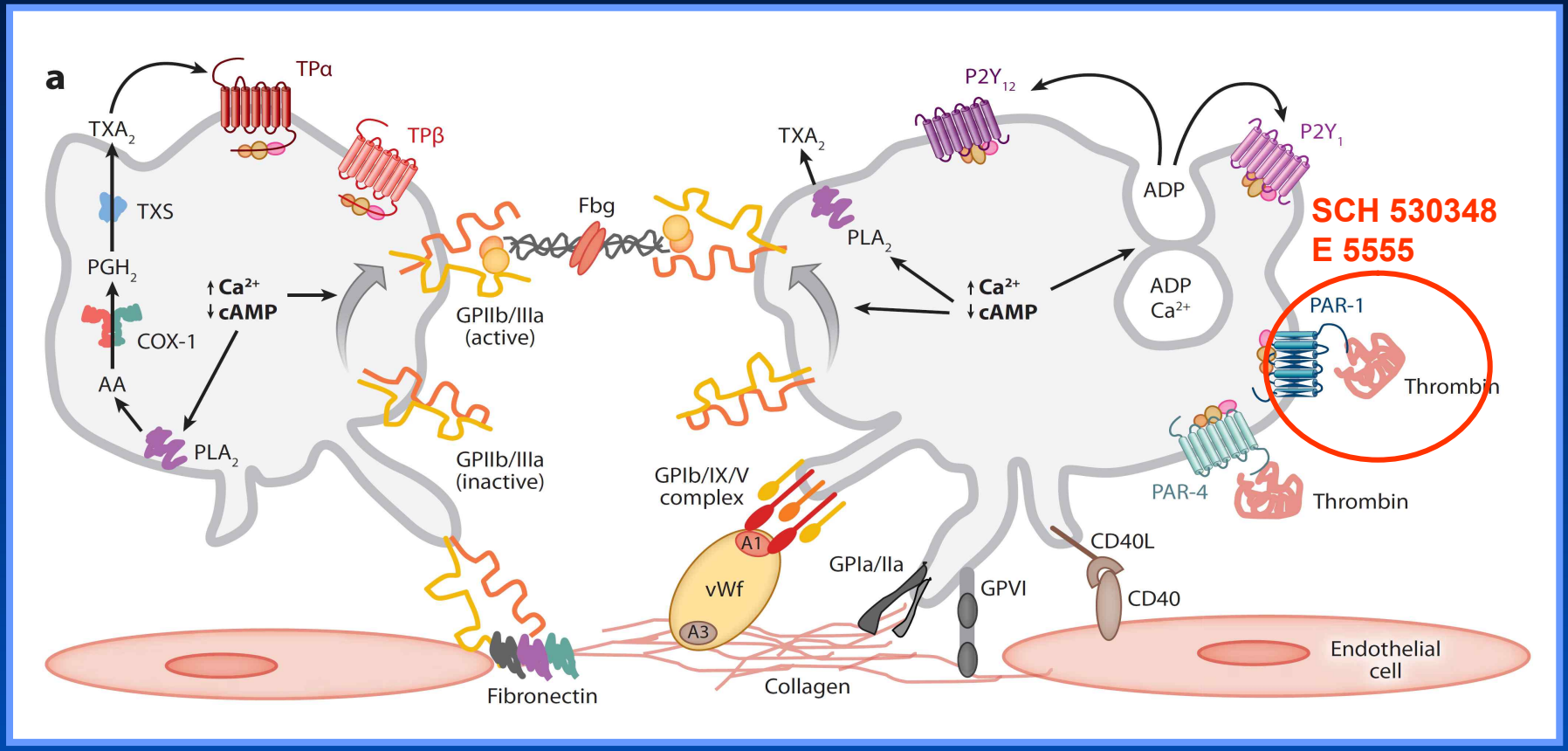
SCH-530348 or E-5555



- **Thrombin** is the most potent platelet activator and has a role in critical intersection point between the coagulation cascade and platelet aggregation.
- **SCH-530348** is an oral antiplatelet agent that antagonizes the main thrombin receptor (PAR-1).

Thrombin Receptor Antagonist (TRA)

- SCH-530348 is an oral, potent, highly selective antagonist of protease-activated receptor-1 (PAR-1), **without affecting other platelet receptors or pathways.**
- Preclinical and early clinical studies have demonstrated SCH-530348 to have antithrombotic properties, **with no increase in bleeding time or clotting times (aPTT, PT, ACT).**

Galbulimima baccata

- **A synthetic analogue of himbacine. .**
- **Bark of the Australian Magnolia**
- **Found in the tropical zones of eastern Malaysia, New Guinea, northern Australia and the Solomon Islands.**

T·R·A-PCI Phase II Trial: Study Design

Non-Urgent PCI or Cath possible PCI (All Receive Aspirin)

Randomization #1 — 3:1 SCH530348:Placebo (Single Loading Dose)

Sequential Groups: 1=10 mg; 2=20 mg; 3=40 mg, or Placebo

Cardiac Catheterization

Planned PCI (All Receive Aspirin, Clopidogrel and Antithrombin)

Randomization #2 1:1:1

Maintenance Therapy Once Daily for 60 days

SCH 530348 Loading Dose → SCH 530348

Or Placebo Loading Dose → Placebo

SCH 530348

0.5 mg n~100	1 mg n~100	2.5 mg n~100	Placebo n~100

Safety: TIMI Major plus Minor Bleeding

Efficacy: Death/MACE

* *Primary Evaluable Cohort*

No PCI**

CABG

Medical Management

Quantify Postoperative Chest-Tube Drainage, Transfusions, and Re-exploration

Safety: TIMI Major plus Minor Bleeding

***Secondary Evaluable Cohort*

CardioVascular Research Foundation

Becker RC et al. Lancet 2009

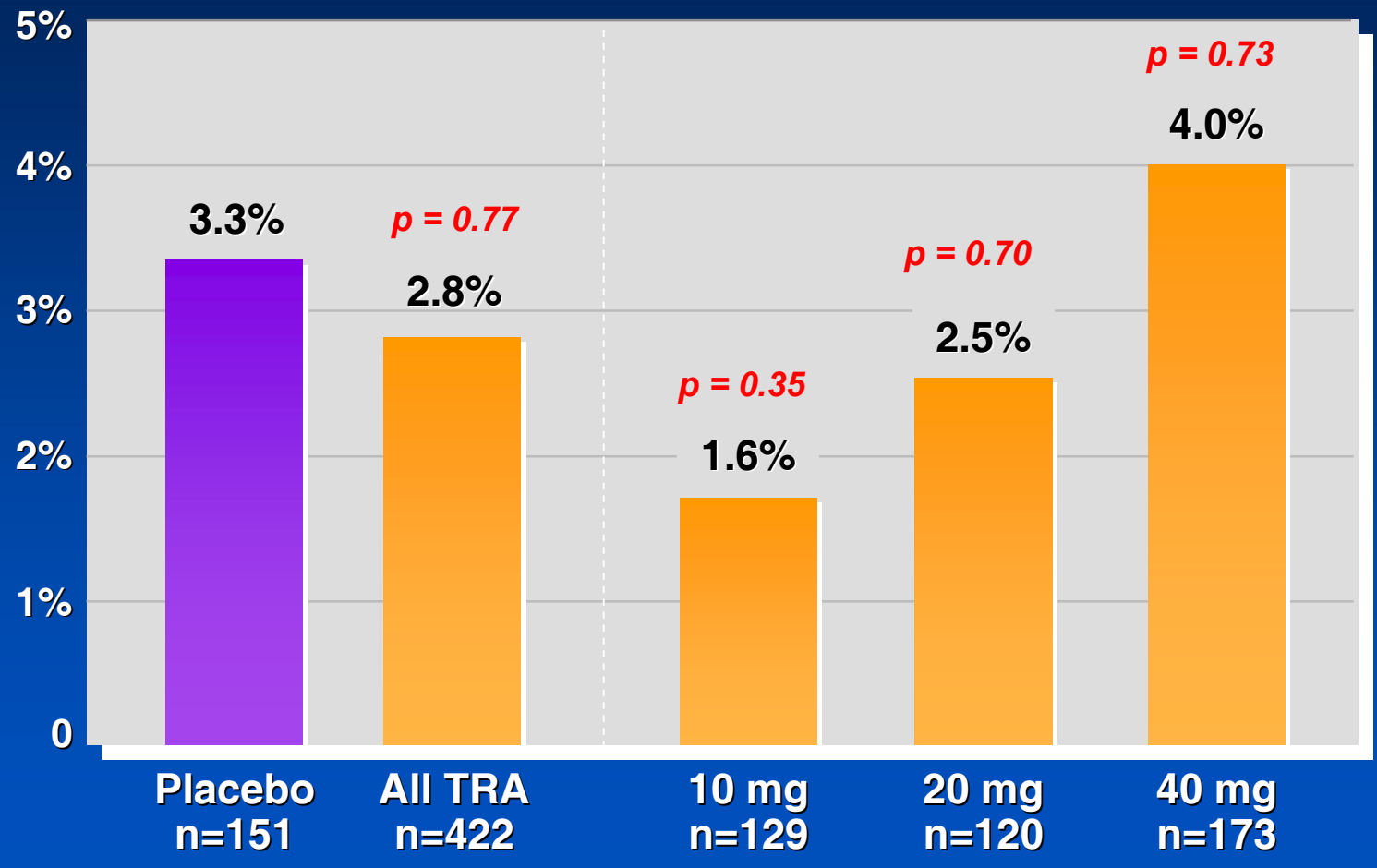
UNIVERSITY OF ULSAN COLLEGE MEDICINE

ASAN Medical Center

T·R·A-PCI

PCI Cohort

Primary Endpoint: TIMI Major/Minor Bleeding

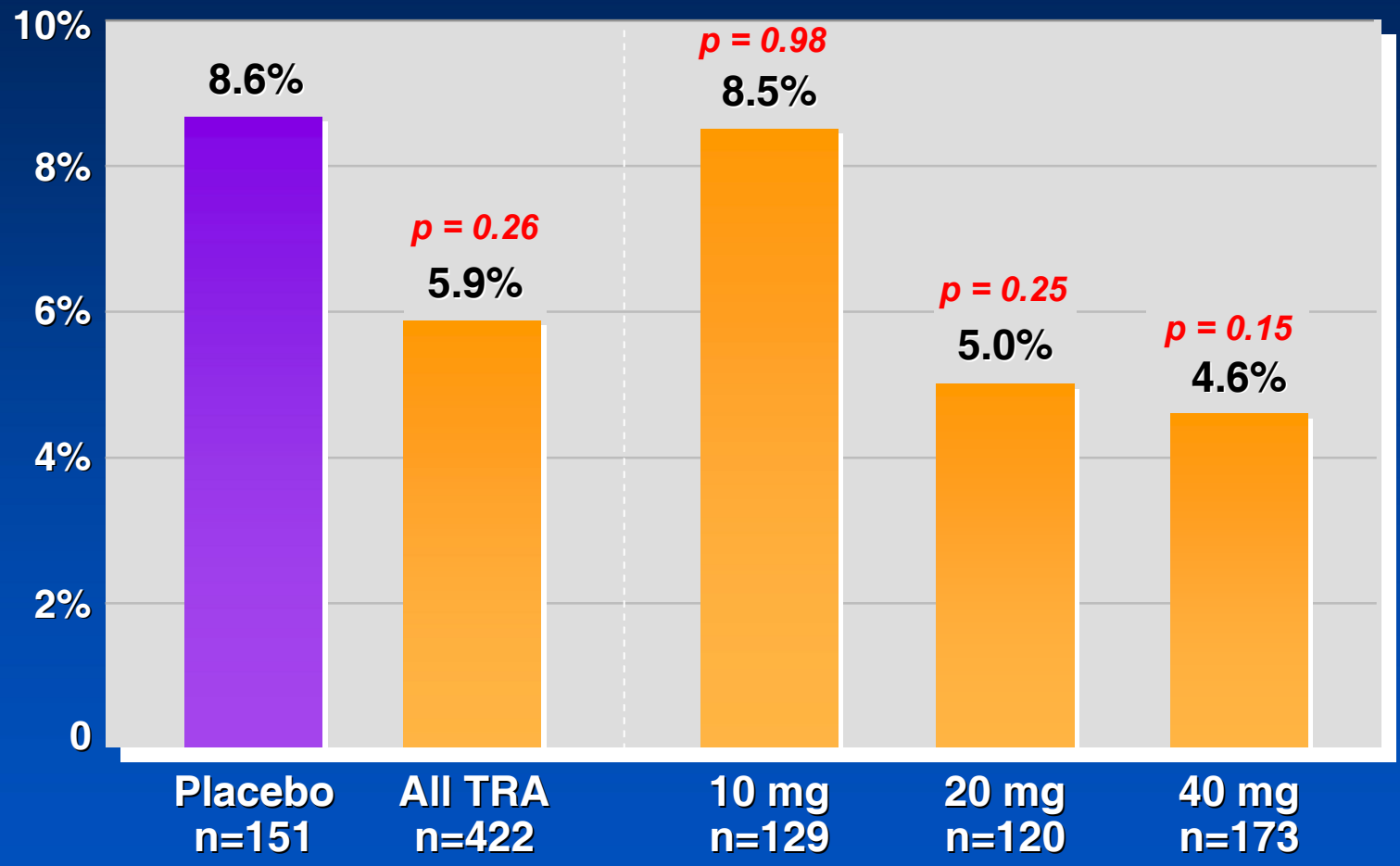


p- value relative to placebo

Becker RC et al. Lancet 2009

T·R·A-PCI PCI Cohort

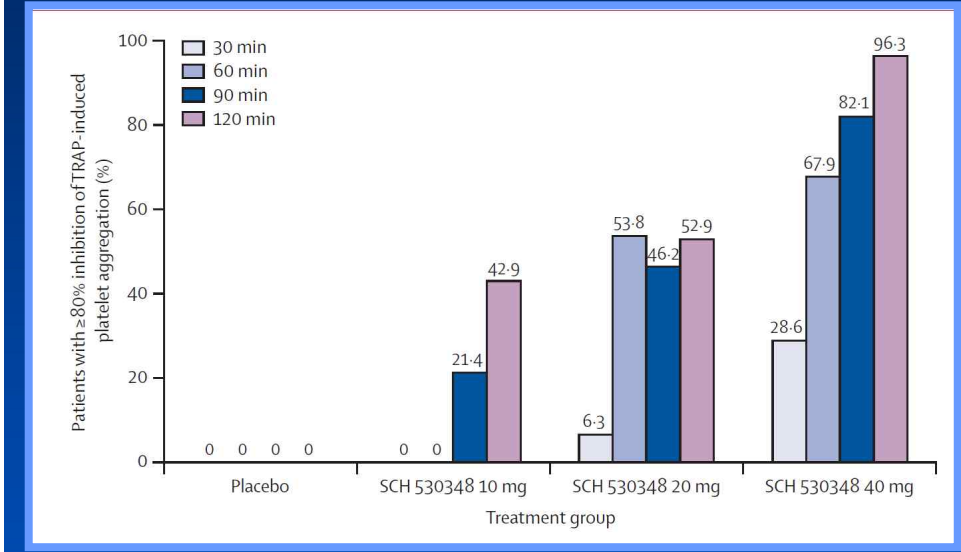
60-Day Death or MACE



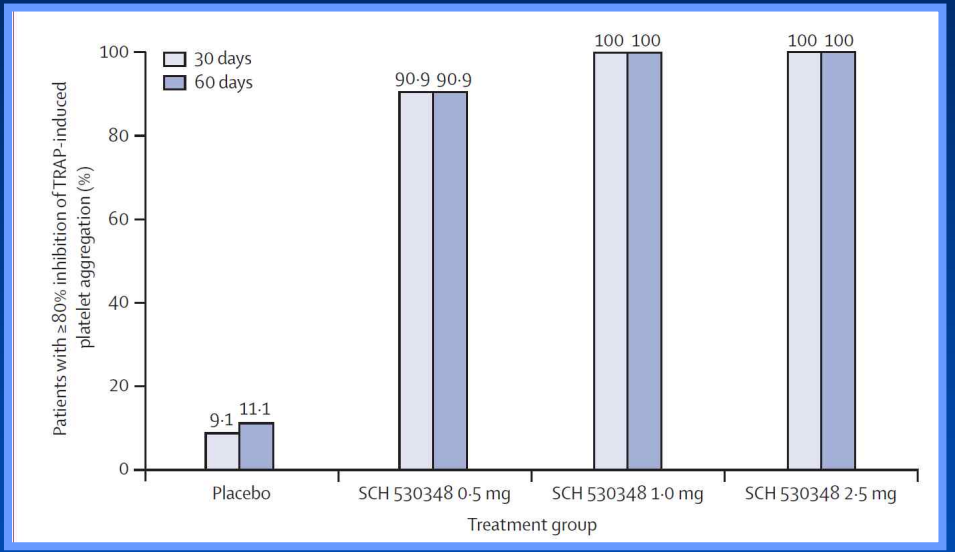
p- value relative to placebo

T·R·A-PCI

Platelet function using LTA



Loading dose



Maintenance dose

TRA•CER Design

TRA•CER
Thrombin Receptor Antagonist for Clinical Events Reduction

Patients with high-risk Non-ST-Segment Elevation Acute Coronary Syndrome ≤24h of symptoms

Double-blind

Standard Medical Therapy

N=10,000

1:1

TRA
40 mg + 2.5 mg/d

Placebo

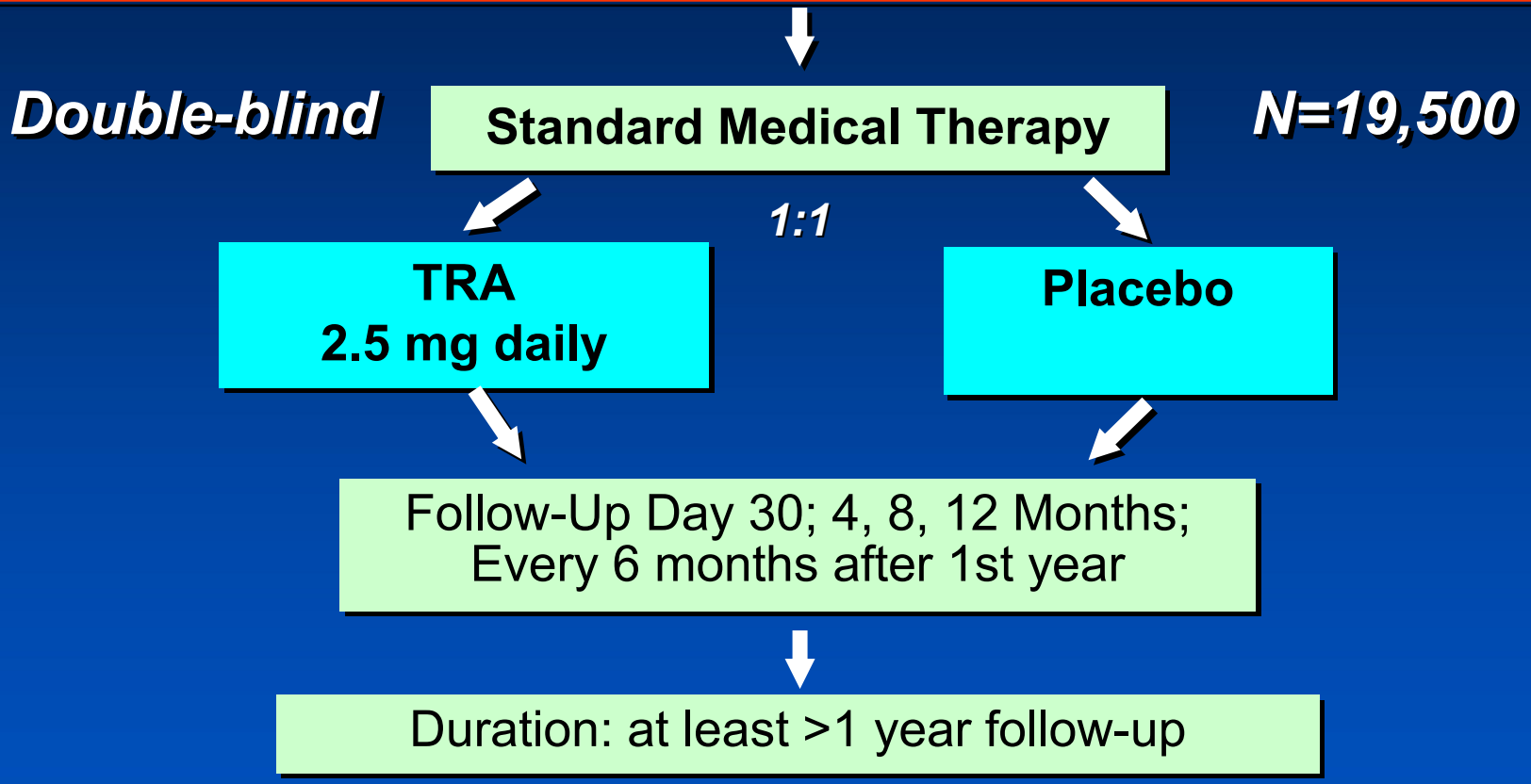
Follow-Up Day 30; 4, 8, 12 Months;
Every 6 months after 1st year

Duration: >1 year follow-up; >2334 1° EP
and >1457 key 2° EP events

1° EP:CV Death/MI/stroke/hosp for RI/urgent coronary revasc.
2° EP: CV Death/MI/stroke

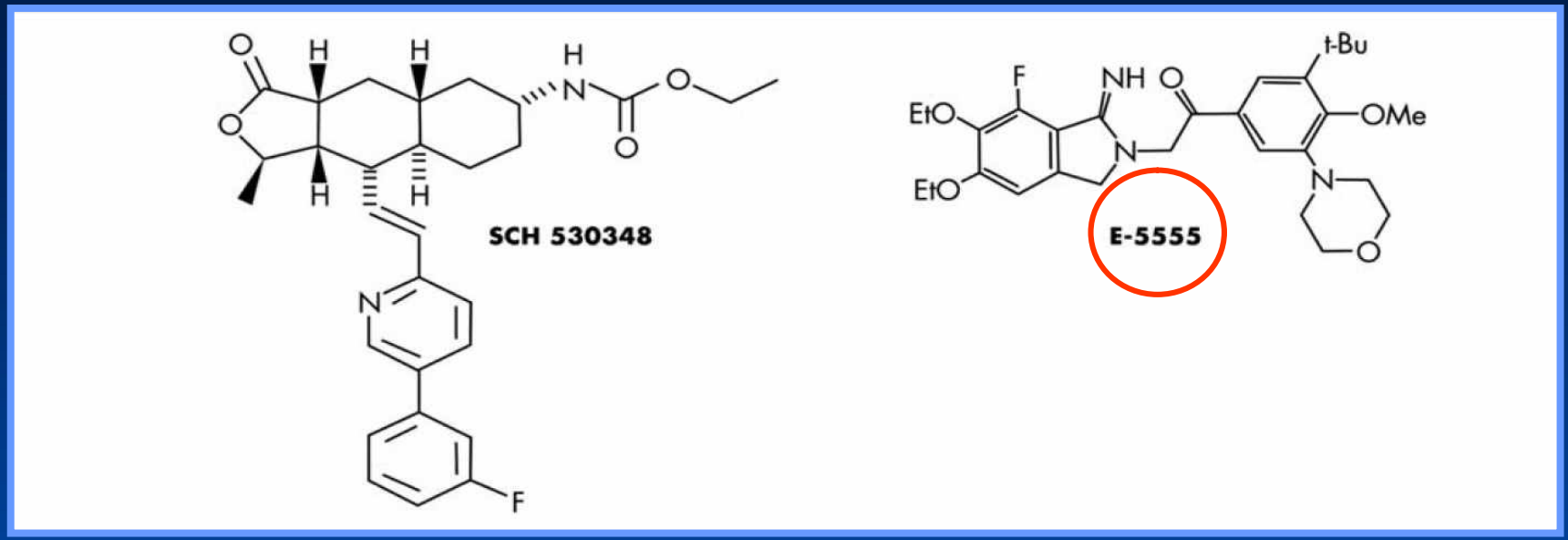
TRA-2P-TIMI 50 Trial

Patients who have a prior history of atherosclerotic vascular disease including previous MI, stroke, PVD



1° EP: Composite of CV death, MI, stroke, and urgent revascularization

E-5555



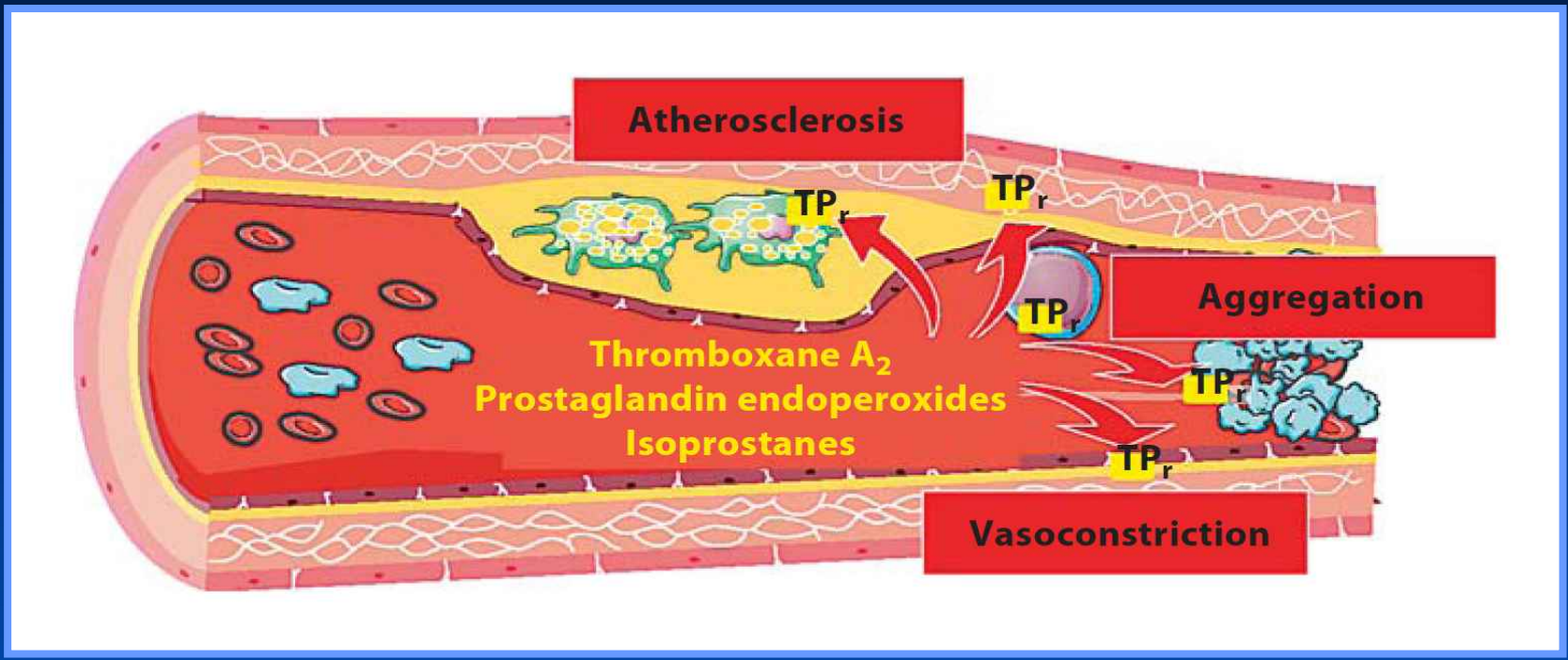
- E-5555 is a novel, orally active, potent PAR-1 antagonist and it has a shorter half-life and faster recovery of platelet function than SCH530348 in pre-clinical studies.

- Two double-blind, Phase 2 RCT; Lessons From Antagonizing the Cellular Effects of Thrombin (LANCELOT)-201 and -202 (NCT00312052 and NCT00548587) is being conducted in patients with stable CAD and NSTE-ACS.

New Antiplatelet Agents Beyond ADP Blockers Under Development and Testing

Antiplatelet	Administration	Mechanism of action	Trials
ARC 1779	Intravenous	**vWF antagonist (A1 domain)**	Phase I trials
SCH 530348 **E 555**	Oral	**Thrombin receptor (PAR-1) antagonist**	Phase III trials Phase II trials
Terutroban	**Oral**	**Thromboxan receptor antagonists**	**Phase III trials**
NCX 4016	Oral	**New type COX-1 inhibitor**	Phase II trials

Thromboxane Receptor Blockade (Terutroban)

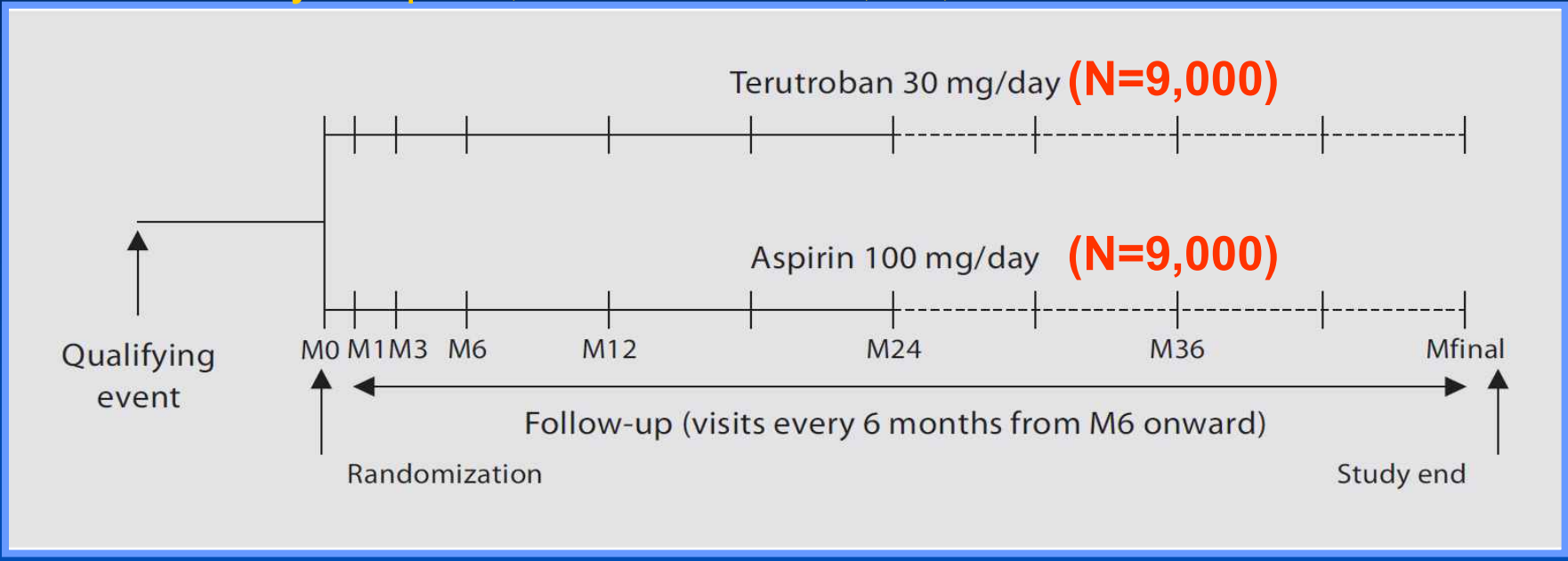


- TP receptors distribute in platelets, vascular wall, circulating monocytes and atherosclerotic plaques.
- Theoretically, TP receptor blocker have advantages over aspirin as they not only block TX-A 2 on platelets, but also inhibit other ligands such as PG endoperoxides and isoprostanes.
- Terutroban is a specific TP receptor antagonist with **antithrombotic, antivasoconstrictive, and antiatherosclerotic** properties.

PERFORM Trial

To demonstrate the superiority of terutroban vs. aspirin
in secondary prevention of cerebrovascular and cardiovascular events
in patients with a history of ischemic stroke or TIA.

Primary endpoint; ischemic stroke, MI, or other vascular death



**PERFORM Trial was recently halted on the basis of an interim analysis failing to support the superiority hypothesis.

New Antiplatelet Agents Beyond ADP Blockers Under Development and Testing

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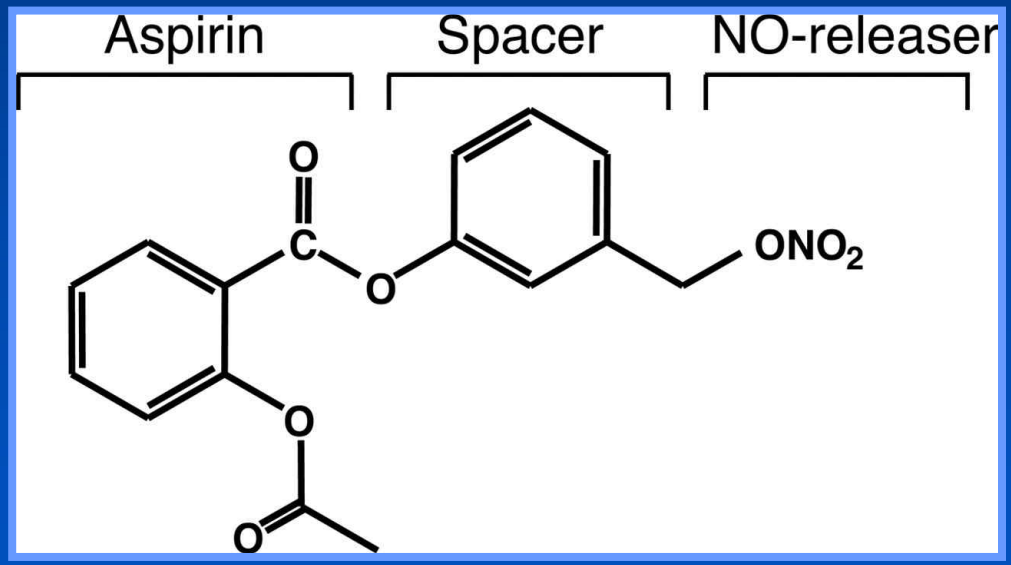
Terutorban	Oral	**Thromboxan receptor antagonists**	Phase III trials
NCX 4016	**Oral**	**New type COX-1 inhibitor**	**Phase II trials**

NCX-4016 (nitric oxide aspirin)

- NCX-4016 (NicOx) have two potential benefit; (1) gastric protection (2) synergic antiplatelet effects of aspirin and nitric oxide.
- Preliminary studies shows that (1) NicOx has a decreased gastrointestinal toxicity, (2) NicOx inhibit high shear stress-related, hyperglycemia-induced, thrombin-induced, and GPIIb/IIIa-induced platelet activation.



NCX-4016 (nitric oxide aspirin)

- NCX 4016 can be used for treating clinical conditions where inflammatory mediators are pivotal factors in the disease progression, such as in ACS/MI, restenosis after PCI, and peripheral vascular disorders.

- Several phase II studies testing the effects of NCX 4016 in several ischemic cardiovascular disease conditions are currently ongoing or just completed.

- However, only the results from large-RCT comparing NCX 4016 to established treatments will provide its potential, a short- and long-term clinical advantage in cardiovascular diseases

Other investigational approaches

- Antagonism of integrin αIIbβ3 (also known as GPIIb–IIIa) with a diminished capacity to induce conformational changes in αIIbβ3.
- Targeting of activated platelets — for example, those with a ligand-induced binding site exposed on αIIbβ3.
- Glycoprotein VI antagonist.
- Glycoprotein 1b antagonist.
- Integrin α2β1 antagonism.
- Antagonists of P-selectin and PSGL1.
- Thromboxane receptor antagonists.
- Combined thromboxane receptor and thromboxane synthase antagonists.
- Serotonin receptor antagonists.
- Antagonism of the platelet EP3 receptor for PGE2.
- Antagonism of both P2Y purinoceptor 1 (P2Y1) and P2Y12 by modified diadenosine tetraphosphonate derivatives.
- Antagonism of the β isoform of phosphoinositide 3-kinase.

New Antiplatelet Agents Summary I

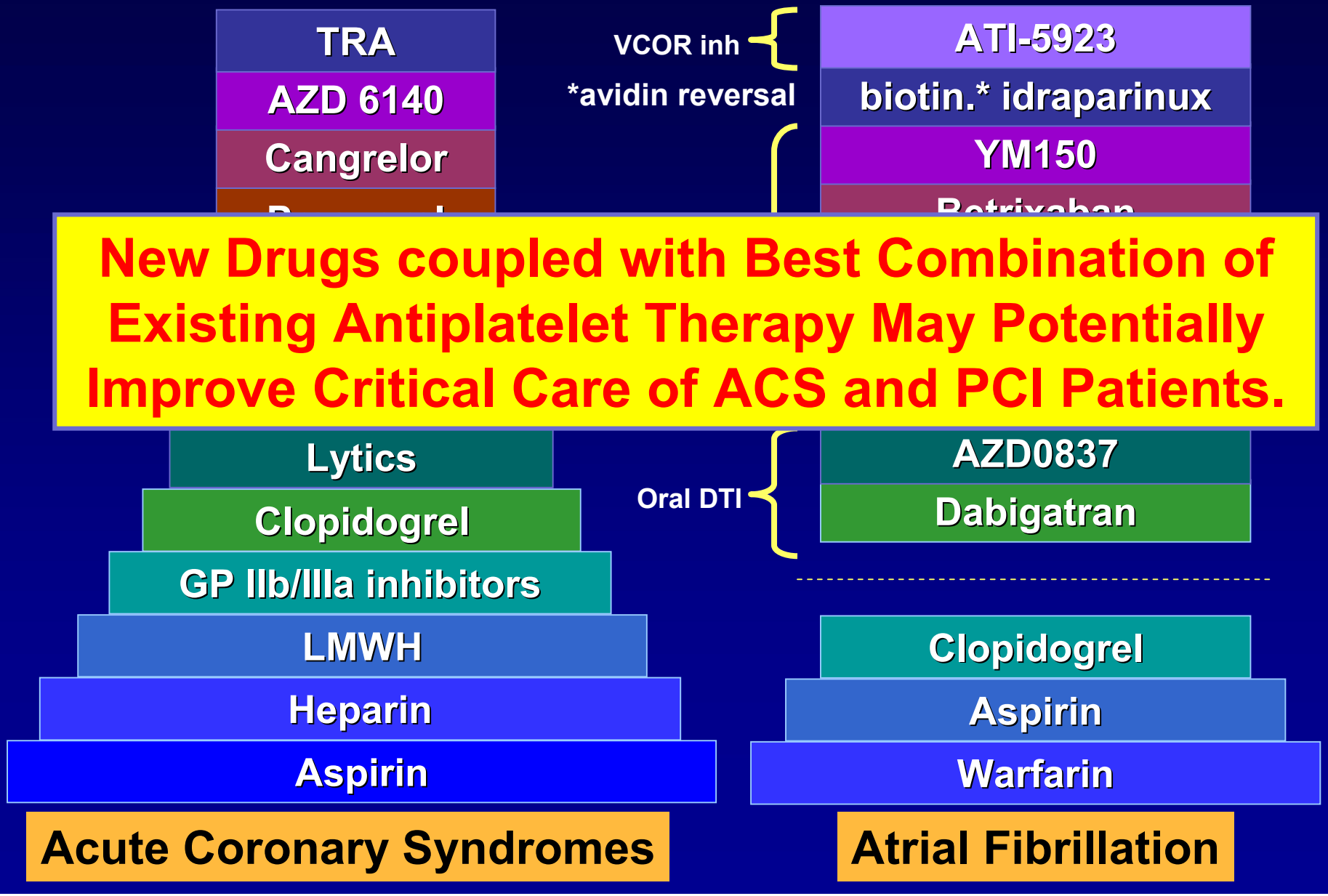
- Current standard clopidogrel is not the perfect drug.
- Multiple new targets with novel antiplatelet therapies for acute and chronic CAD are developing and are under investigation.
- Each of these new antiplatelet therapies has a unique profile and theoretical advantages, aiming incremental efficacy and decreased complications.

New Antiplatelet Agents Summary II

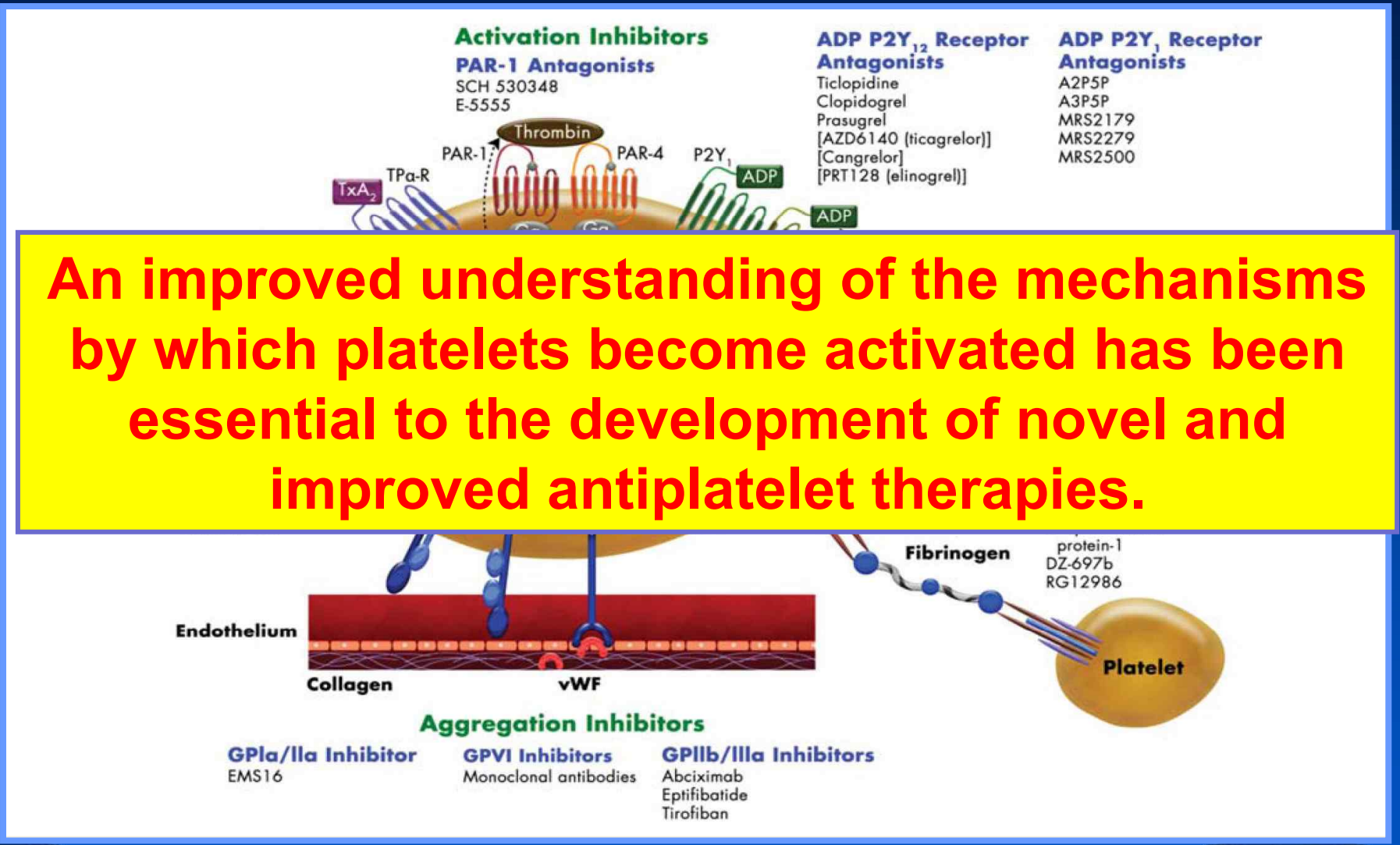
- As an increasing number of antiplatelet therapies become available, a individualized and tailored therapy for specific patient populations may become more of a reality.
- Therefore, studies optimizing combination (dual or triple) antiplatelet therapy and balancing risk-benefit ratio represents the next challenge.
- More large clinical outcomes trials and continued investigation into the pathophysiology of atherothrombosis is critical to advancing patient care/outcomes.

Antithrombotic Environmental Scan

Available (or in phase IIb/III clinical trials)



Sites of action of current and emerging antithrombotic drugs and antiplatelet agents.



An improved understanding of the mechanisms by which platelets become activated has been essential to the development of novel and improved antiplatelet therapies.


Thank You