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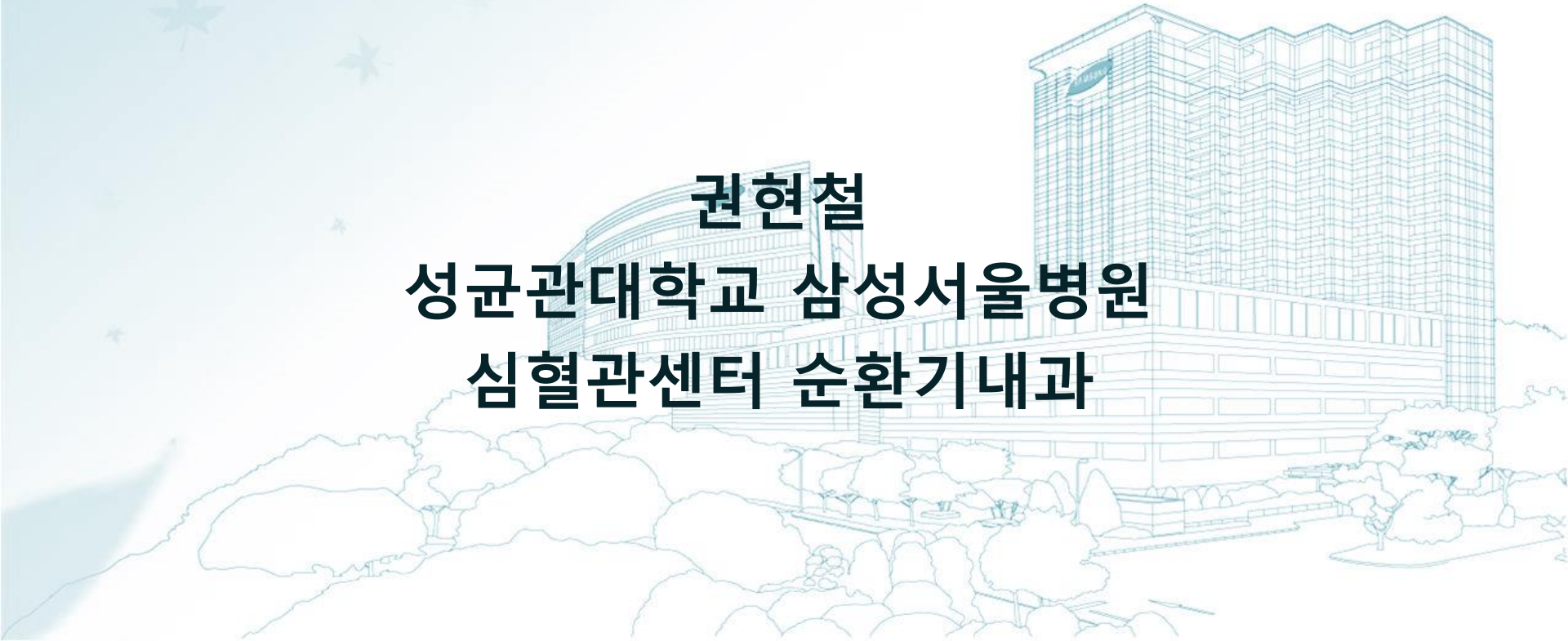
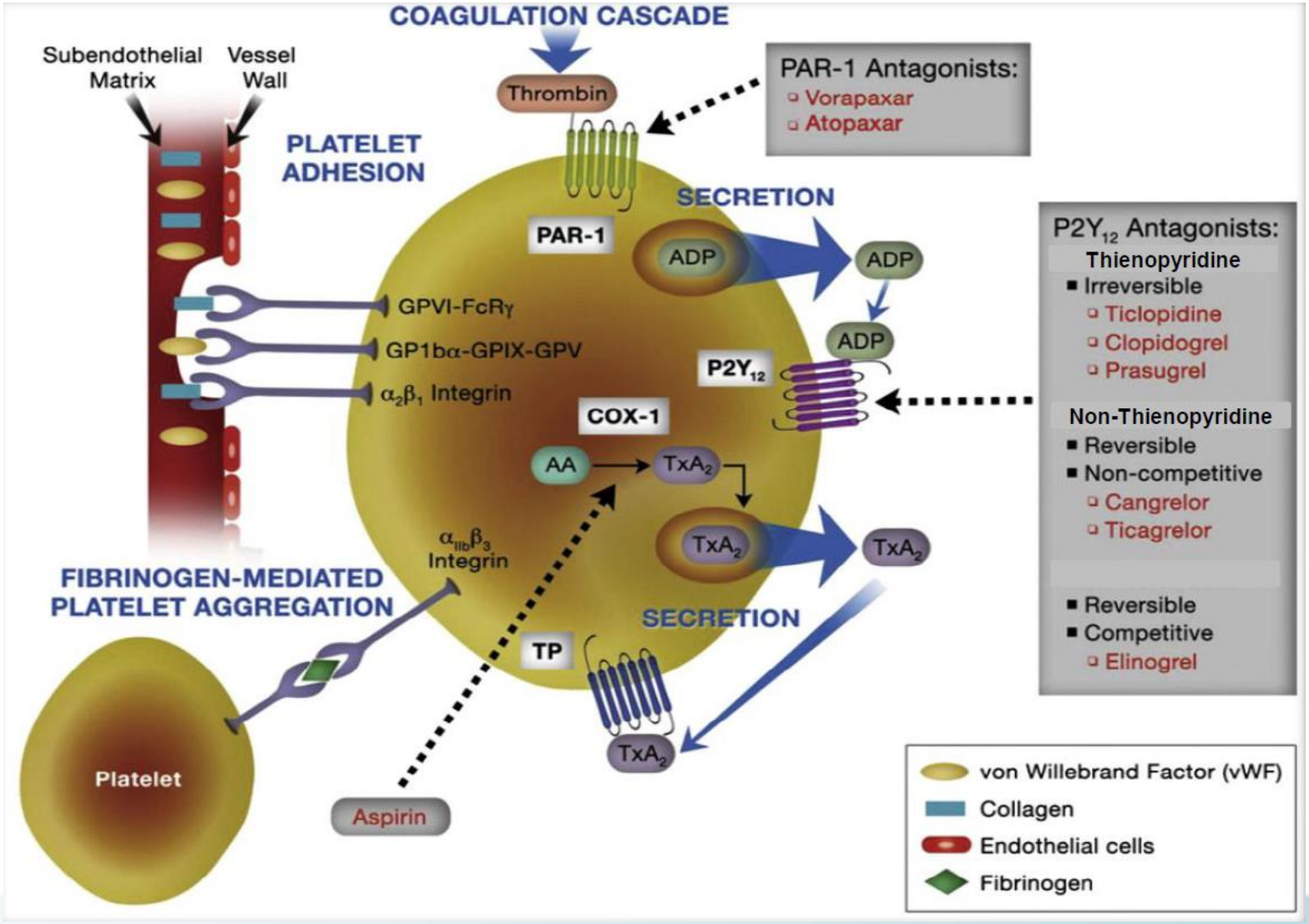
New Potent Antiplatelet Therapy



권현철
성균관대학교 삼성서울병원
심혈관센터 순환기내과

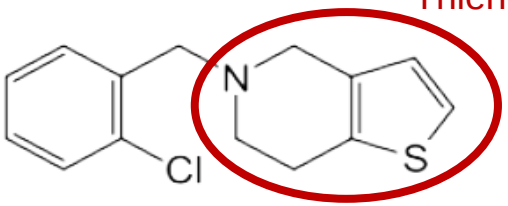
Antiplatelet Agents



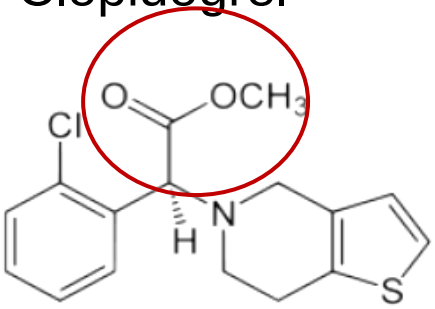
ADP P2Y12 Receptor Blockers

Ticlopidine

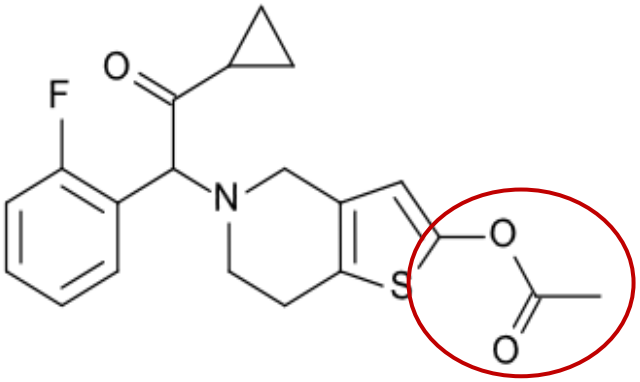
Thienopyridine



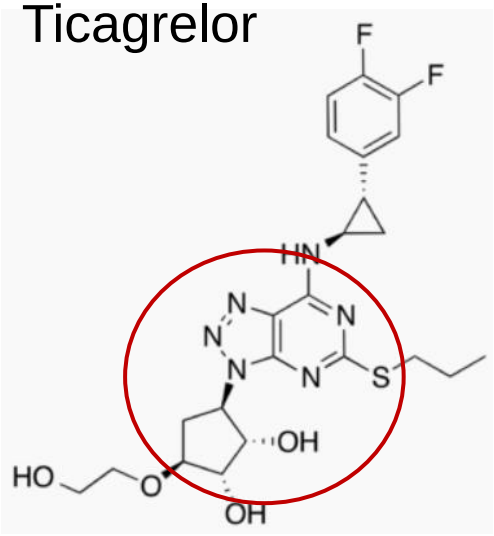
Clopidogrel



Prasugrel



Ticagrelor



http://en.wikipedia.org

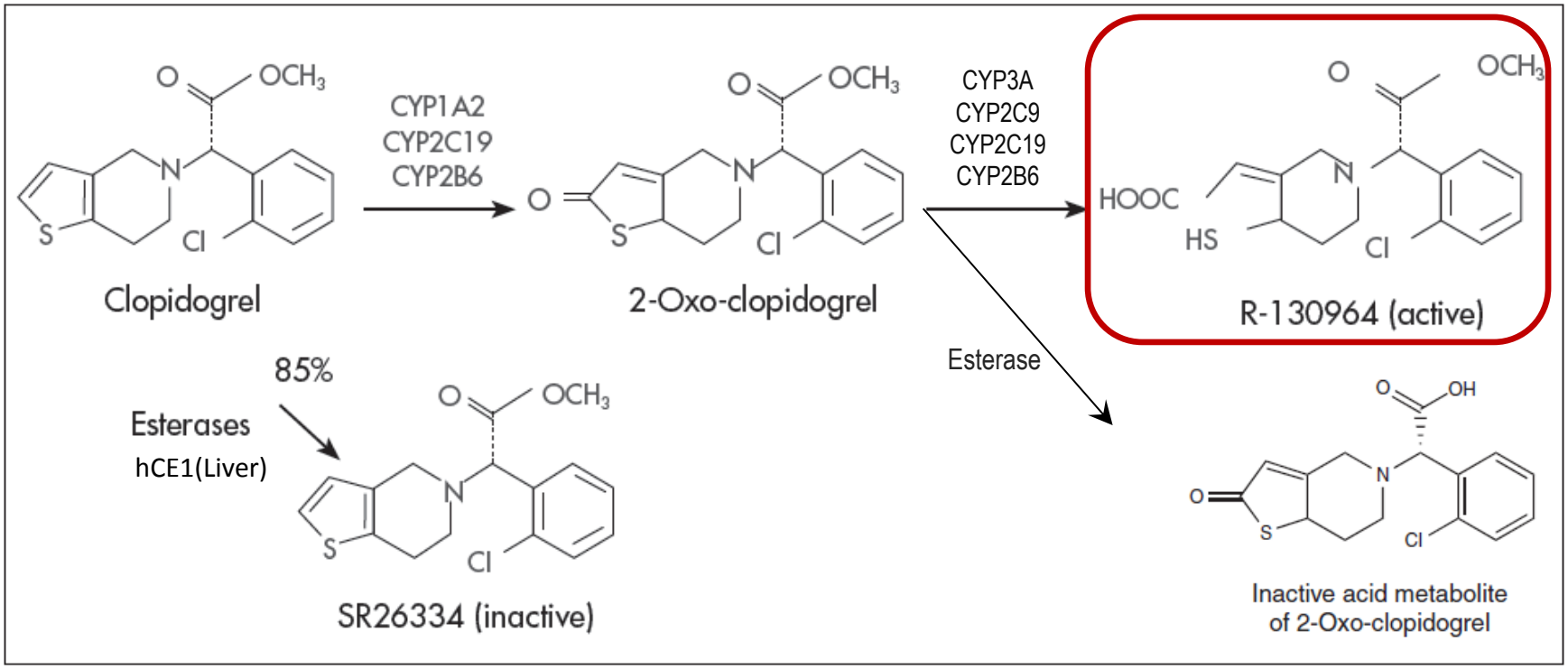
Clopidogrel

- Strengths
  - Well studied in large RCTs
  - Long and extensive clinical experience
- Limitations
  - Delayed onset of action
  - Large variability in platelet response
  - Prolonged effect

Schoemig A, N Engl J Med 2009

Metabolic pathway of clopidogrel

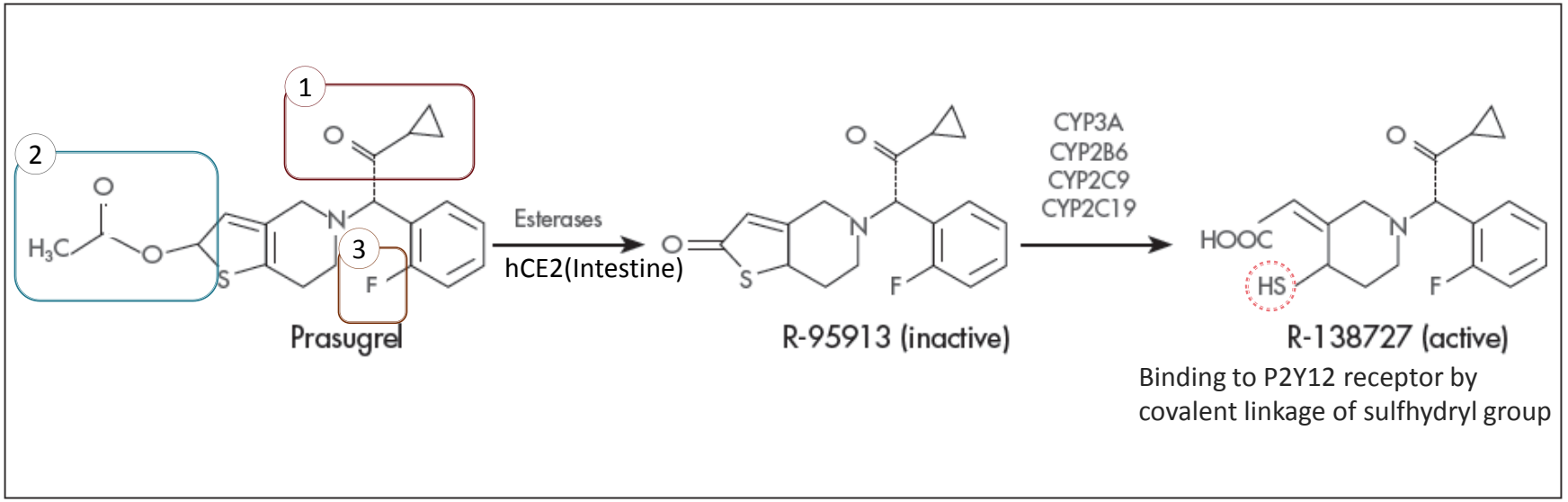
5~10% of administered clopidogrel



* hCE(human carboxylesterase)

Mega JL, Circulation 2009
Jeong YH, Expert Opin Pharmacother 2012

Metabolic pathway of prasugrel

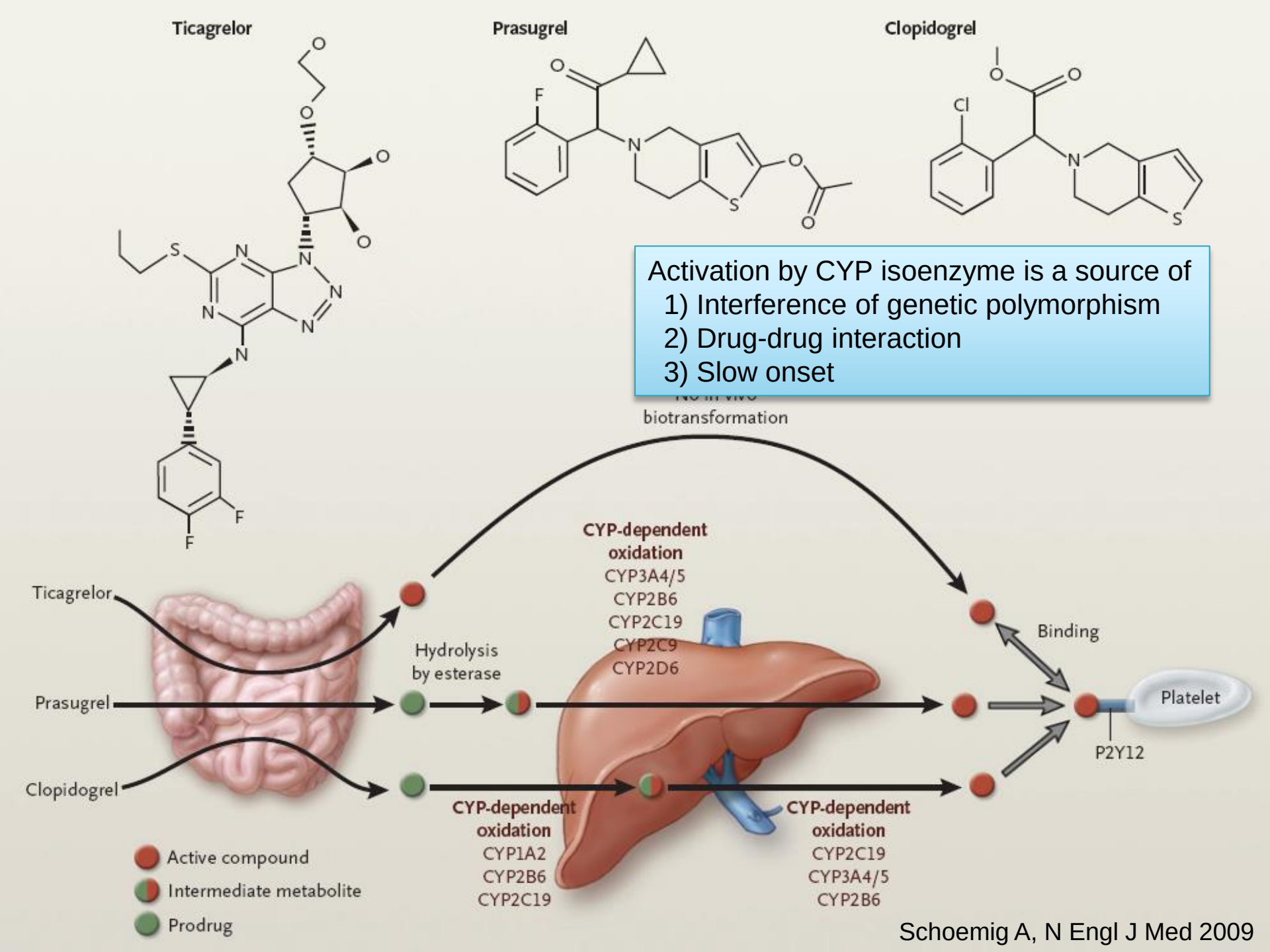


* hCE(human carboxylesterase)

- Prasugrel has different structure compared to clopidogrel

1. Cyclopropylcarbonyl group: ***greater stability toward enzymatic hydrolysis***
2. Acetoxy group of thiophene ring: ***elimination the need of CYP dependent oxidation***
3. Fluorine instead of chlorine in clopidogrel: ***enhance antiplatelet effect***

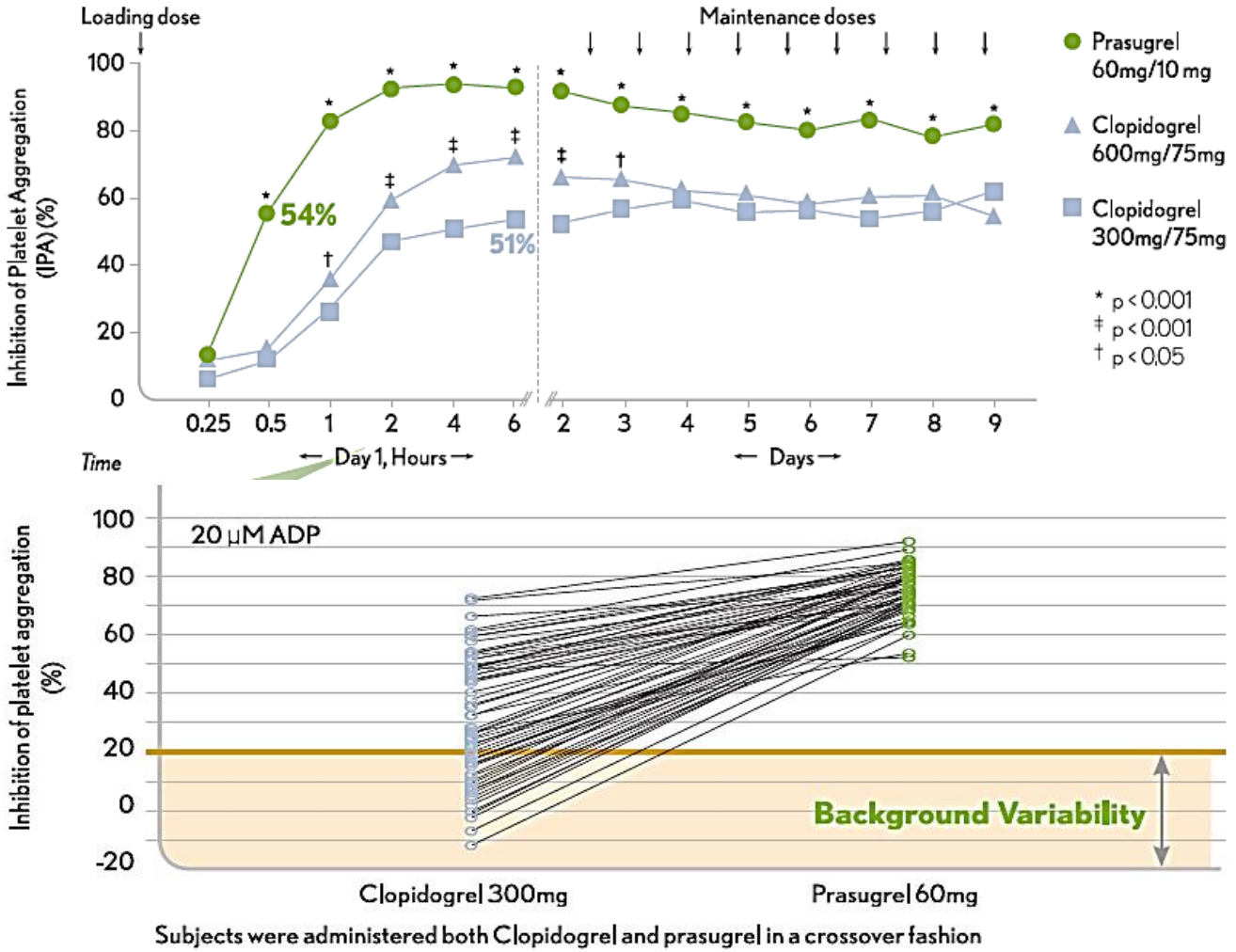
Mega JL, Circulation 2009
Jeong YH, Expert Opin Pharmacother 2012



Schoemig A, N Engl J Med 2009

Stronger and less variable inhibition of platelet aggregation by prasugrel

Inhibition of platelet aggregation (20 uM ADP)



Pyane CD, J Cardiovasc Pharmacol 2007

Ticagrelor achieved more rapid onset and offset of IPA

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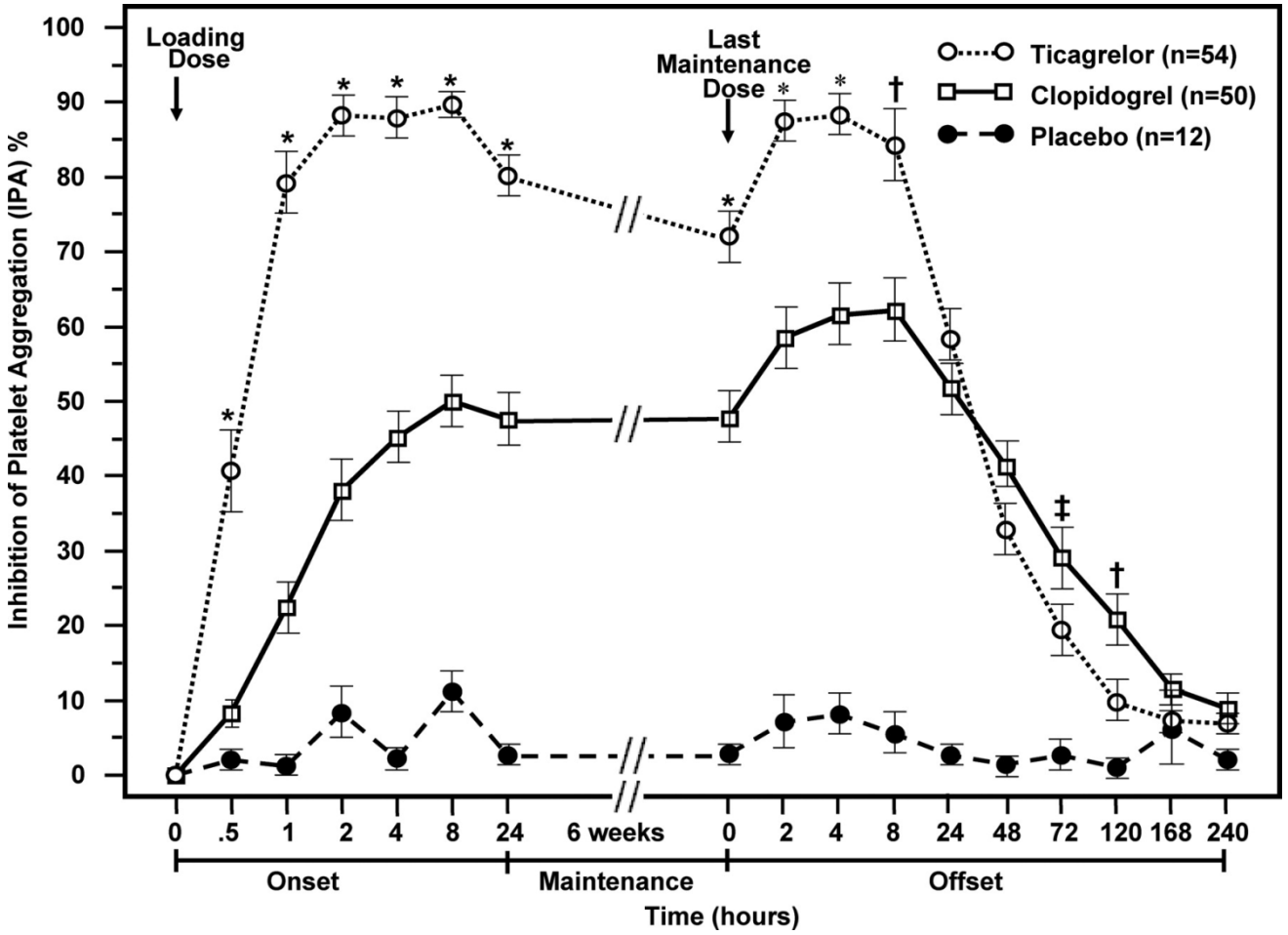
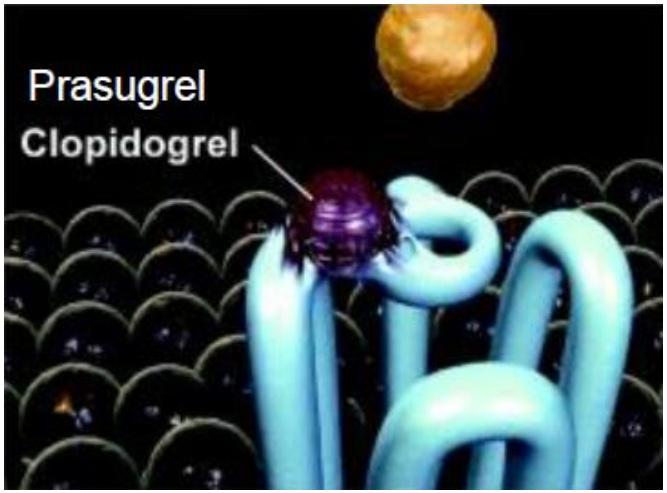
- N=123, stable CAD

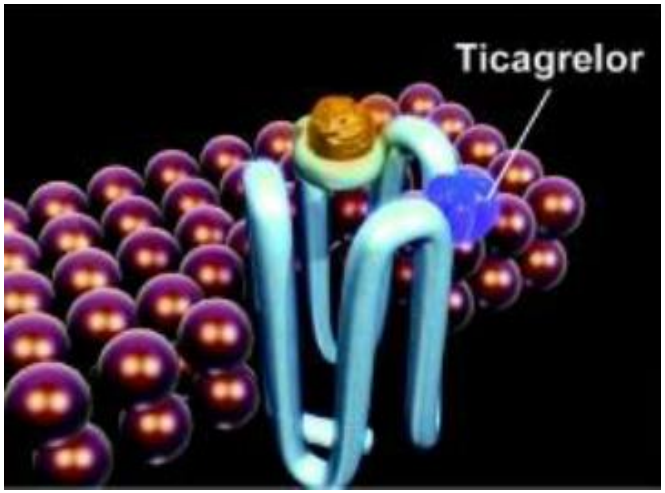


Gurbel P, Circulation 2009

P2Y12 Receptor Binding



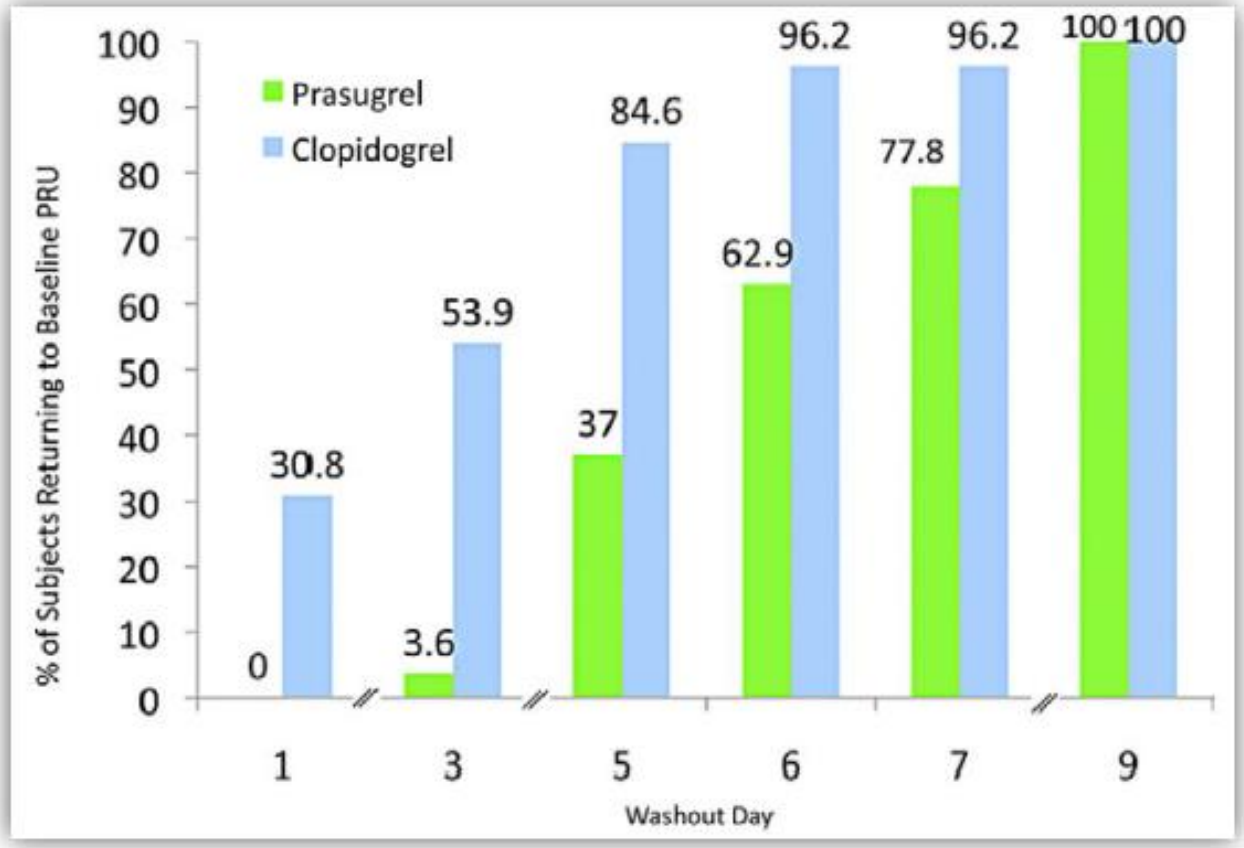
Thienopyridines bind covalently to P2Y12 receptor **Irreversibly**



Ticagrelor binds directly to P2Y12 receptor **reversibly**

Longer returning to baseline platelet reactivity after discontinuation of prasugrel

RECOVERY Trial : Cumulative Proportion of Patients Returning to Baseline Reactivity After Thienopyridine Discontinuation

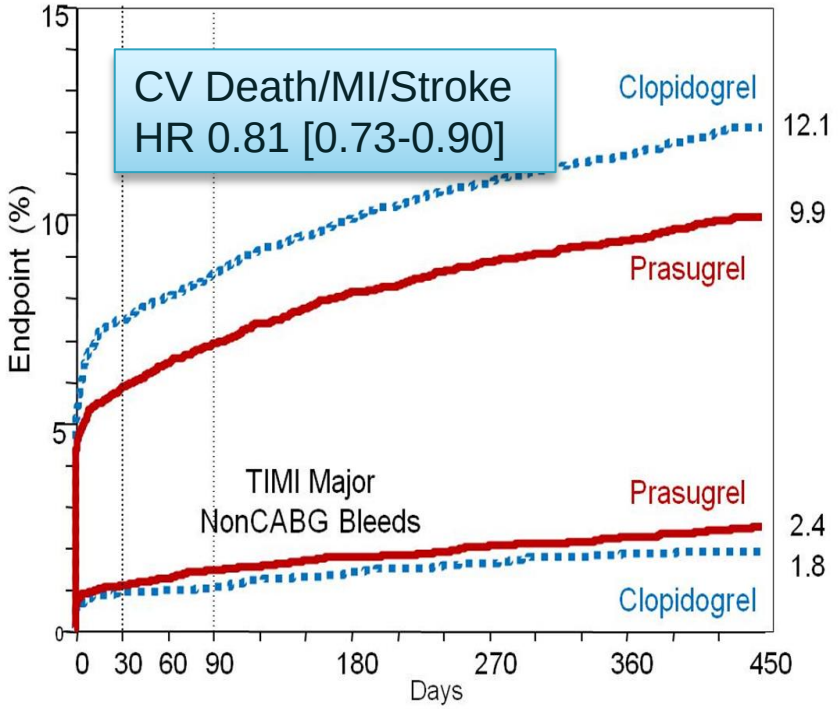


Baseline platelet reactivity defined as within 60 PRU of the reactivity measured before study drug exposure

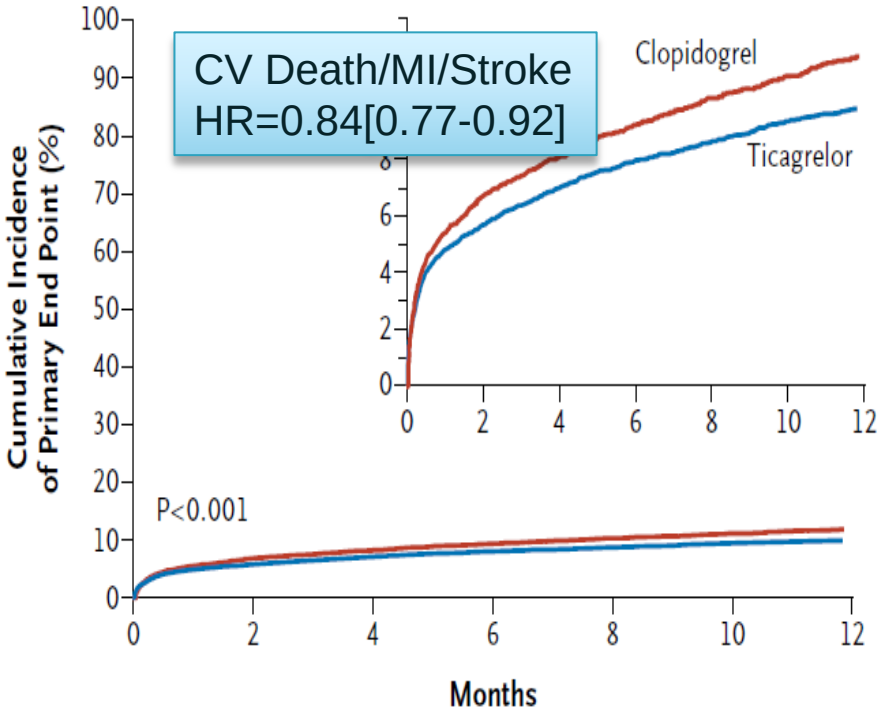
Price MJ, J Am Coll Cardiol 2012

Clinical outcome of new P2Y12 inhibitors

Prasugrel
TRITON trial (N=13,628)



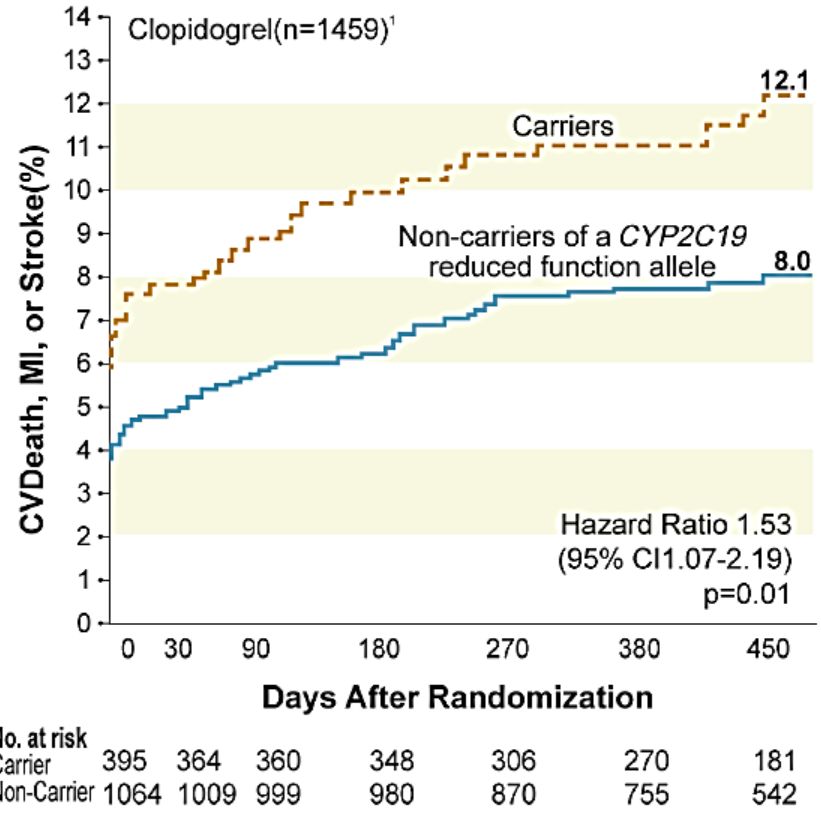
Ticagrelor
PLATO trial (N=18,624)

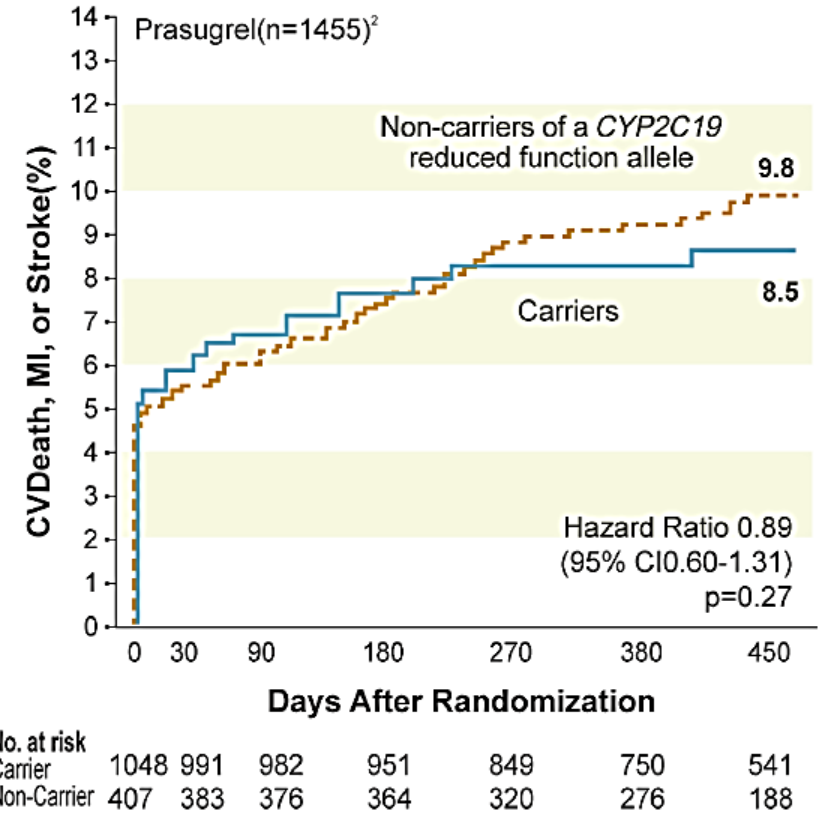


Wiviott SD, NEJM 2007, Wallentine L, NEJM 2009

No impact of reduced function CYP2C19 alleles

- No impact of reduced function CYP2C19 alleles on clinical outcome only in the prasugrel group





Mega JL, NEJM 2009, Mega JM, Circulation 2009

Clinical outcome of new P2Y12 inhibitors

TRITON

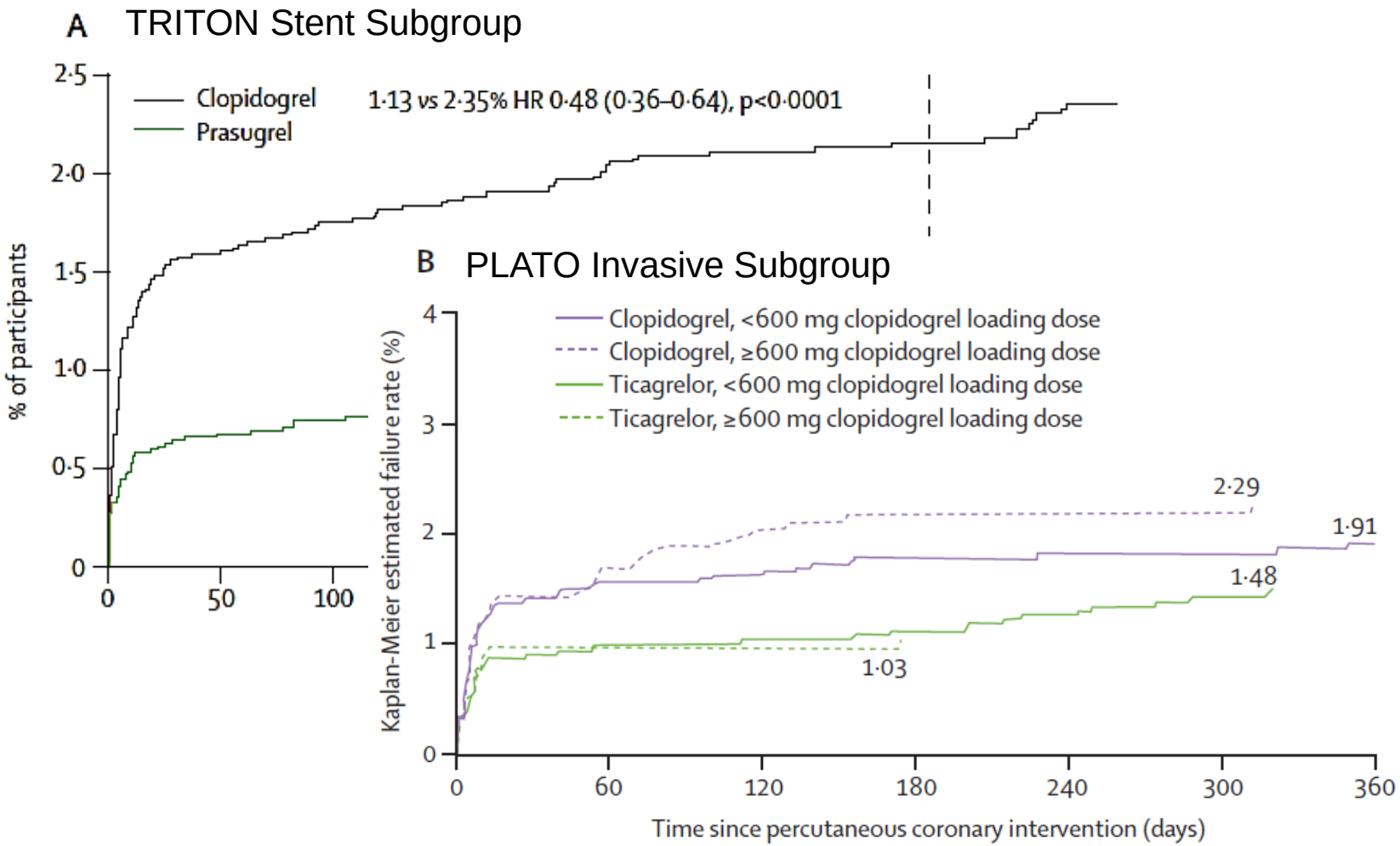
	Prasugrel	Clopidogrel	HR	P-value
1° EP	9.9%	12.1%	0.81	<0.001
CV death	2.1%	2.4%	0.89	0.31
MI	7.3%	9.5%	0.76	<0.001
Stroke	1.0%	1.0%	1.02	0.93

PLATO

	Ticagrelor	Clopidogrel	HR	P-value
1° EP	9.8%	11.7%	0.84	<0.001
CV death	4.0%	5.1%	0.79	0.001
MI	5.8%	6.9%	0.84	0.005
Stroke	1.5%	1.3%	1.17	0.22

Wiviott SD, NEJM 2007, Wallentine L, NEJM 2009

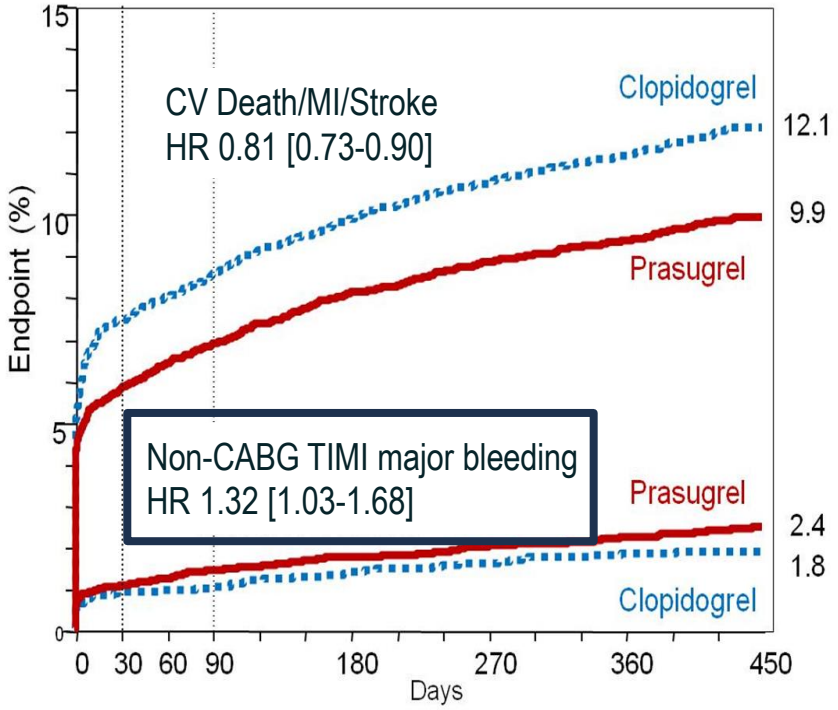
Stent thrombosis of new P2Y12 inhibitors



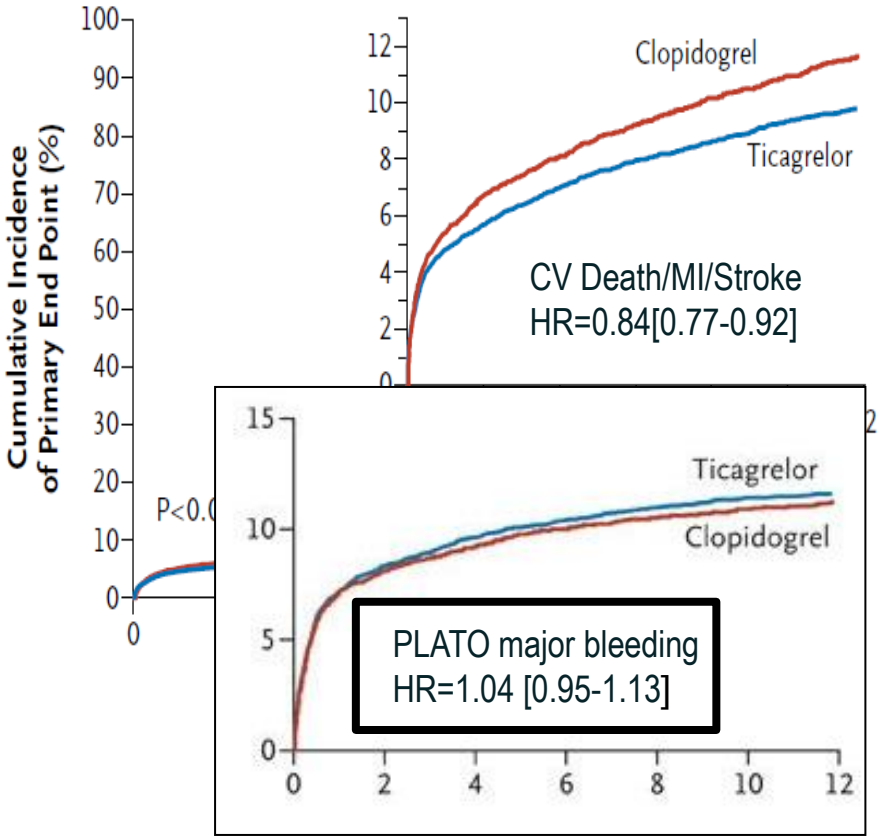
Wiviott SD, Lancet 2008, Cannon PA, Lancet 2010

Bleeding risk of new P2Y12 inhibitors

Prasugrel
TRITON (N=13,628)



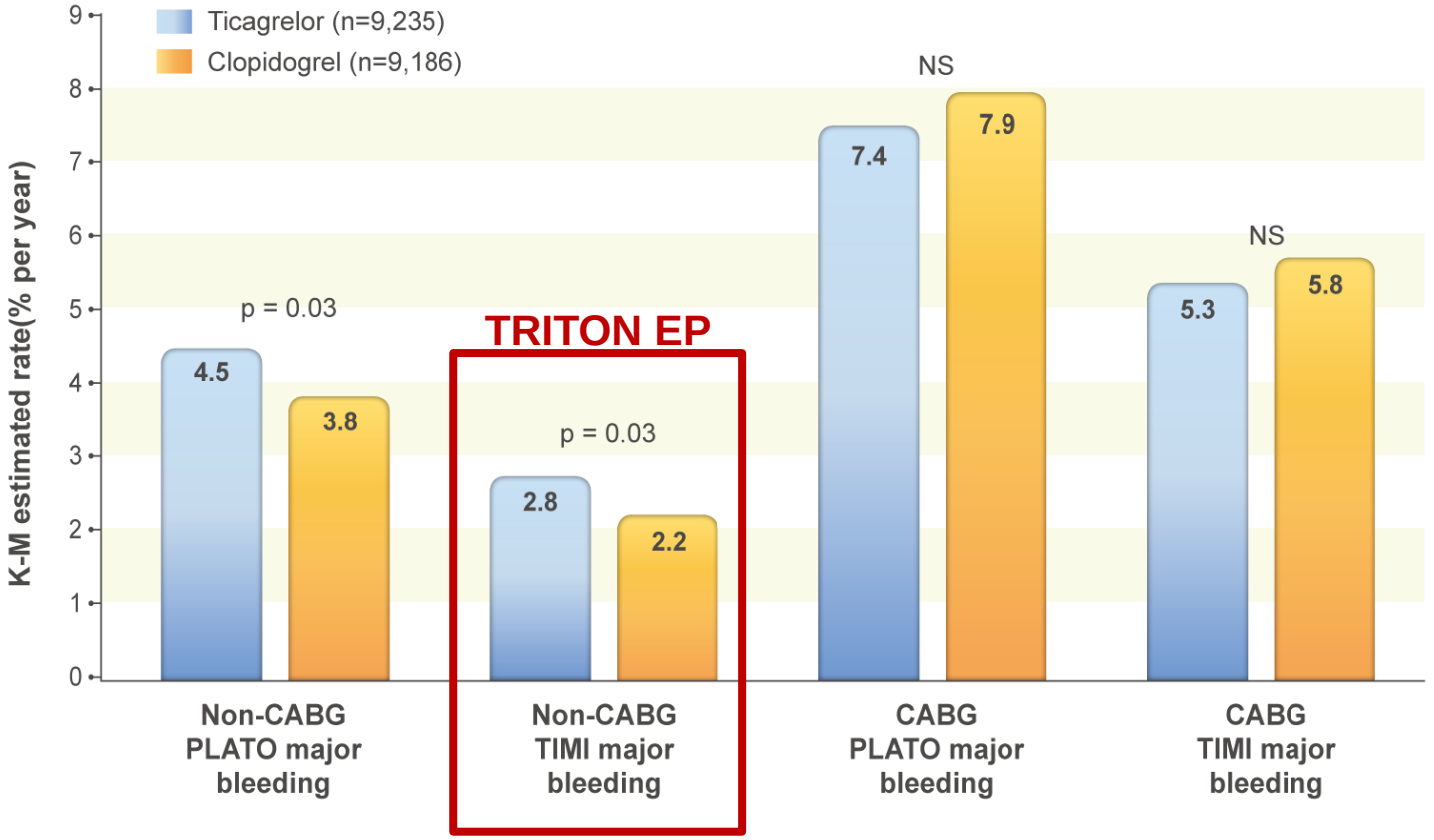
Ticagrelor
PLATO trial (N=18,624)



Wiviott SD, NEJM 2007, Wallentine L, NEJM 2009

Bleeding in PLATO trial

- **Bleeding endpoint**
  - TRITON: non-CABG TIMI major bleeding
  - PLATO: PLATO major bleeding



Wallentine L, NEJM 2009

Prasugrel was not beneficial in some subgroups

	Prasugrel	Clopidogrel	HR for Prasugrel	P-value
History of stroke or TIA				
CVdeath/MI/stroke	19.1	14.4	1.37	0.15
Bleeding*	5.0	2.9	2.46	0.06
Combined EP	23.0	16.0	1.54	0.04
Age≥75, Bwt<60kg, or Hx of stroke or TIA				
CVdeath/MI/stroke	16.1	16.0	1.02	0.83
Bleeding*	4.3	3.3	1.42	0.10
Combined EP	20.2	19.0	1.07	0.43
Age<75, Bwt≥60kg, and no Hx of stroke or TIA				
CVdeath/MI/stroke	8.3	11.0	0.74	<0.001
Bleeding*	2.0	1.5	1.24	0.17
Combined EP	10.2	12.5	0.80	<0.001

*Bleeding = non-CABG TIMI major bleeding

Wiviott SD, NEJM 2007

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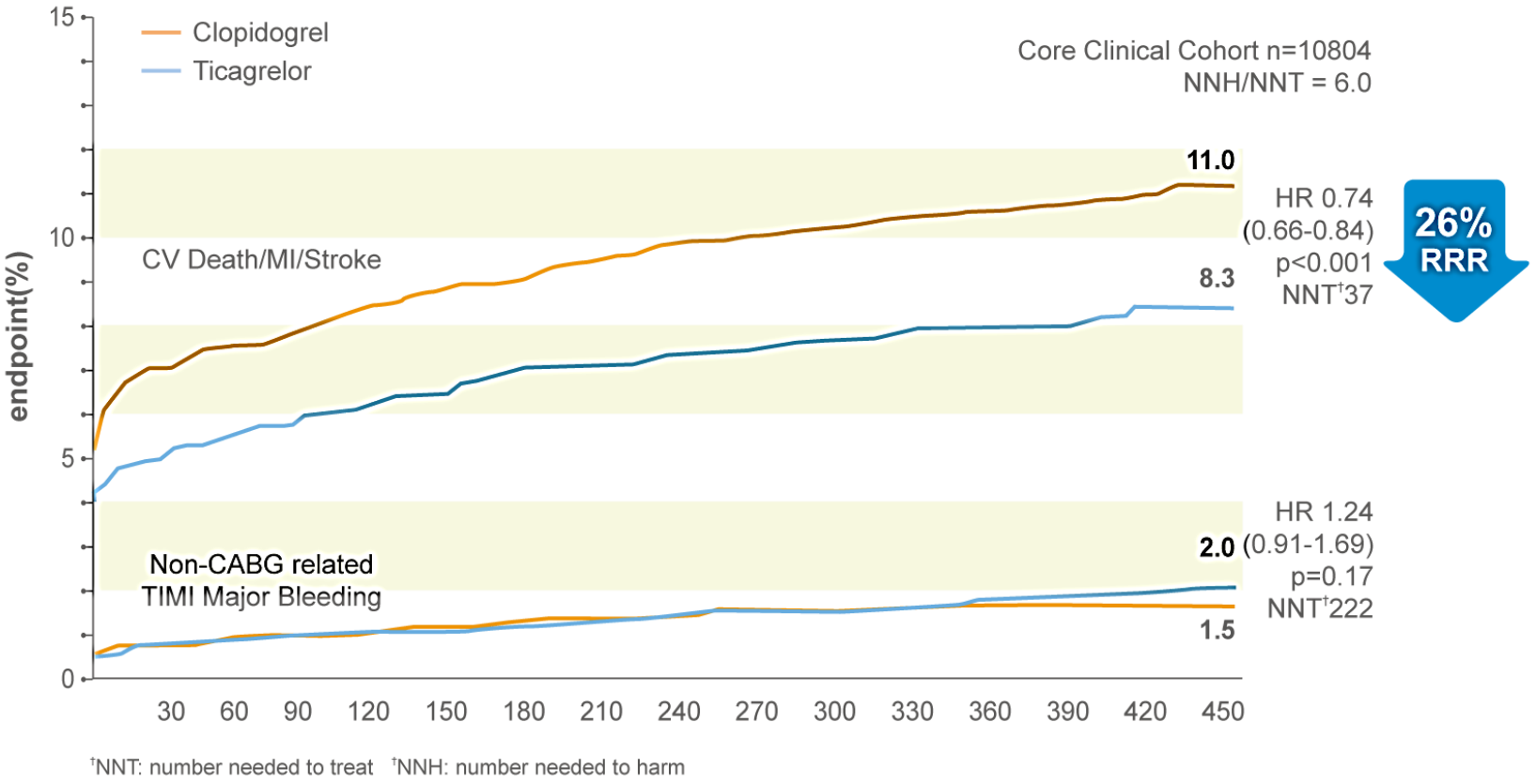
Core Cohort: Superior efficacy with no increase in the bleeding risk

Core Clinical Cohort (**KFDA Approved Indication**):
No history of stroke/TIA, age<75 years, and weight≥60kg[1]

Main Results figure in Core Clinical Cohort



1. KFDA Effient PI
2. Wiviott SD et al. N Engl J Med 007;357:2001-15.

Invasive procedures performed
PLATO vs. TRITON

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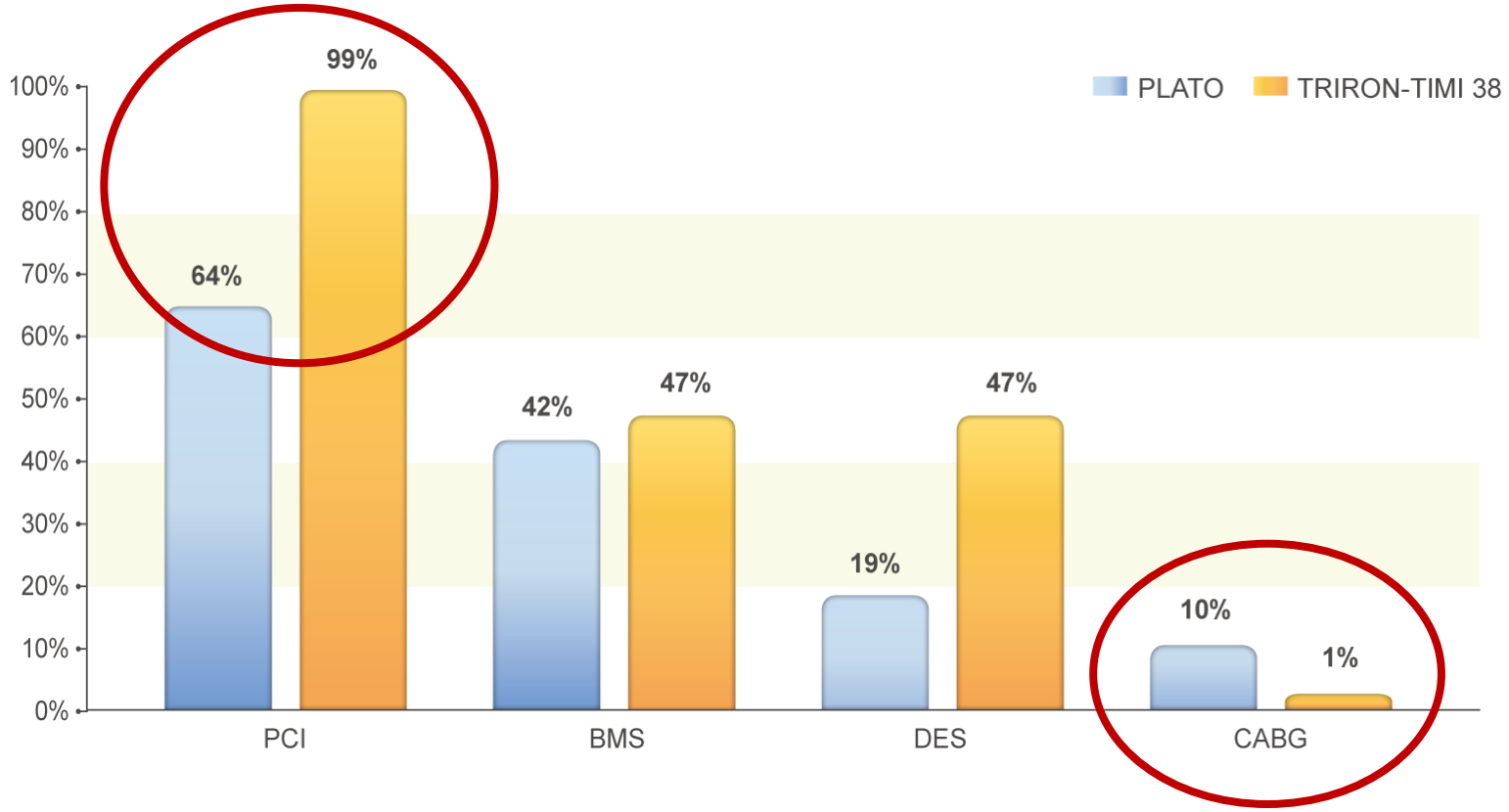
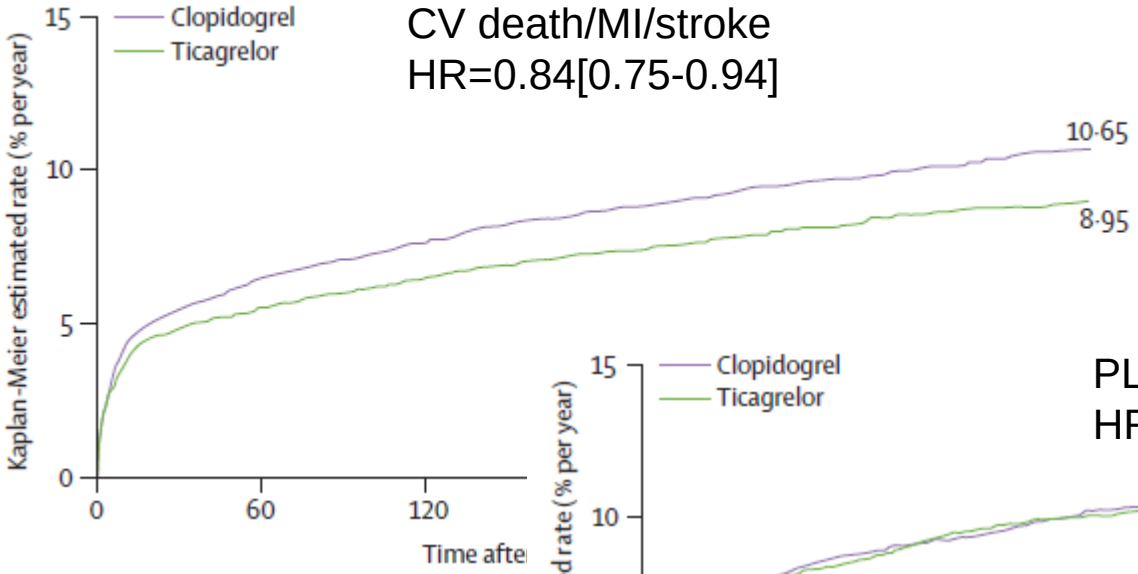
- Subjects
  - TRITON: ACS patients with scheduled PCI
  - PLATO: ACS patients



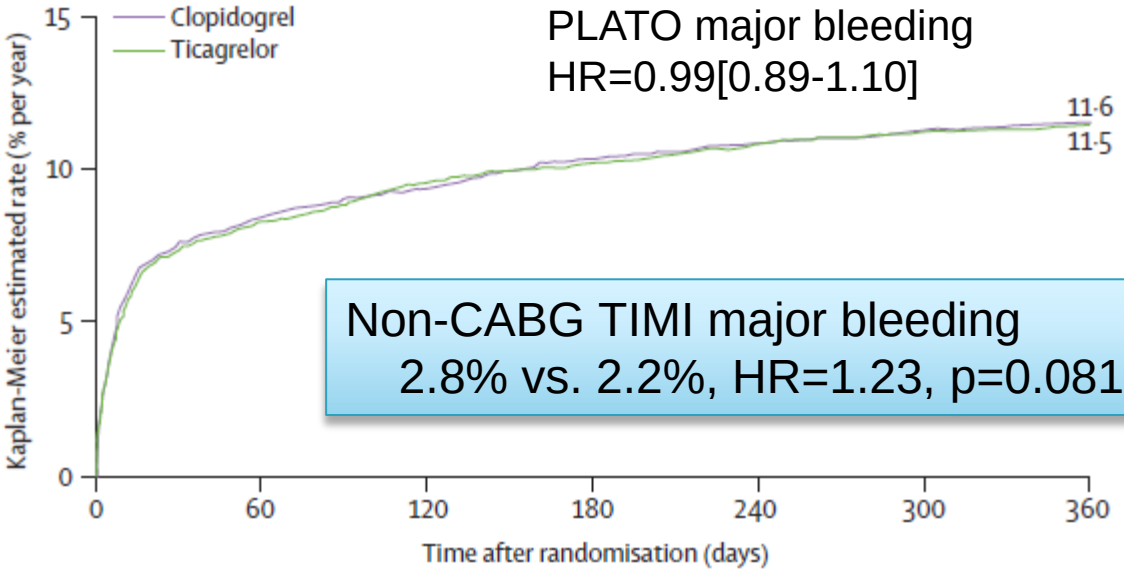
1. Wiviott SD et al. *N Engl J Med*. 2007;357:2001-15
2. Wallentin L et al. *N Engl J Med*. 2009;361

PLATO Invasive

- N=13,408 (72% of total cohort) invasive strategy planned



CV death/MI/stroke
HR=0.84[0.75-0.94]



PLATO major bleeding
HR=0.99[0.89-1.10]

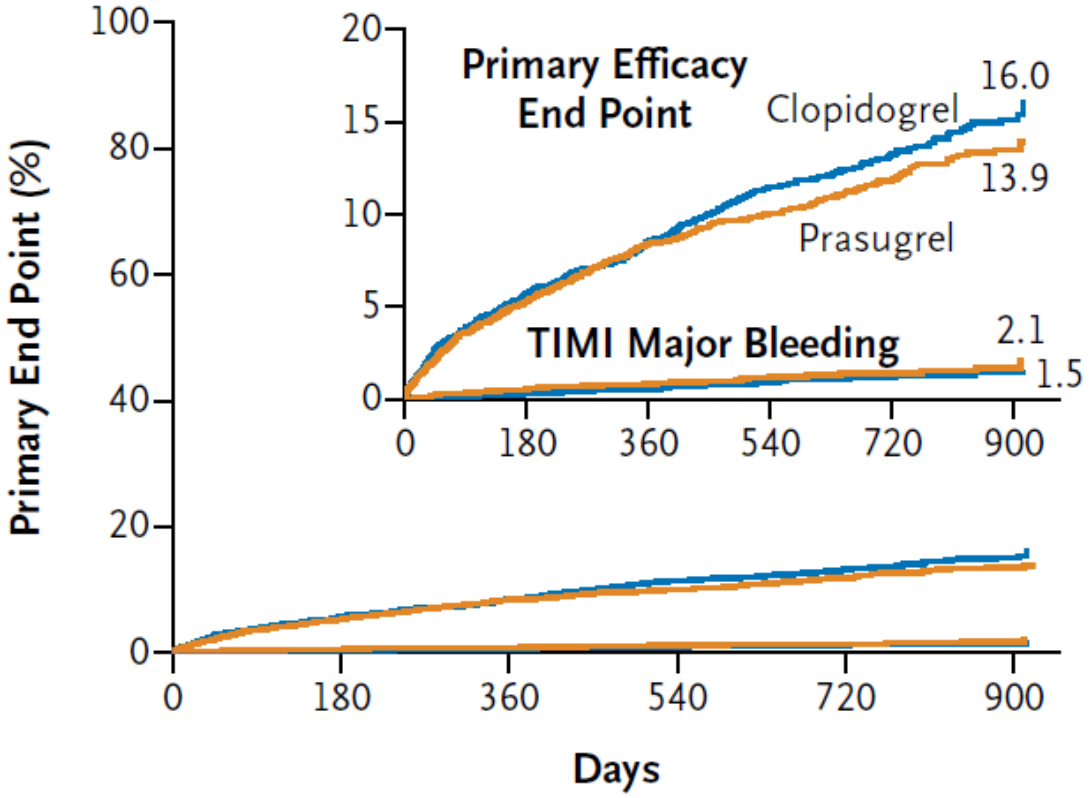
Non-CABG TIMI major bleeding
2.8% vs. 2.2%, HR=1.23, p=0.081

Cannon PA, Lancet 2010

TRILOGY ACS

Prasugrel vs. clopidogrel for ACS without PCI

- N=7243, Non-STE ACS, not planned for PCI
- Patients with history of TIA or stroke was excluded
- 5 mg of prasugrel for patients ≥ 75 years or body weight < 60 kg



HR=0.91 [0.79-1.05]
p=0.21

HR=1.23 [0.84-1.81]
p=0.29

Roe MT, N Engl J Med 2012

TRILOGY ACS
Angiographic cohort

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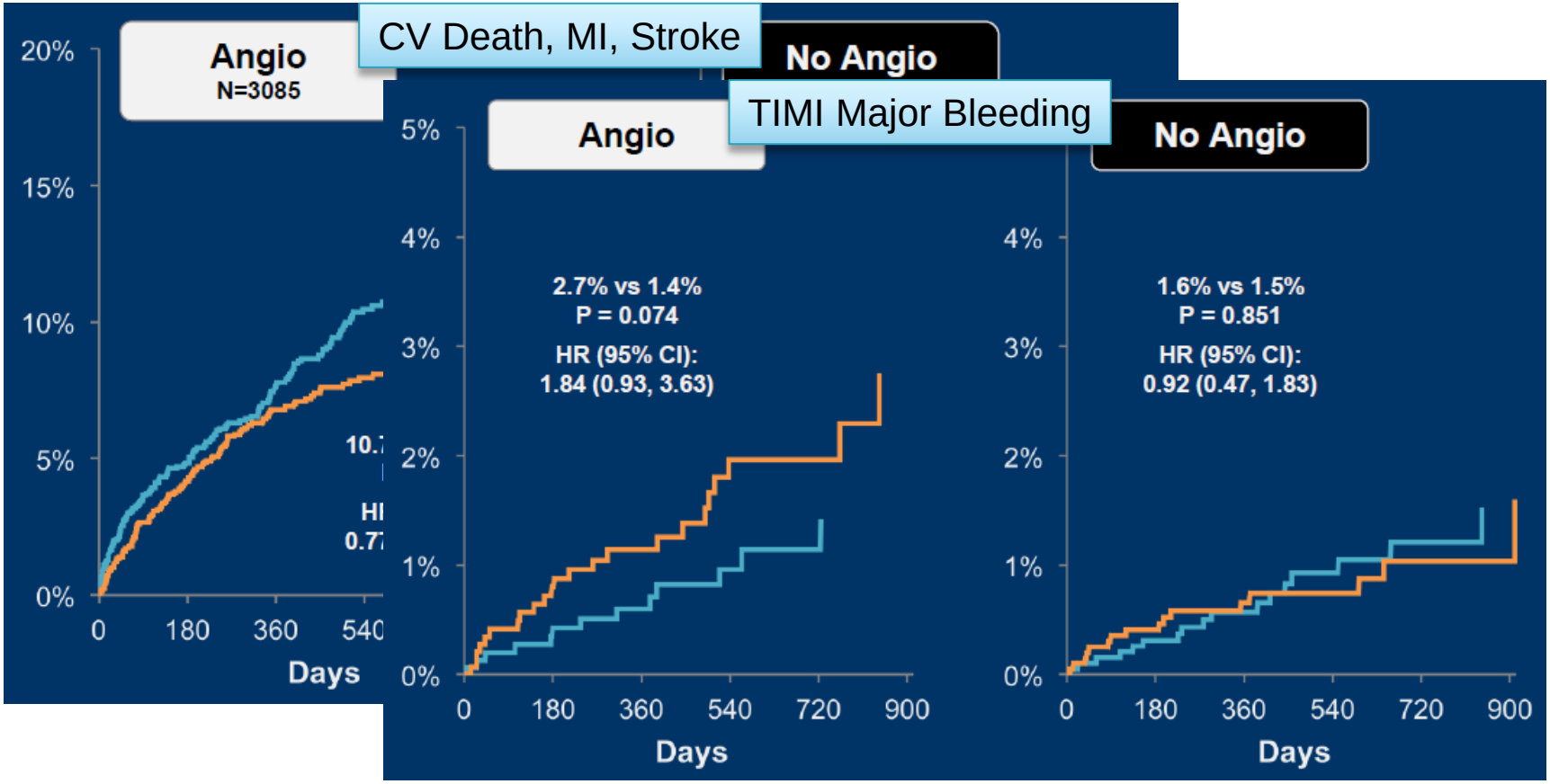
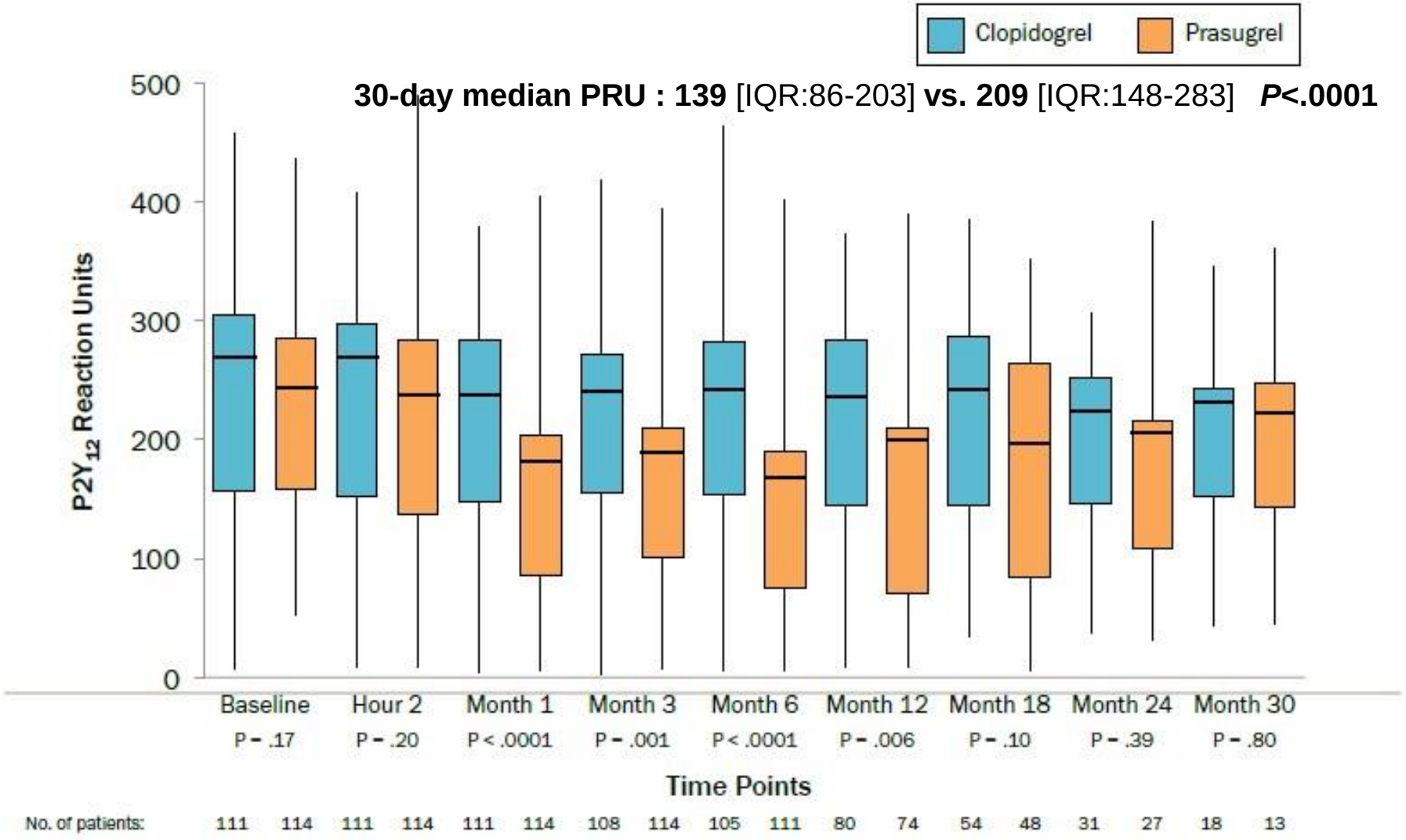
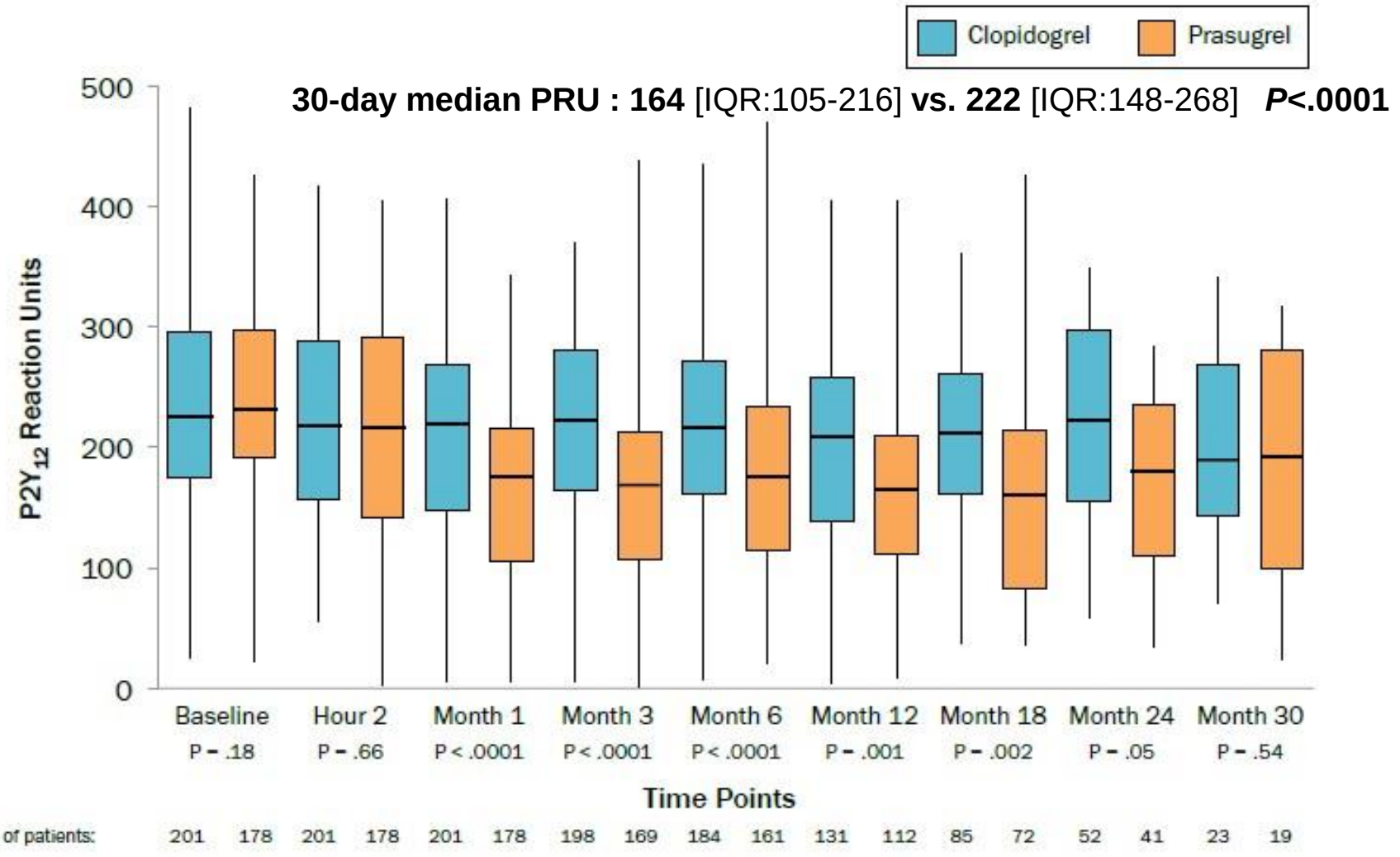
- In patients < 75 years
- Triaged after angiography 43%, and without angiography 57%



Median PRU values by treatment through 30 month follow up : <75 years who were <60kg



Median PRU values by treatment through 30 month follow up : ≥ 75 years



Adverse effects of ticagrelor

	Ticagrelor	Clopidogrel	HR (95%CI)	P-value
Dyspnea				
Any	1270 (13.8)	721 (7.8)	1.84 (1.68-2.02)	**<0.001**
Requiring D/C of Tx	79(0.9)	13(0.1)	6.12 (3.41-11.0)	**<0.001**
Bradycardia				
Pacemaker insertion	82(0.9)	79(0.9)		0.87
Syncope	100(1.1)	76(0.8)		0.08
Bradycardia	409(4.4)	372(4.0)		0.21
Heart block	67(0.7)	66(0.7)		1.00
Holter monitoring(1st wk)				
Pause ≥ 3 sec	84 (5.8%)	51 (3.6%)		**0.01**
Pause ≥ 5 sec	29 (2.0%)	17 (1.2%)		0.10

Possible role of adenosine in CV mortality benefit and dyspnea

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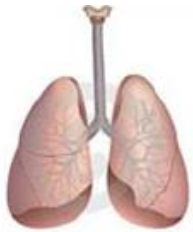
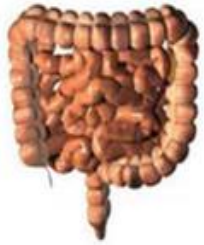
Asystole
Cytoprotection
Apoptosis
Vasodiatation

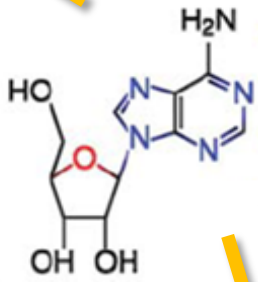


Dyspnea
Bronchospasm

Agitation
Anxiety

TICAGRELOR

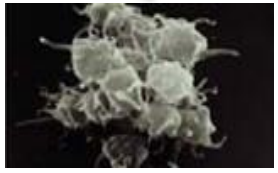




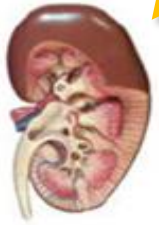
A1
A2A
A2B
A3

CLOPIDOGREL, PRASUGREL

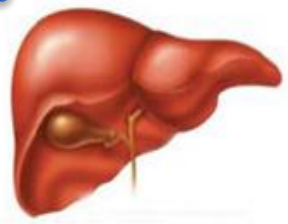
ADENOSINE



P2Y12 inhibition
Aggregation
Secretion



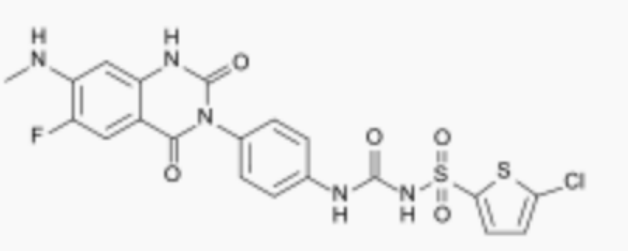
Uric acid
Creatinine



Serebruany VL, Eur Heart J 2010

Dyspnea by reversible P2Y12 inhibitors

- Suggested mechanisms
  - Inhibition of adenosine clearance
  - Transfusion-related acute lung injury
  - Inhibition of P2Y12 on sensory neurons

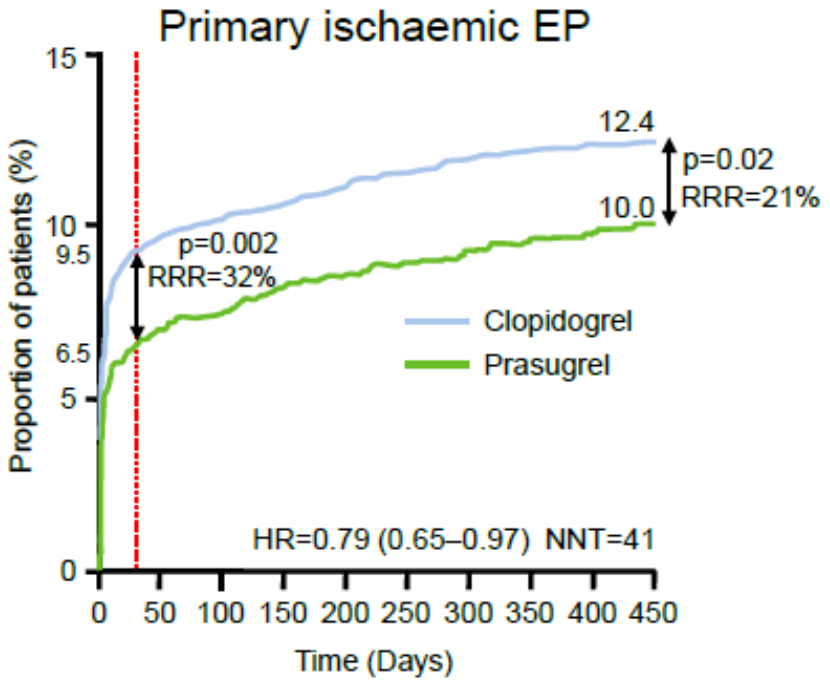


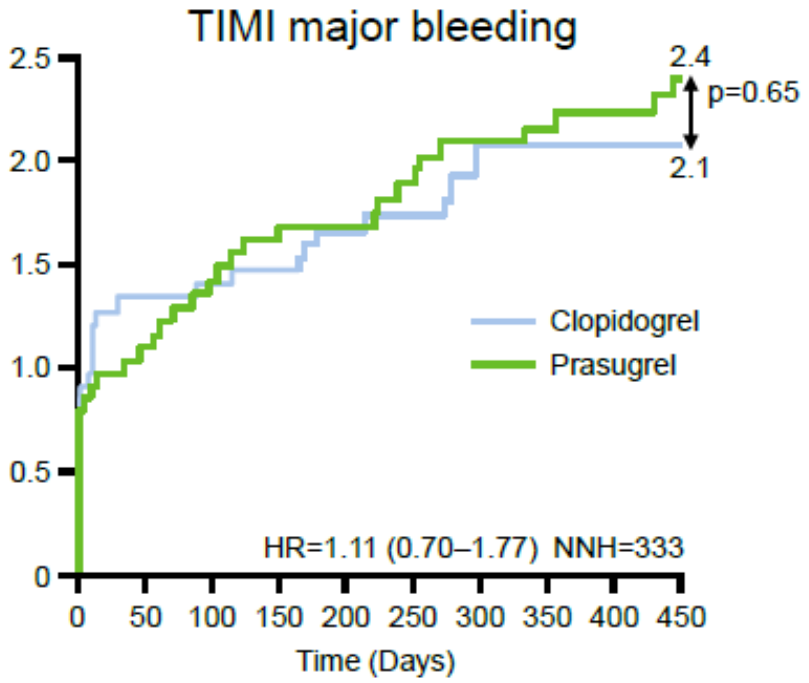
Study drug (reversible $P2Y_{12}$ inhibitor)	Patients (total n)	Dose	Duration of treatment	A Percent of dyspnea in study drug group	B Percent of dyspnea in clopidorel group	A/B	Study (reference)
Ticagrelor*	Patients with atherosclerosis (200)	50 mg b.i.d. 100 mg b.i.d. 200 mg b.i.d. 400 mg q.d.	28 d 28 d 28 d 28 d	10 10 16 20	0 0 0 0	∞ ∞ ∞ ∞	DISPERSE (4)
Ticagrelor	NSTE-ACS (990)	90 mg b.i.d. 180 mg b.i.d.	12 wk 12 wk	10.5 15.8	6.4 6.4	1.64 2.47	DISPERSE-2 (5)
Ticagrelor#	Stable CAD (123)	90 mg b.i.d.	6 wk	38.6	9.3	4.15	ONSET/OFFSET (6,7)
Ticagrelor	Stable CAD (98)	90 mg b.i.d.	14 d	13	4	3.25	RESPOND (8)
Ticagrelor	ACS (18,624)	90 mg b.i.d.	12 mo	13.8	7.8	1.77	PLATO (3)
Cangrelor§	ACS (8,877)	4 µg/Kg/min IV	2–4 h	1	0.4	2.5	CHAMPION-PCI (10)
Elinogrel	Nonurgent PCI (626)	100 mg b.i.d. 150 mg b.i.d.	120 d 120 d	12.4 12.1	3.8 3.8	3.26 3.18	INNOVATE-PCI (11)

Cattaneo M, Thromb Haemost 2012, Serebruany VL, Thromb Haemost 2012

TRITON trial – STEMI subgroup

Prasugrel provided superior benefit without an increase of TIMI major bleeding



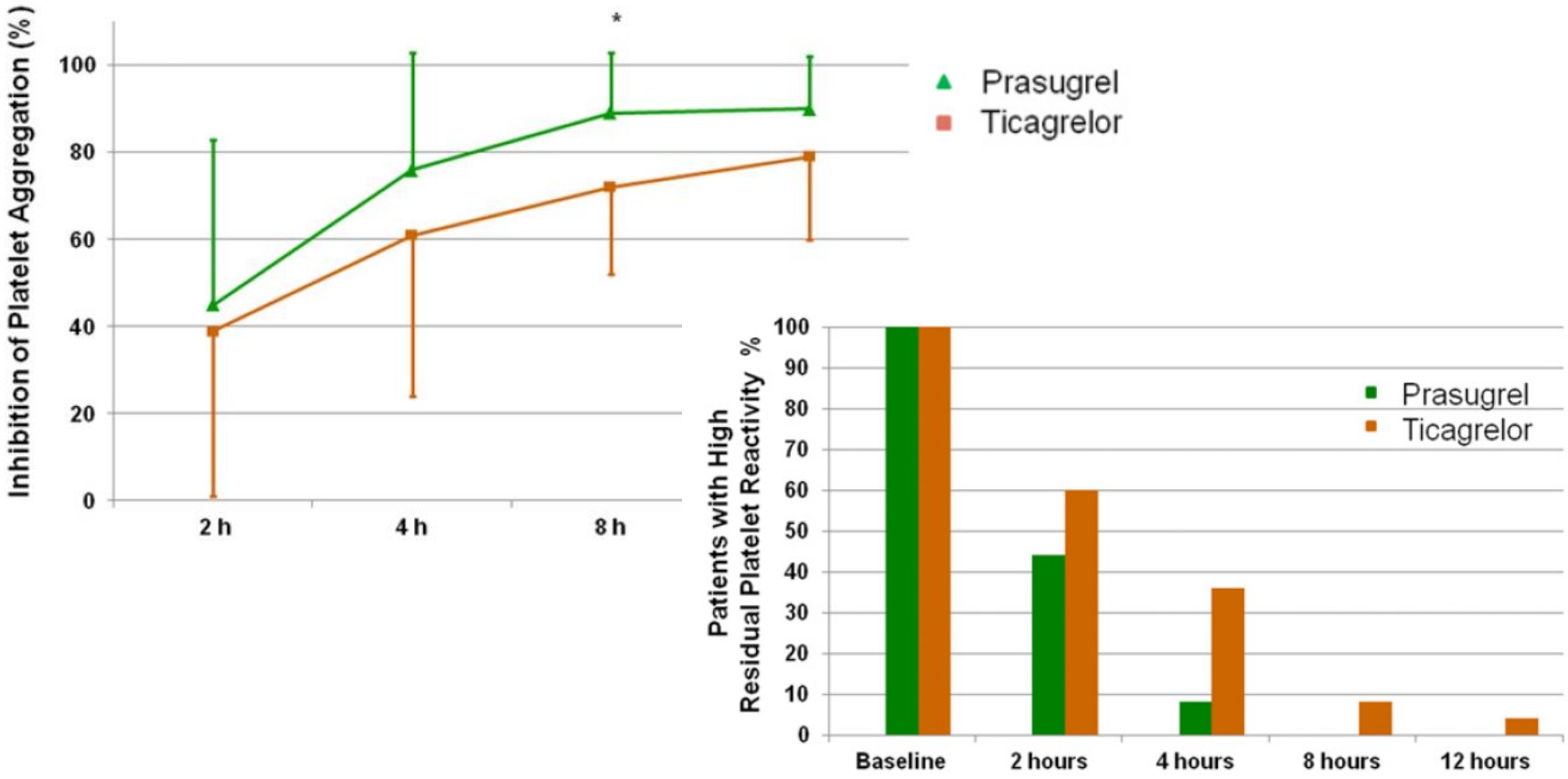


Montalescot G, Lancet 2009

Prasugrel vs. Ticagrelor Loading Dose in Patients with STEMI

Samsung Medical Center
Sungkyunkwan University
School of Medicine

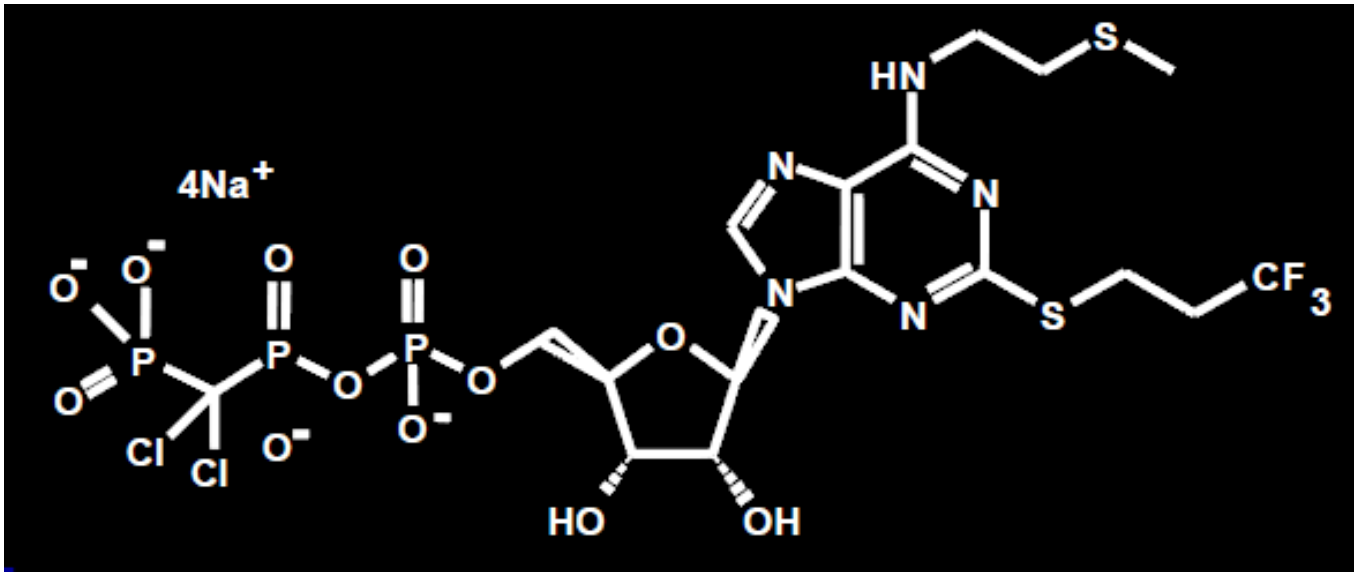
- N=50, randomized to prasugrel 60 mg or ticagrelor 180 mg
- Delayed initial onset of antiplatelet action



Parodi G, J Am Coll Cardiol 2013

Cangrelor

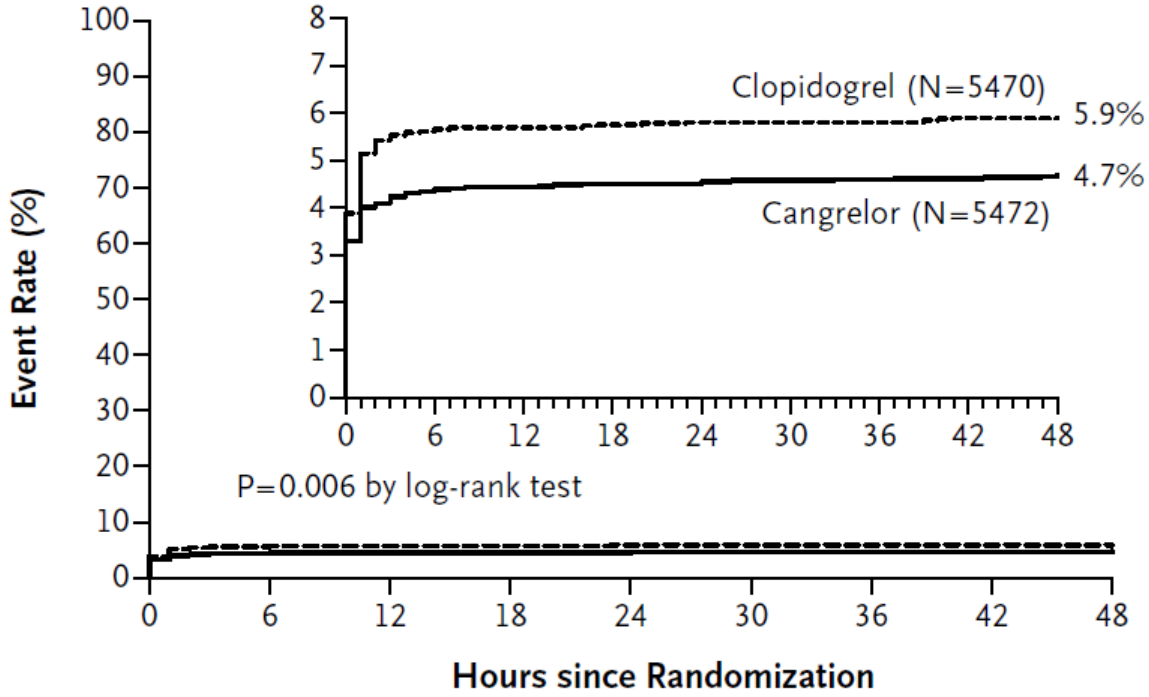
- Intravenous P2Y12 reversible inhibitor
- ADP analogue
- Plasma half-life: 3-5 minutes
- Full recovery of platelet function < 60 minutes



CHAMPION PHOENIX Trial

- N=11,145, urgent or elective PCI
- Cangrelor IV bolus and infusion vs. Clopidogrel 300-600/75 mg

Death, MI, ischemia-revasc, or stent thrombosis at 48 hours



Bhatt DL, NEJM 2013

CHAMPION PHOENIX Trial

- N=11,145, urgent or elective PCI
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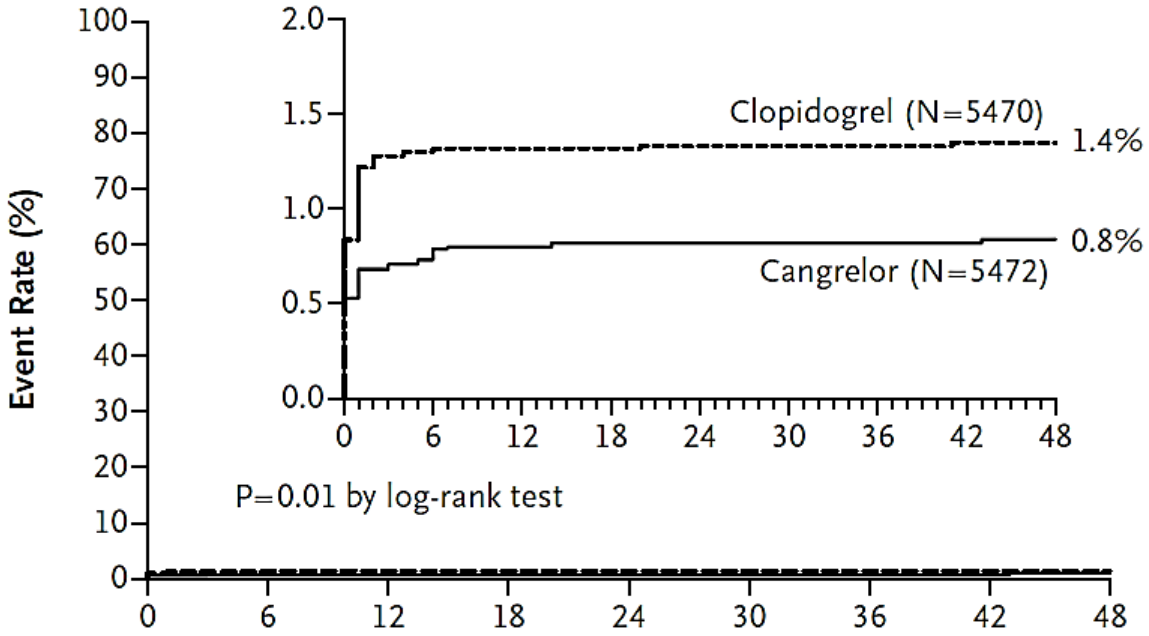
Stent thrombosis at 48 hours

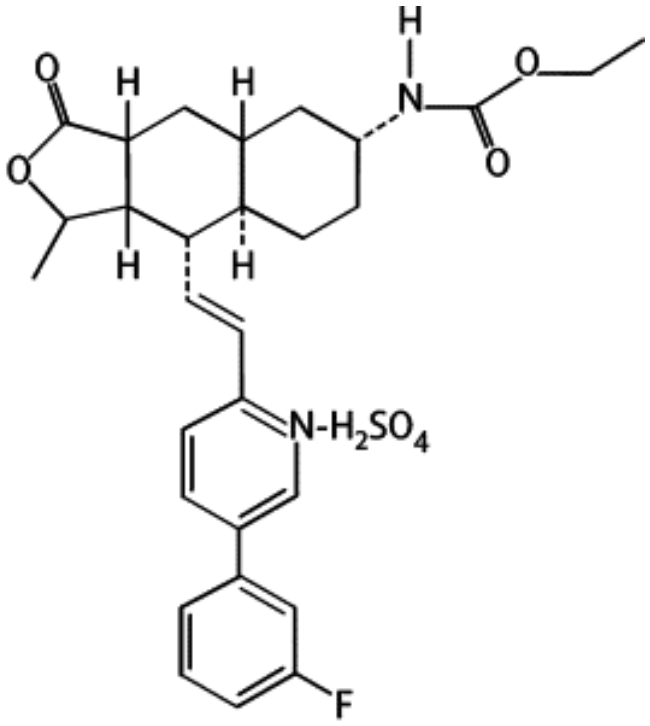


GUSTO-defined severe bleeding at 48 hours
Cangrelor 0.16%, Clopidogrel 0.11% (OR=1.50 [0.53-4.22], p=0.44).

Bhatt DL, NEJM 2013

Vorapaxar (PAR-1 inhibitor)

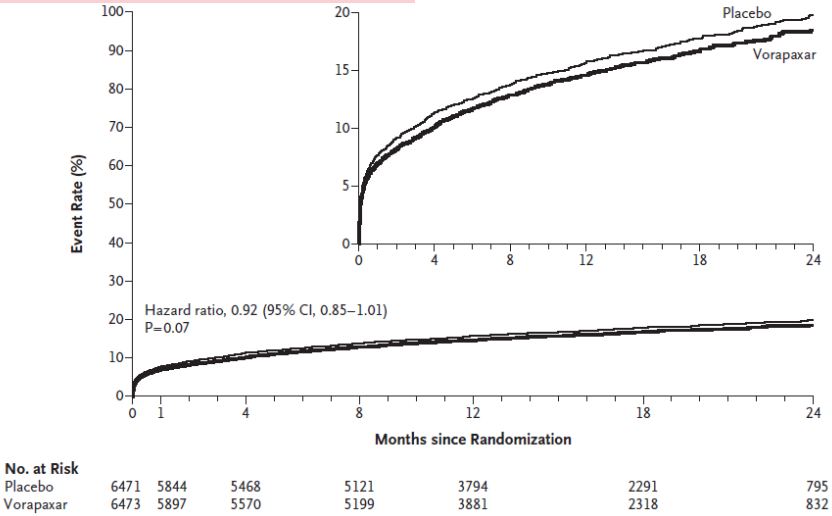
- Thrombin receptor (protease-activated receptor, PAR-1) antagonist based on the natural product himbacine
- Phase 2 study showed a trend of decreased MI risk without no increased bleeding risk



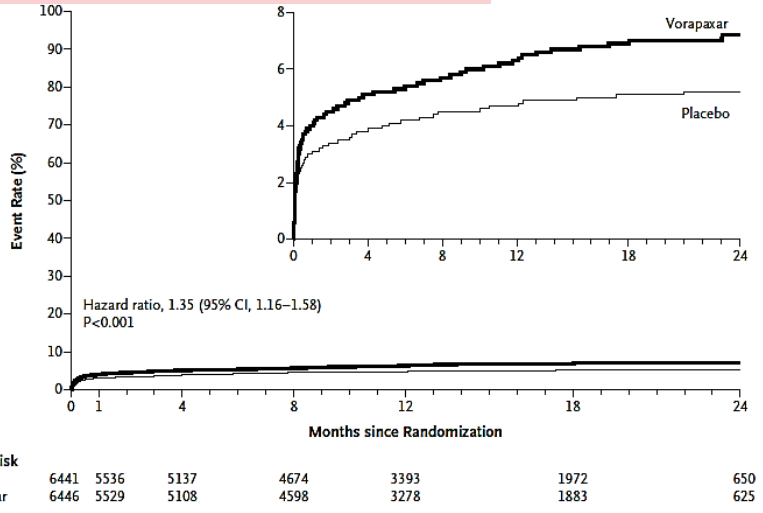
TRACER
Vorapaxar in NSTE-ACS

- Vorapaxar vs. placebo in 12,944 patients with NSTE- ACS
- **Prematurely halted** due to increased risk of hemorrhagic stroke (0.1% vs. 0.3%, p=0.02)

1° EP: HR=0.92, p=0.07



Bleeding EP: HR=1.35, p<0.001



* 1° EP = CV death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization.
* Bleeding EP = GUSTO moderate or severe bleeding

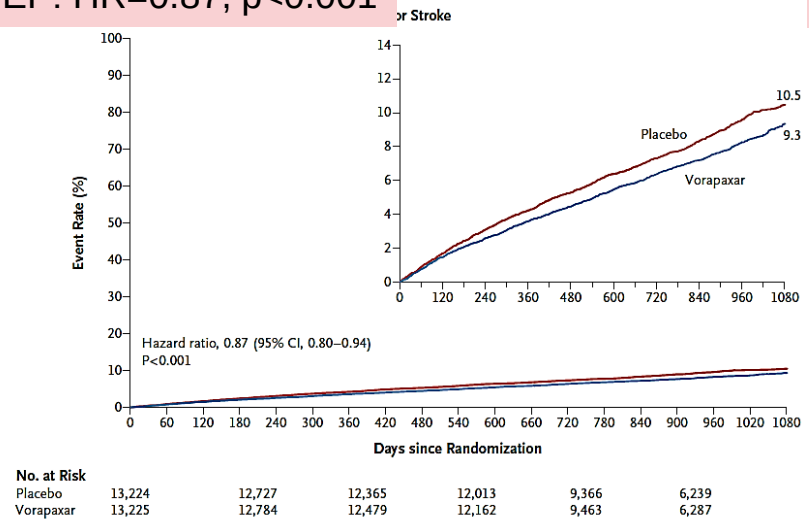
Tricoci P, NEJM 2011

TRA 2P TIMI 50

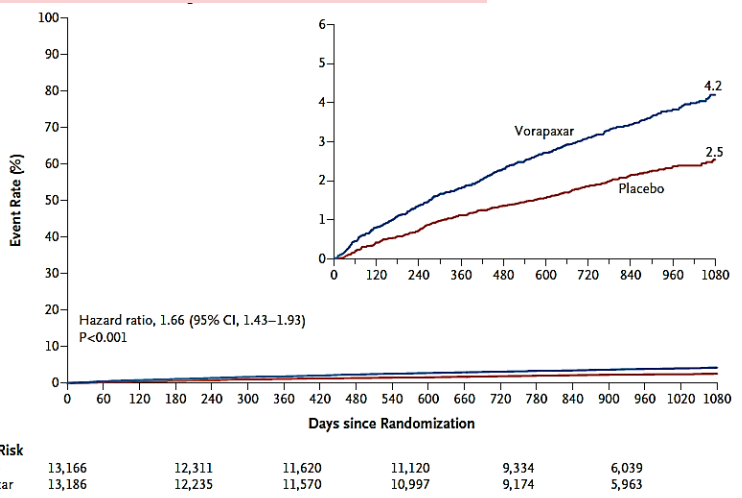
Vorapaxar for secondary prevention

- N=26,449, pts with a Hx of MI, ischemic stroke, or PAD
- After 2 years, DSMB recommended discontinuation of the study treatment in patients with a history of stroke owing to the risk of intracranial hemorrhage

1° EP: HR=0.87, p<0.001



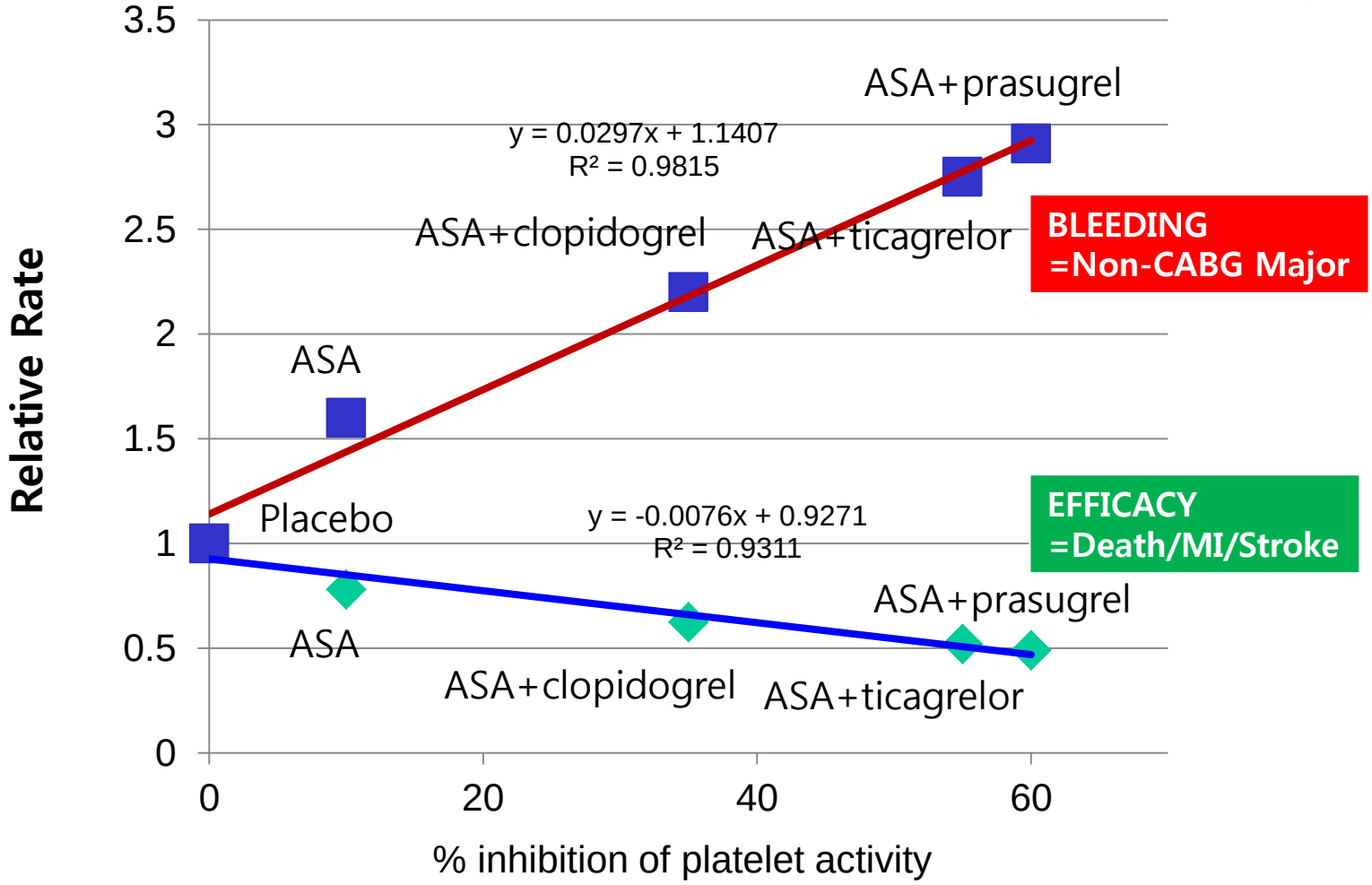
Bleeding EP: HR=1.66, p<0.001



* 1° EP = CV death, MI, stroke
* Bleeding EP = GUSTO moderate or severe bleeding

Morrow DA, NEJM 2012

Efficacy and Safety Correlated with IPA

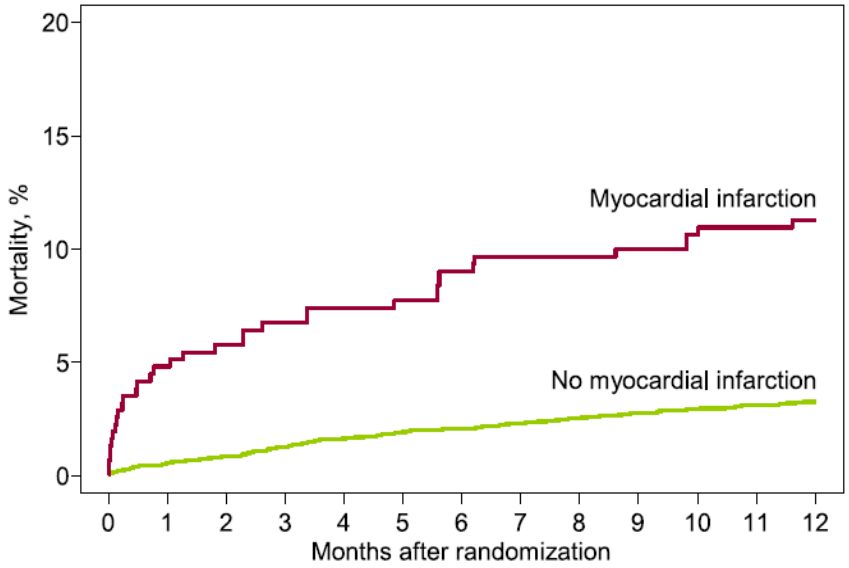


Antithrombotic Trialists' Collaboration. BMJ. 2002;324:71
Yusuf et al. N Engl J Med. 2001;345:494
Wiviott et al. N Engl J Med 2007;357:2001-2015
Wallentin et al. N Engl J Med 2009;361:1-13

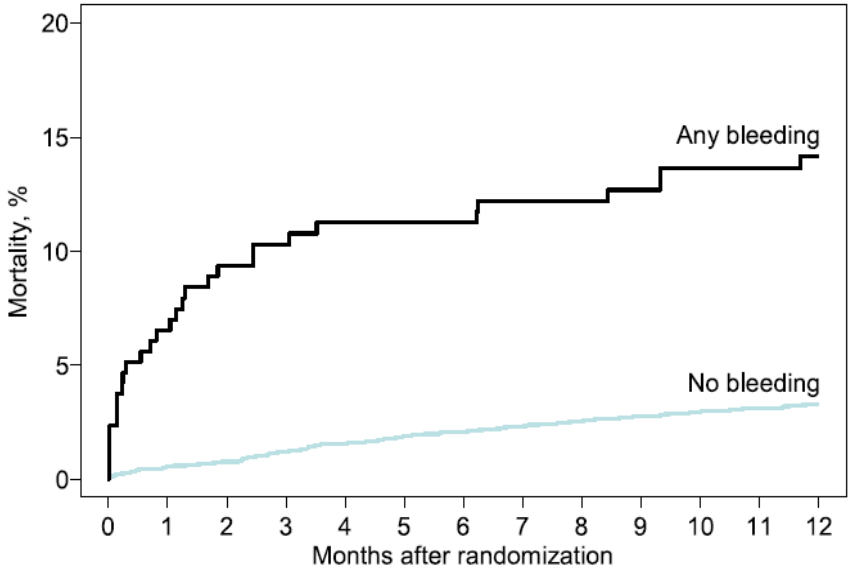
MI and bleeding after PCI

- Both ischemic and bleeding complications have shown a strong association with overall mortality rates in the first 12 months after coronary stenting.

Post-procedural MI



Post-procedural bleeding



Ndrepepa, J Am Coll Cardiol 2008

SMART-DATE Trial

Samsung Medical Center
Sungkyunkwan University
School of Medicine

PI. Gwon HC

Patients Matching Enrollment Criteria (N=3,000)

- **EES N=1,000**
- **ZES N=1,000**
- **BES N=1,000**

Percutaneous Coronary Intervention

- **Clopidogrel 6 months N=1,500**
- **Clopidogrel >12 months N=1,500**

Stratified by
Diabetes
ST elevation

Primary clinical endpoint evaluation

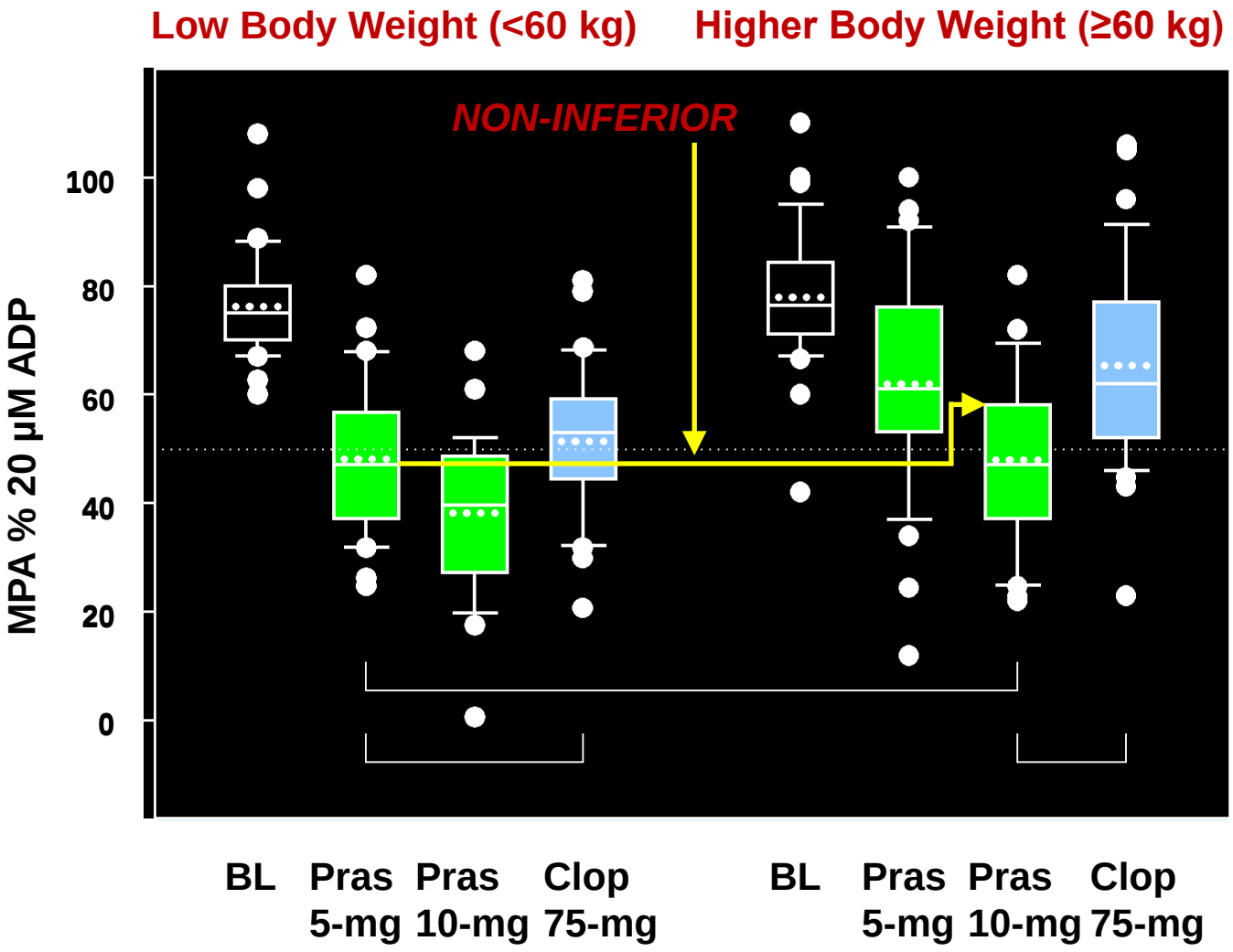
Clinical

1mo | 6mo | 12mo | 18mo | 3yr | 5yr

Thank you for your attention

FEATHER study

Prasugrel 5 mg for < 60 kg vs. 10 mg for ≥ 60 kg

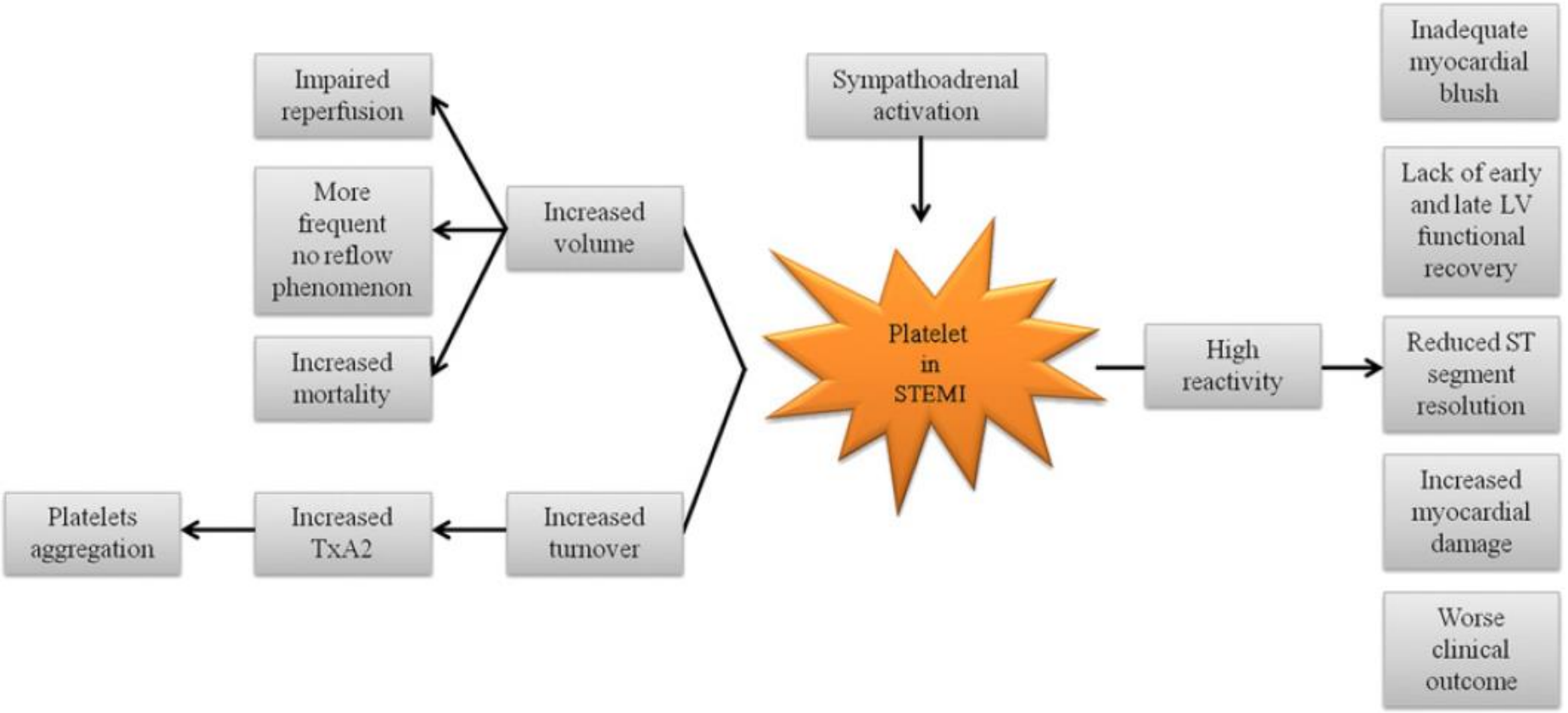


Data from Lilly

p-values adjusted for covariates

Activation of platelets in STEMI influencing adverse clinical outcomes

Samsung Medical Center
Sungkyunkwan University
School of Medicine



Alexopulos D, Int J Cardiol 2013

Prasugrel resistance 논문
정영훈 IPA 슬라이드를 넣을까