Joint Meeting of Coronary Revascularization
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The University of Nottingham

ADP and $P2Y_{12}$ antagonists

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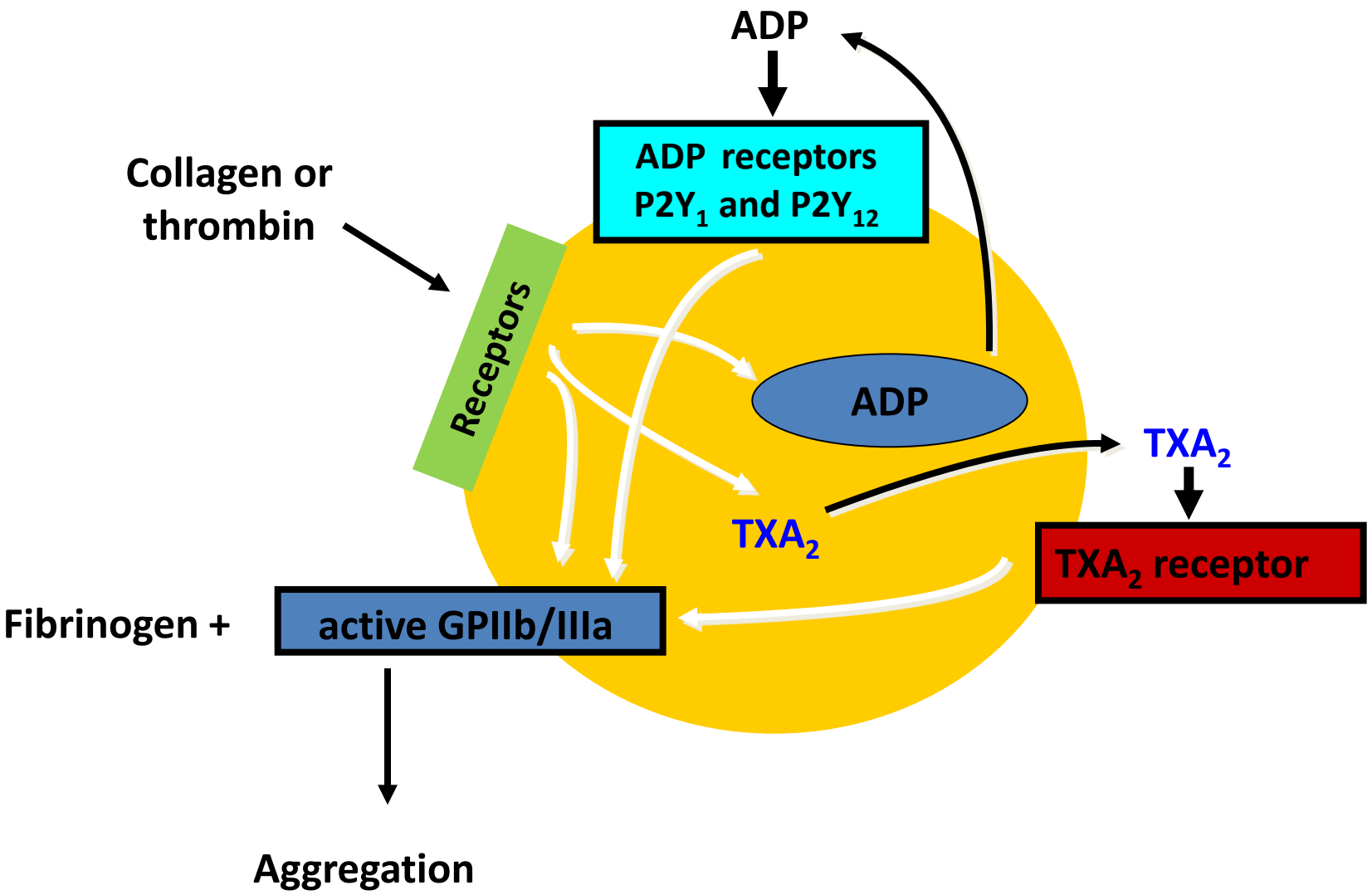
Important roles of ADP and TXA_2 in platelet function



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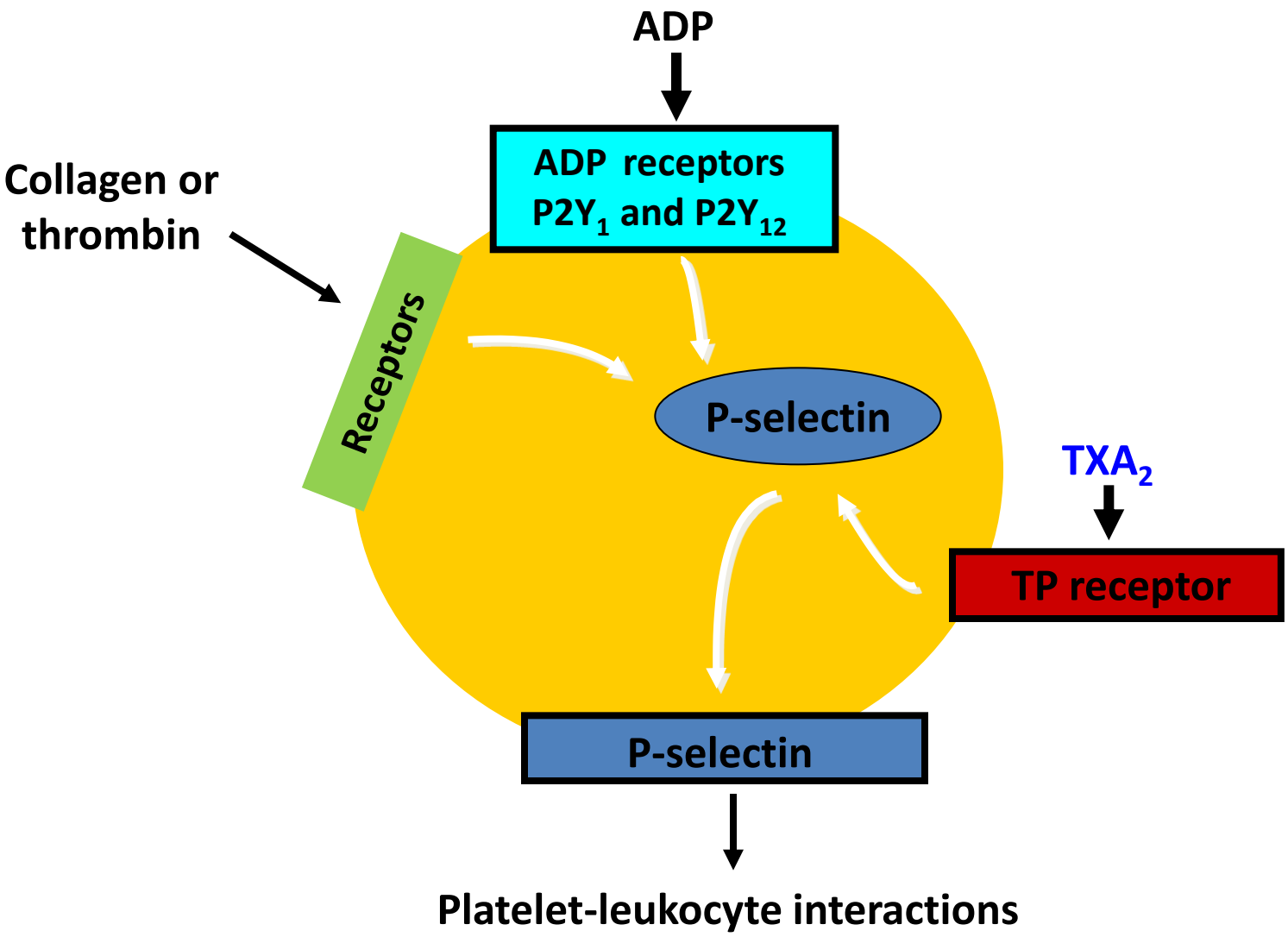
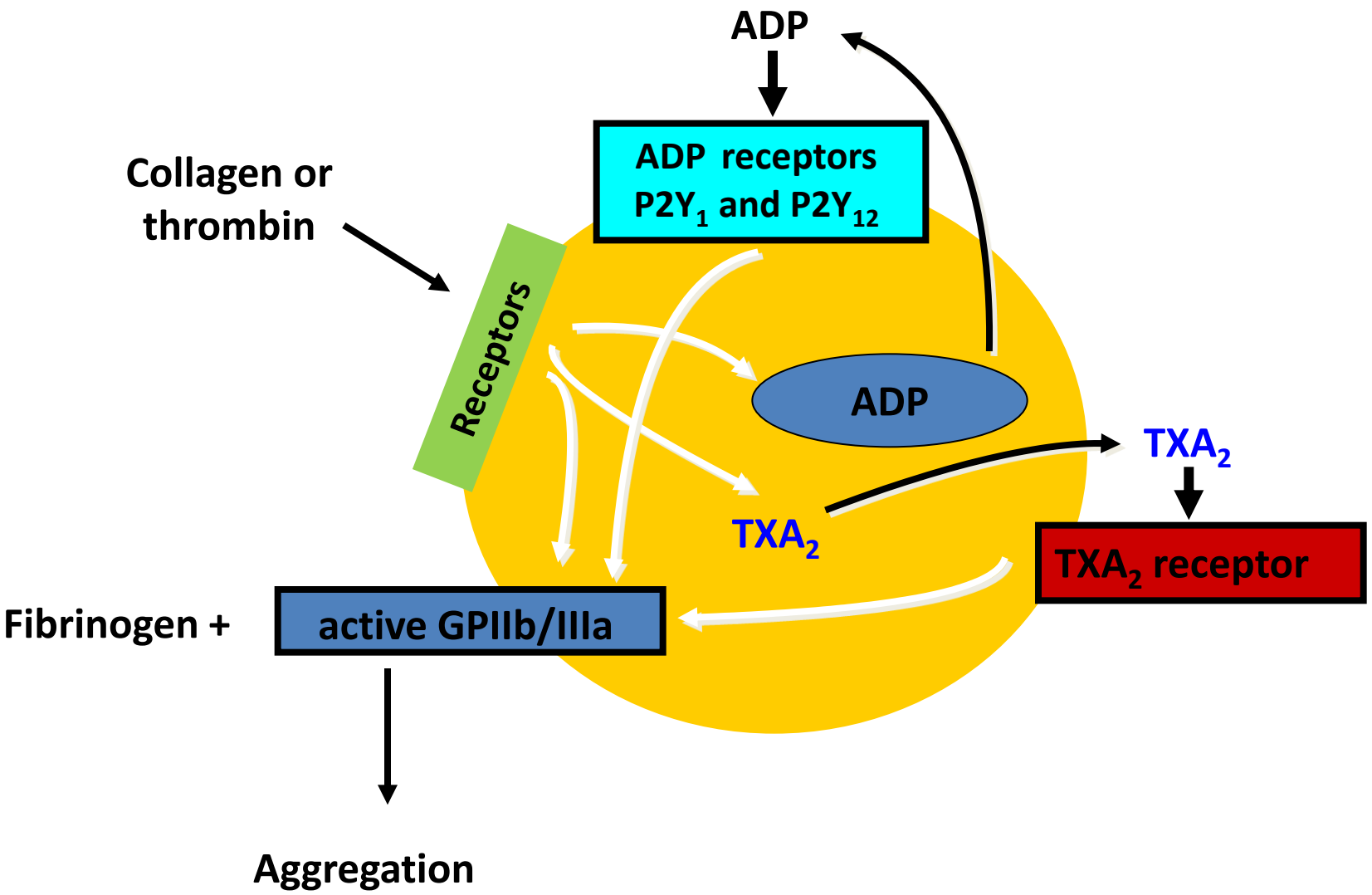


Aspirin and $P2Y_{12}$ antagonists are the most common form of antithrombotic therapy



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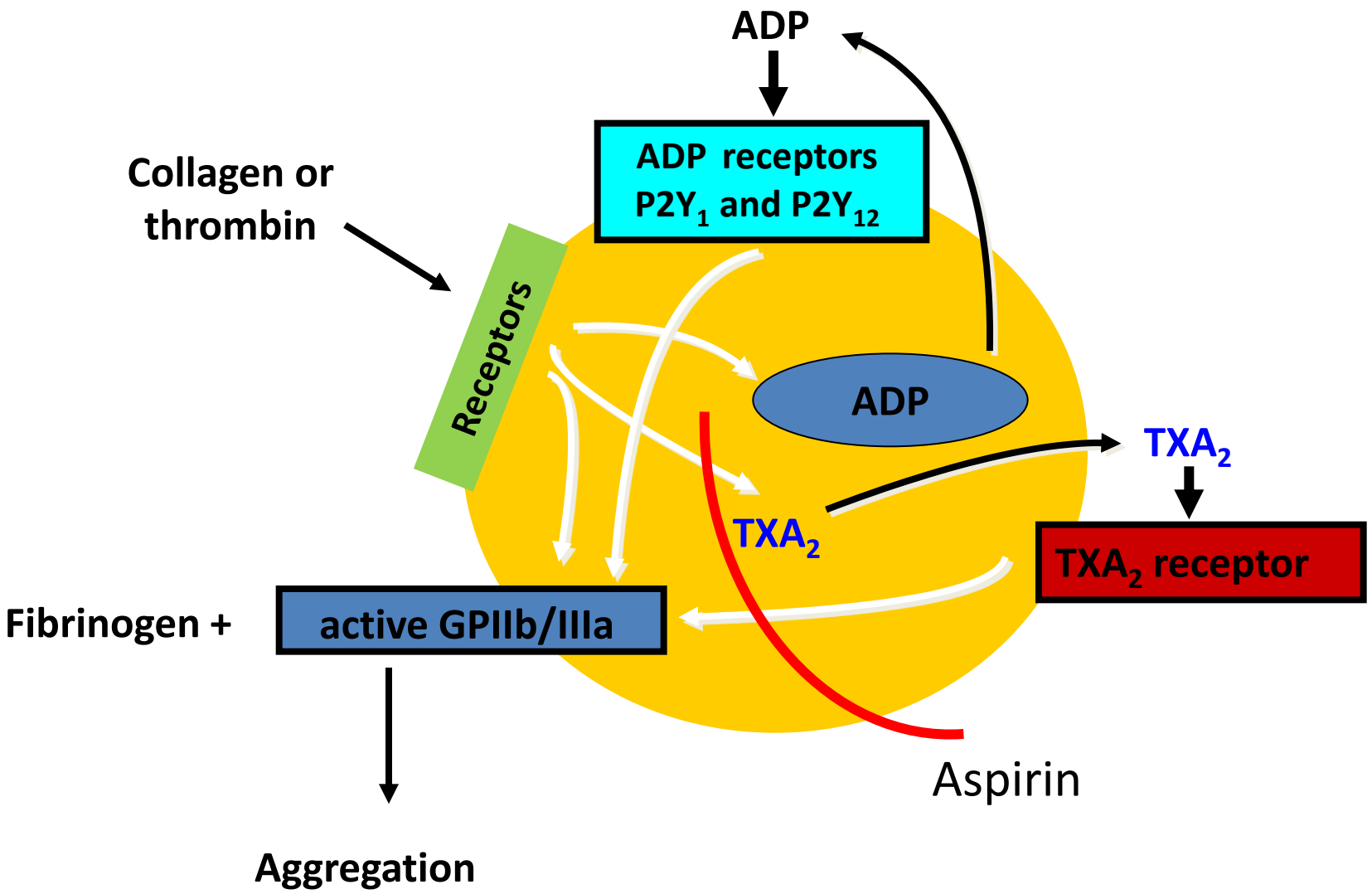

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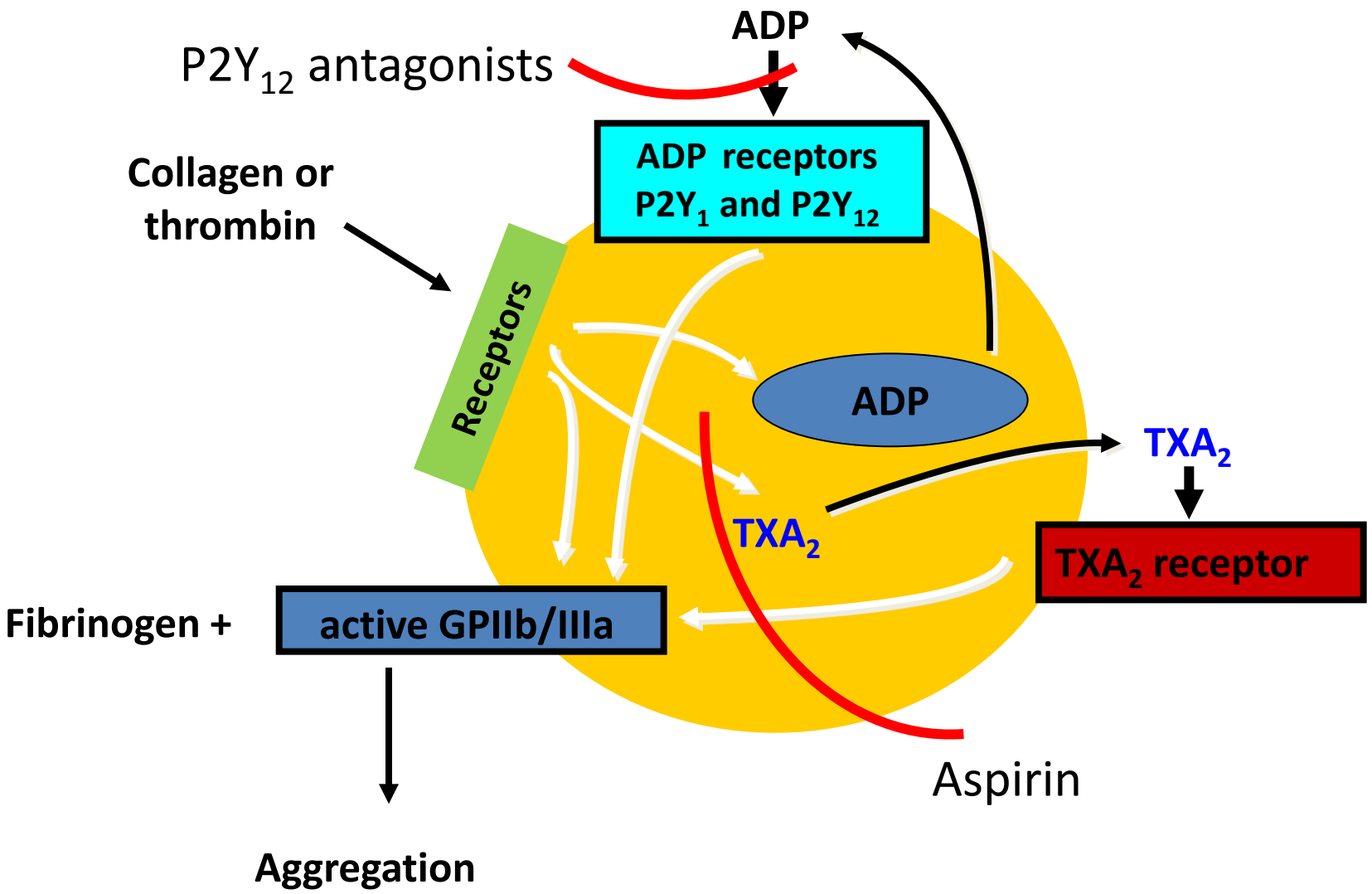


$P2Y_{12}$ antagonists in current use (in combination with low dose aspirin)

- Clopidogrel –
  very widely used as an oral agent in patients with acute coronary syndromes

- Prasugrel –
  an oral agent proven to provide better antithrombotic therapy than clopidogrel in STEMI patients (TRITON TIMI-38)

- Ticagrelor –
  an oral agent proven to provide better antithrombotic therapy than clopidogrel in patients with ACS (PLATO)

- Cangrelor –
  under development as an agent for intravenous use during acute coronary interventions

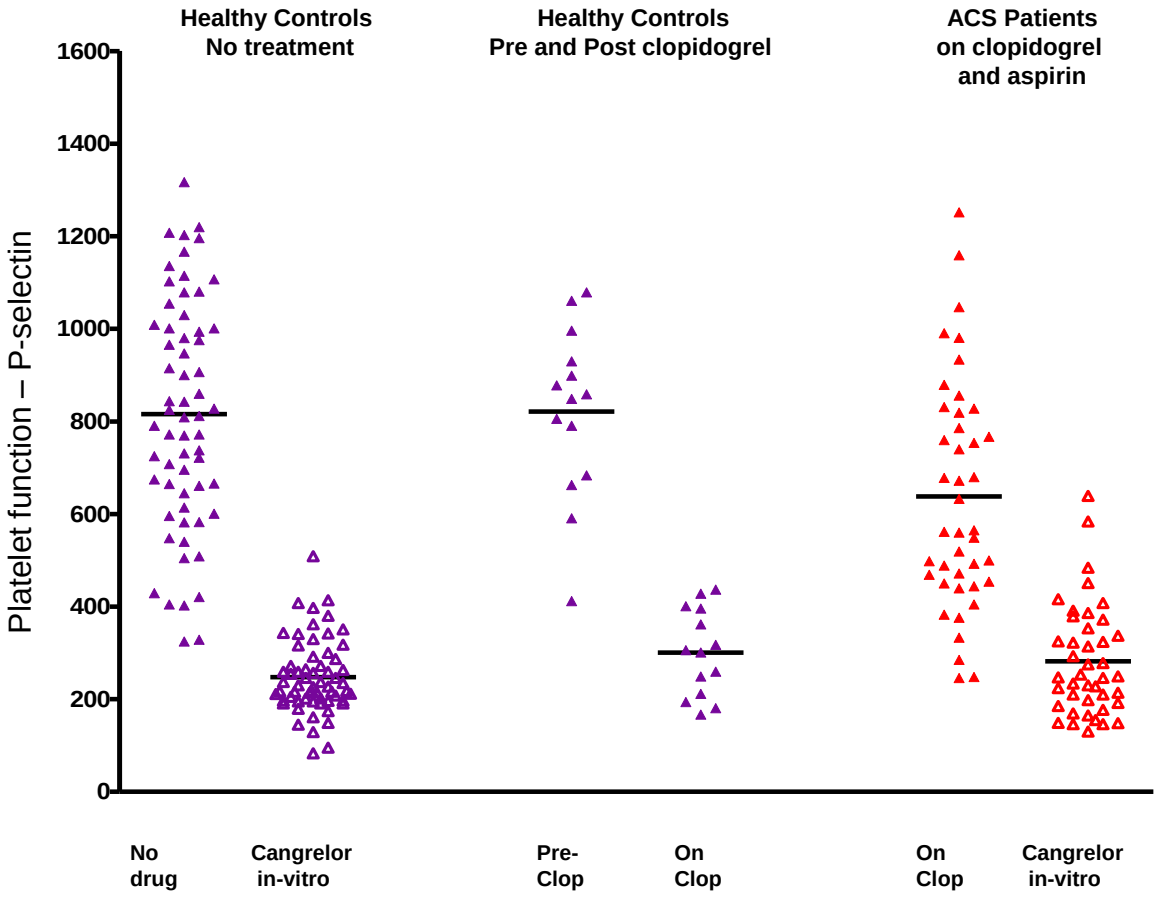
Differences between $P2Y_{12}$ antagonists

drug	action	reversibility	onset	offset	inhibition of platelet function	variability of effect
clopidogrel	prodrug	irreversible	slow	slow	partial	variable
prasugrel	prodrug	irreversible	fast	slow	more complete	less variable
ticagrelor*	direct	reversible	fast	faster	more complete	less variable
cangrelor**	direct	reversible	immediate	very rapid	more complete	less variable

* significant effect on mortality in PLATO

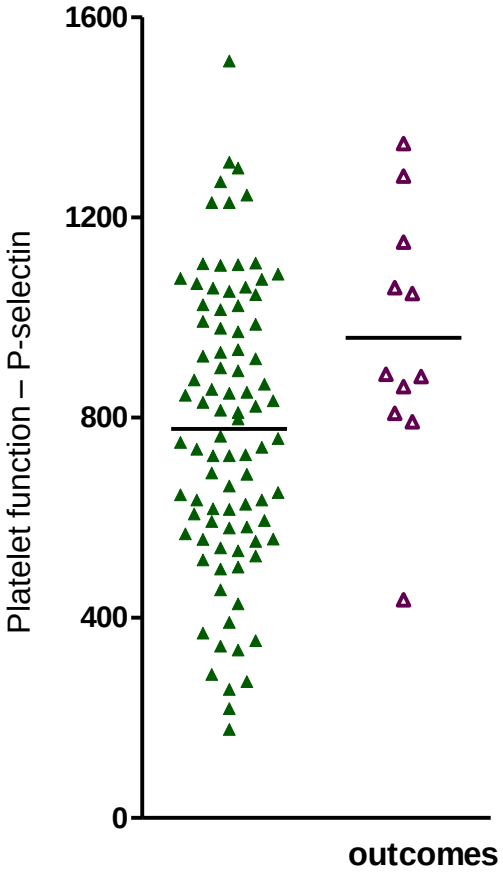
** clinical trials still incomplete

Clopidogrel - variable effect in different patients



Fox et al, Platelets 2009; 20(4): 250-259

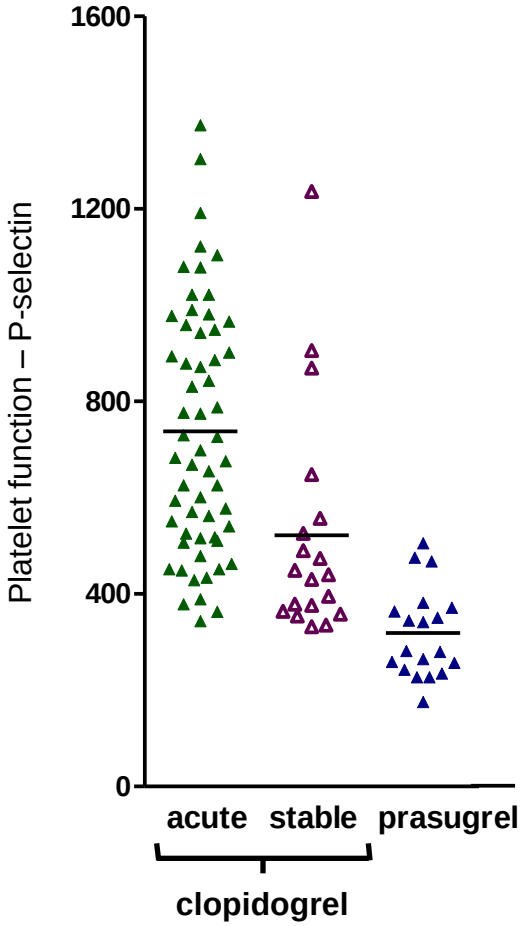
Outcomes at 9 months



- P-selectin test on blood samples from ACS patients on treatment with clopidogrel (n=100)
- Results for patients who developed a cardiovascular event (MI / cardiovascular death) within 9 months are shown on the right (outcomes, n=11)
- Patients who remained stable are shown on the left (n=89)

Thomas et al, paper in preparation

Clopidogrel vs prasugrel

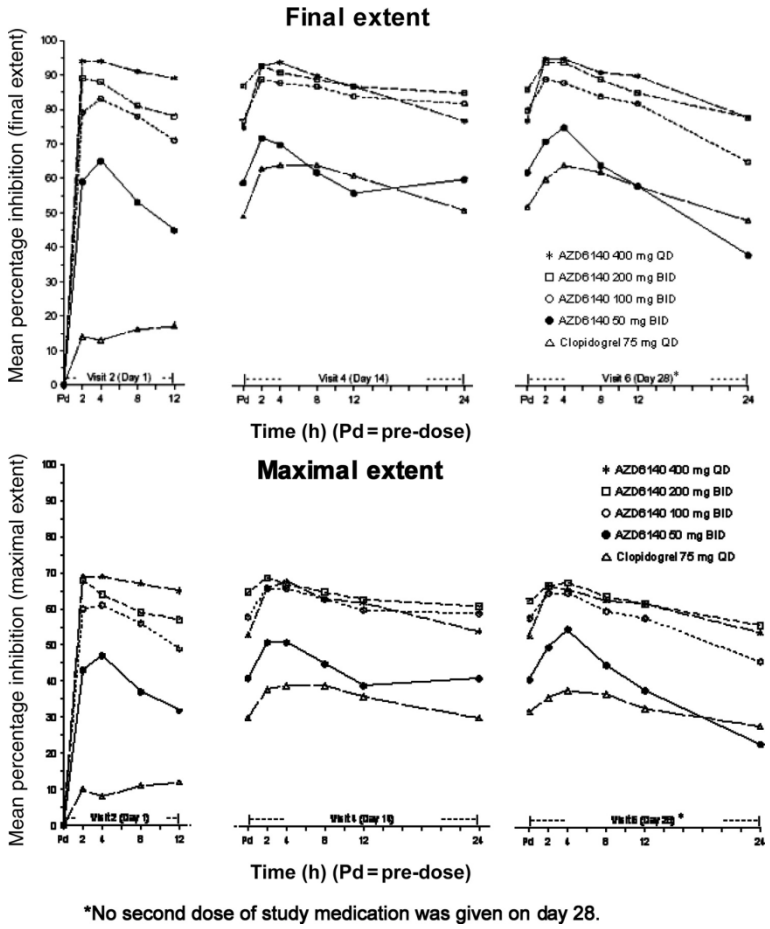


P-selectin test on blood samples from

- ACS patients in the acute setting after a cardiovascular event (n=58)
- Stable patients with a history of ACS (n=19) on clopidogrel for secondary prevention
- ACS patients in the acute setting after a cardiovascular event on prasugrel (n=19)

Wijeyeratne et al, paper in preparation

Inhibition of platelet aggregation by clopidogrel and ticagrelor

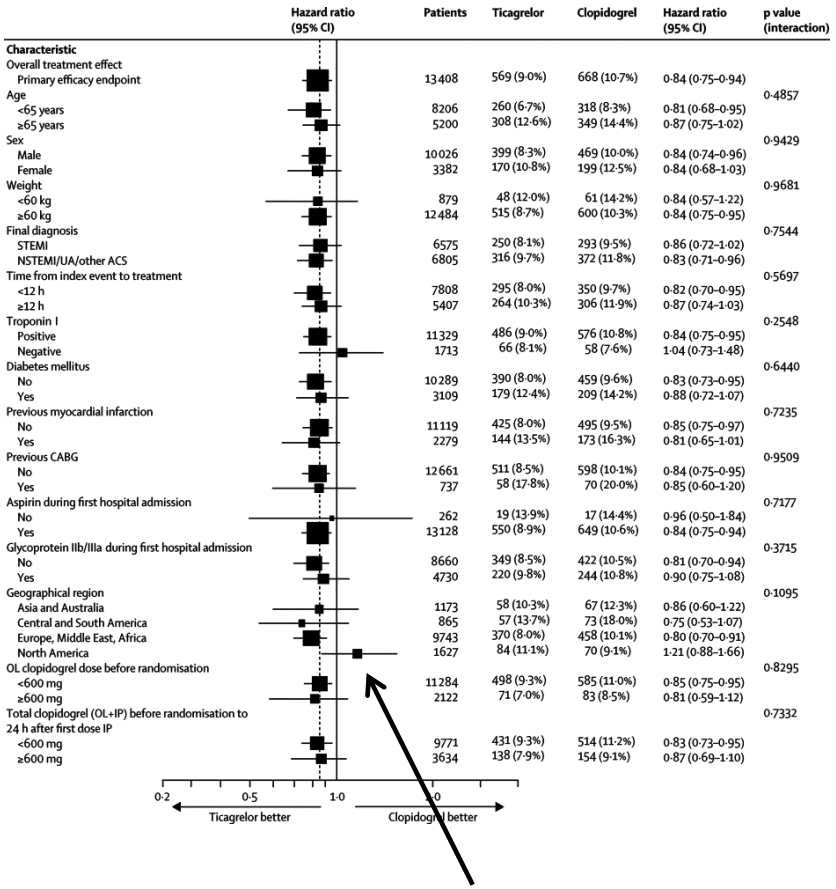


*No second dose of study medication was given on day 28.

- Mean percentage inhibition of ADP-induced platelet aggregation in patients with atherosclerotic disease treated with AZD6140 50mg bid, 100mg bid, 200mg bid, or 400mg qd or clopidogrel 75mg qd for 28 days

Husted et al. Eur Heart J 2006; 27: 1038-47 (DISPERSE study)

PLATO study - North American paradox and Dyspnoea



North American paradox
(use of higher doses of aspirin?)

	ticagrelor	clopidogrel	hazard ratio for ticagrelor group (95% CI)	P value
any	1270/9235 (13.8)	721/9186 (7.8)	1.84 (1.68-2.02)	<0.001
requiring discontinuation of study treatment	79/9235 (0.9)	13/9186 (0.1)	6.12 (3.41-11.01)	<0.001

Dyspnea – no./total no. (%)

Dyspnoea
(inhibition of adenosine uptake?)

Wallentin *et al*. N Engl J Med 2009;361:1045-1057 (PLATO Study)

North American paradox
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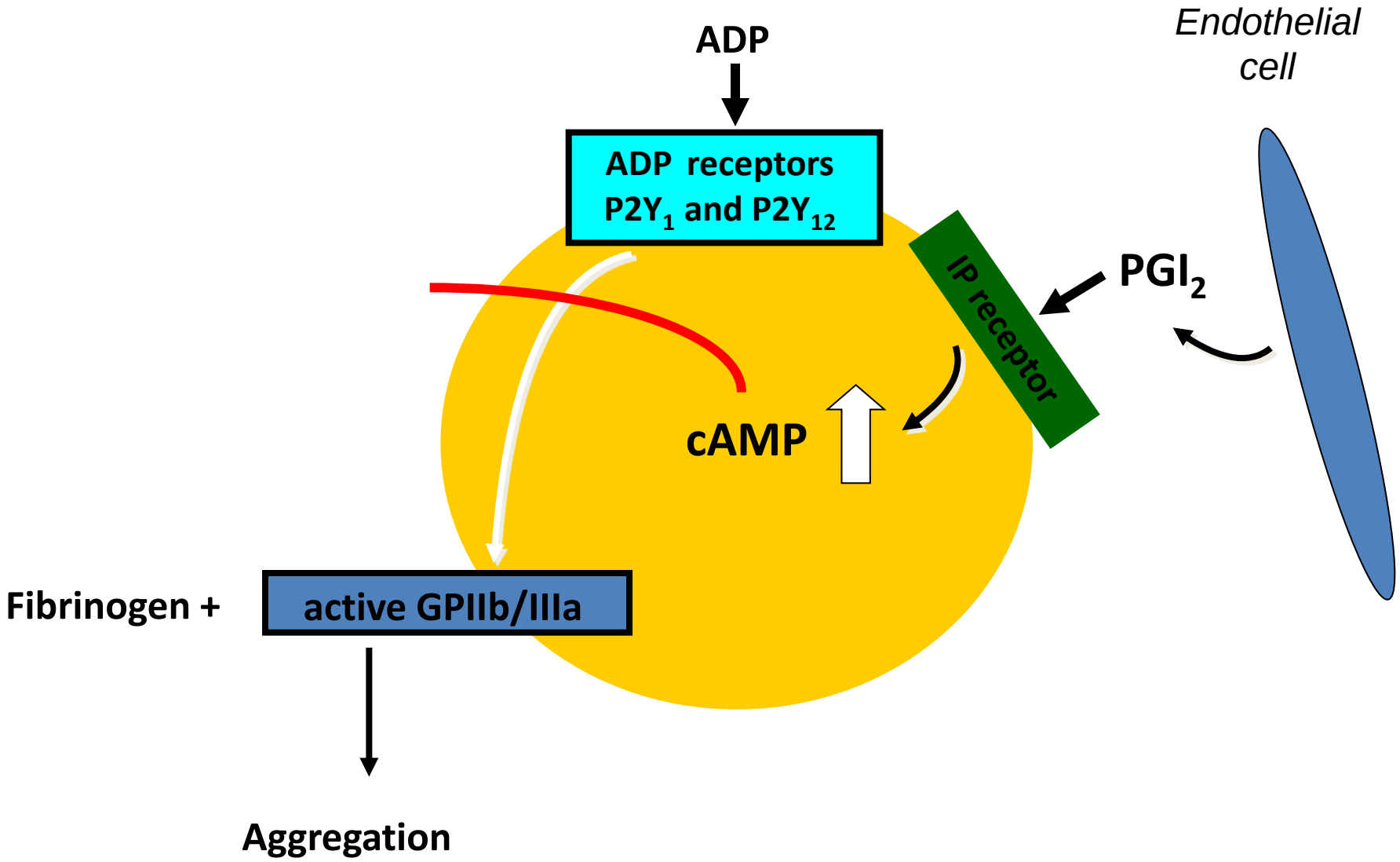
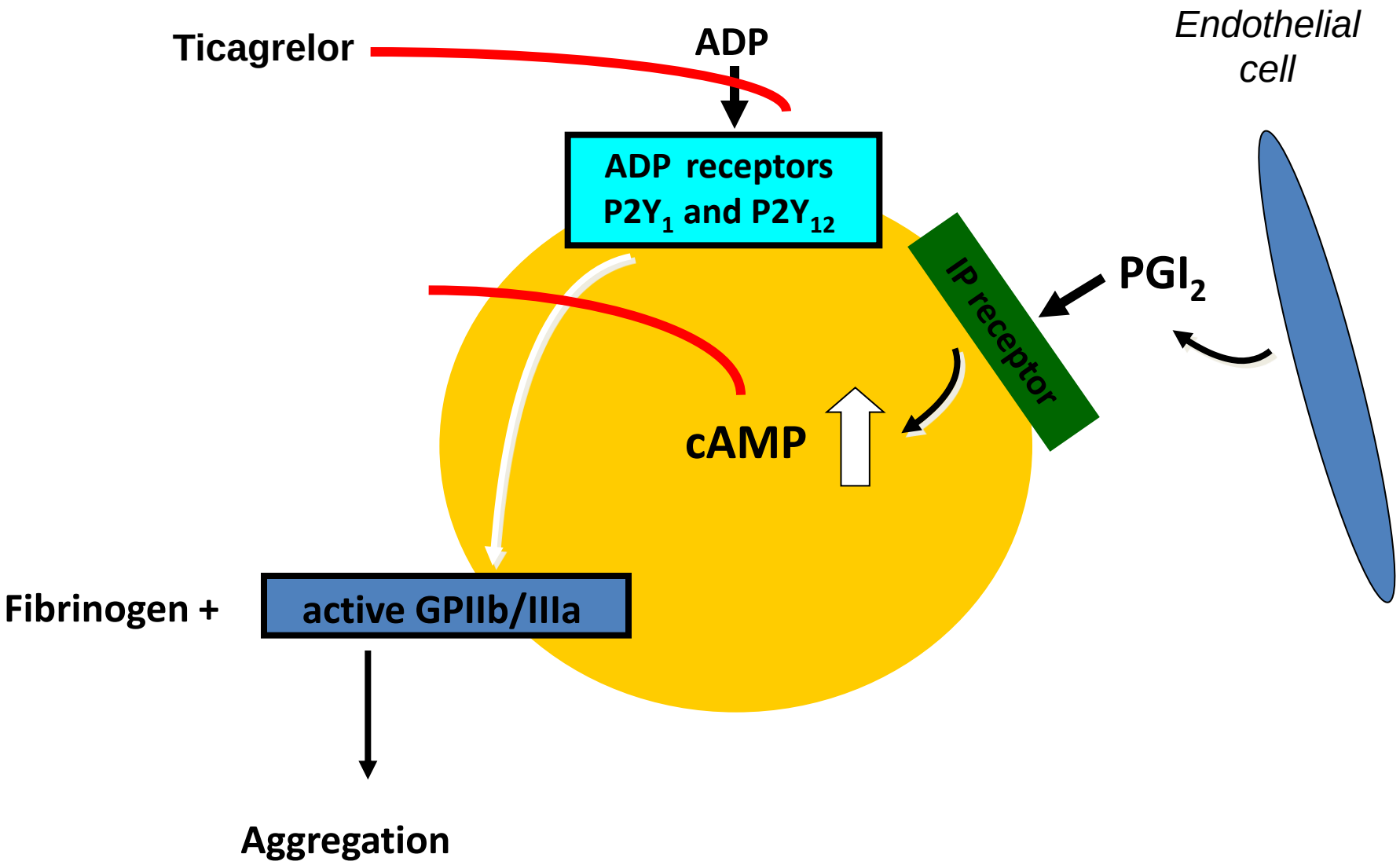
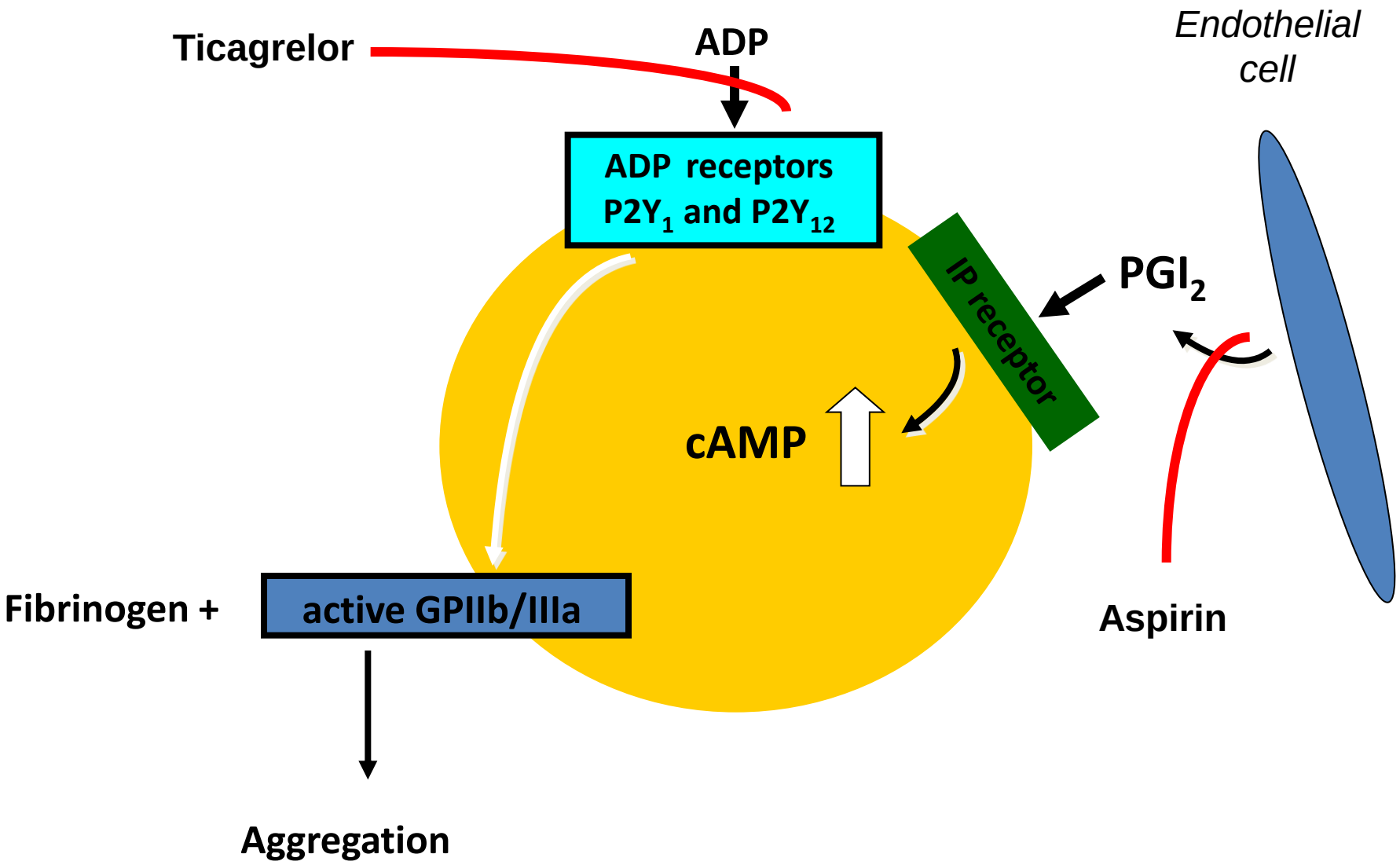


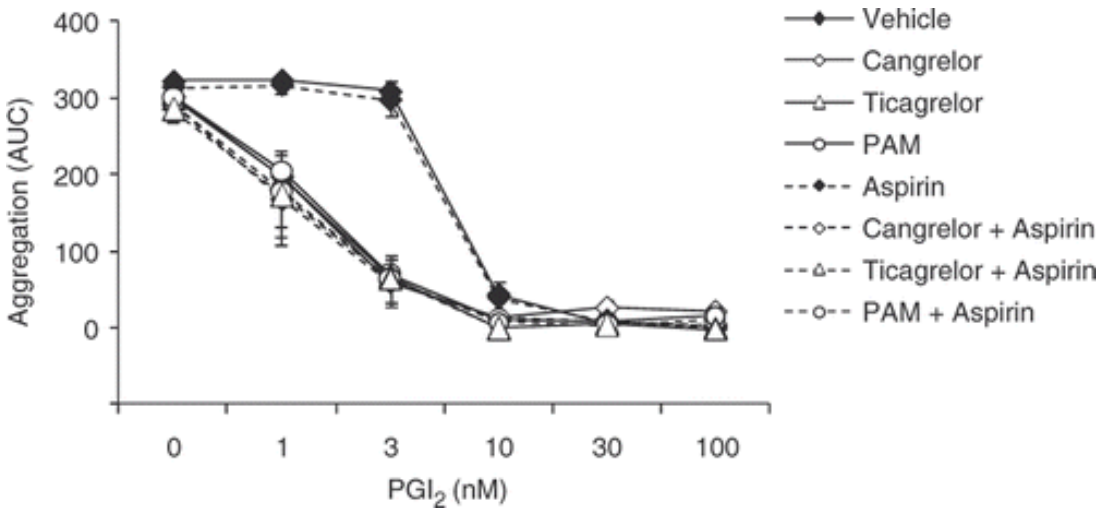
Low-dose aspirin

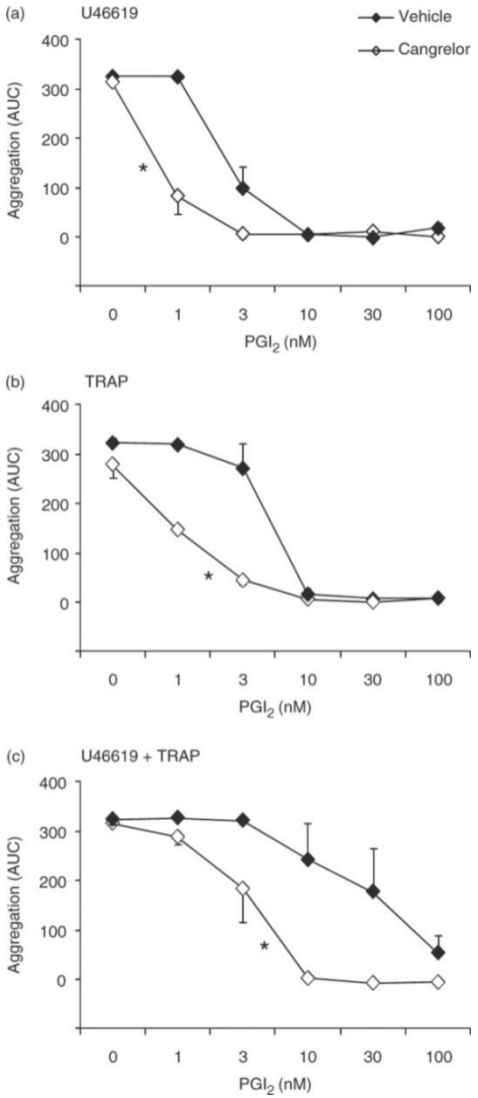


High-dose aspirin



- All $P2Y_{12}$ antagonists promote inhibition of platelet aggregation by PGI_2





Iyú et al, Platelets 2011;22(7):504-15

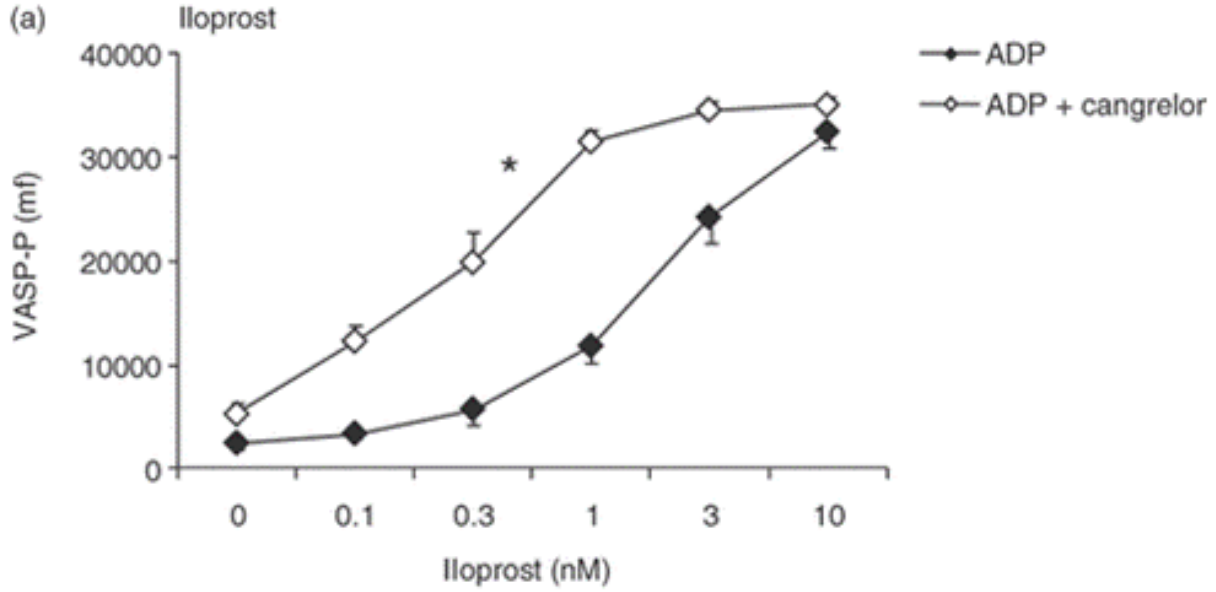
Table I. IC_{50} values for various cAMP-elevating agents in the absence and presence of cangrelor.

cAMP-elevating agent	Aggregating agent	Vehicle	Cangrelor
PGI_2 (nM)	U46619	2.8 ± 0.6	0.8 ± 0.2
	TRAP	6.0 ± 1.0	1.1 ± 0.4
	U46619 + TRAP	49 ± 22.6	4.3 ± 1.2
Iloprost (nM)	U46619	3.3 ± 1.3	0.9 ± 0.1
	TRAP	4.5 ± 1.1	1.0 ± 0.0
	U46619 + TRAP	19.7 ± 0.3	2.1 ± 0.1
PGD_2 (nM)	U46619	33 ± 13	19 ± 5
	TRAP	117 ± 62	15 ± 8
	U46619 + TRAP	413 ± 213	43 ± 24
Adenosine (μM)	U46619	>10	0.7 ± 0.1
	TRAP	>10	2.3 ± 0.4
	U46619 + TRAP	>10	>10
Forskolin (μM)	U46619	>10	1.9 ± 0.5
	TRAP	>10	3.2 ± 1.3
	U46619 + TRAP	>10	6.4 ± 2

Notes: IC_{50} values were determined in response to aggregation induced by U46619, TRAP or a combination of U46619 and TRAP in whole blood. For determination of the IC_{50} value for adenosine, experiments were performed in the presence of dipyridamole.

- All $P2Y_{12}$ antagonists promote inhibition of platelet aggregation by all agents that raise cAMP in platelets

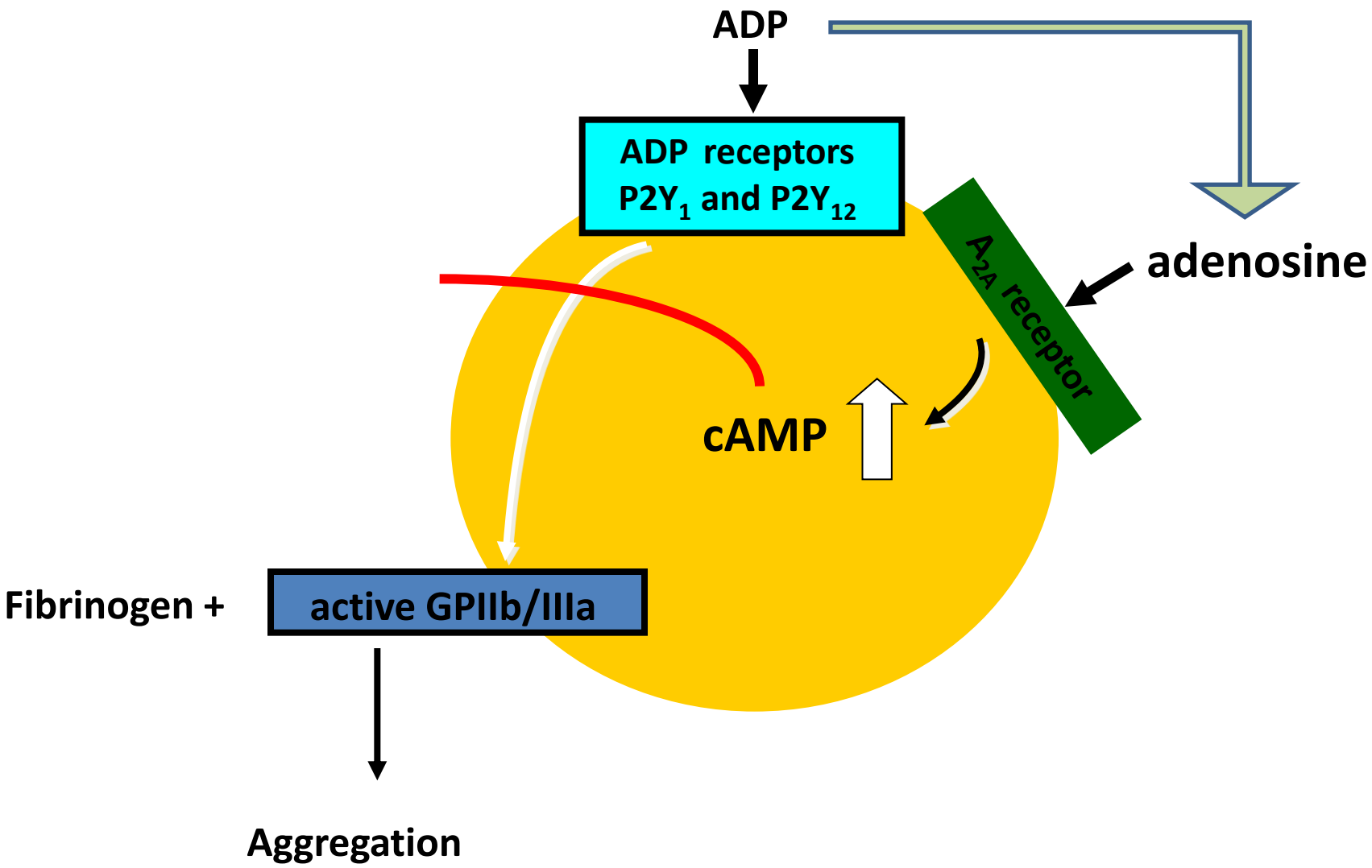
Iyú et al, Platelets 2011;22(7):504-15



- All $P2Y_{12}$ antagonists promote inhibition of platelet aggregation by increasing the levels of cAMP attained

Iyú et al, Platelets 2011;22(7):504-15

Additional mechanism of action of ticagrelor?



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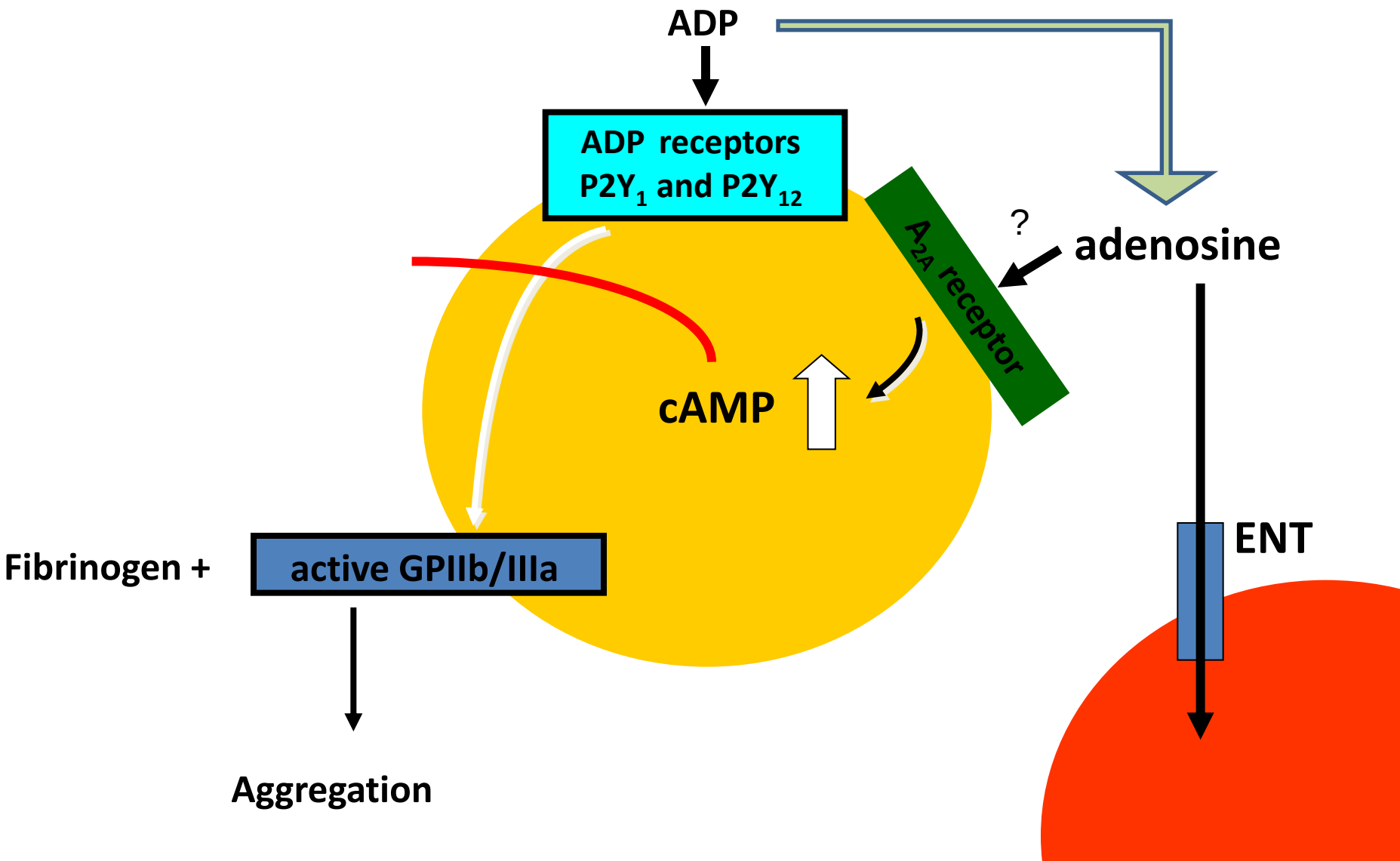

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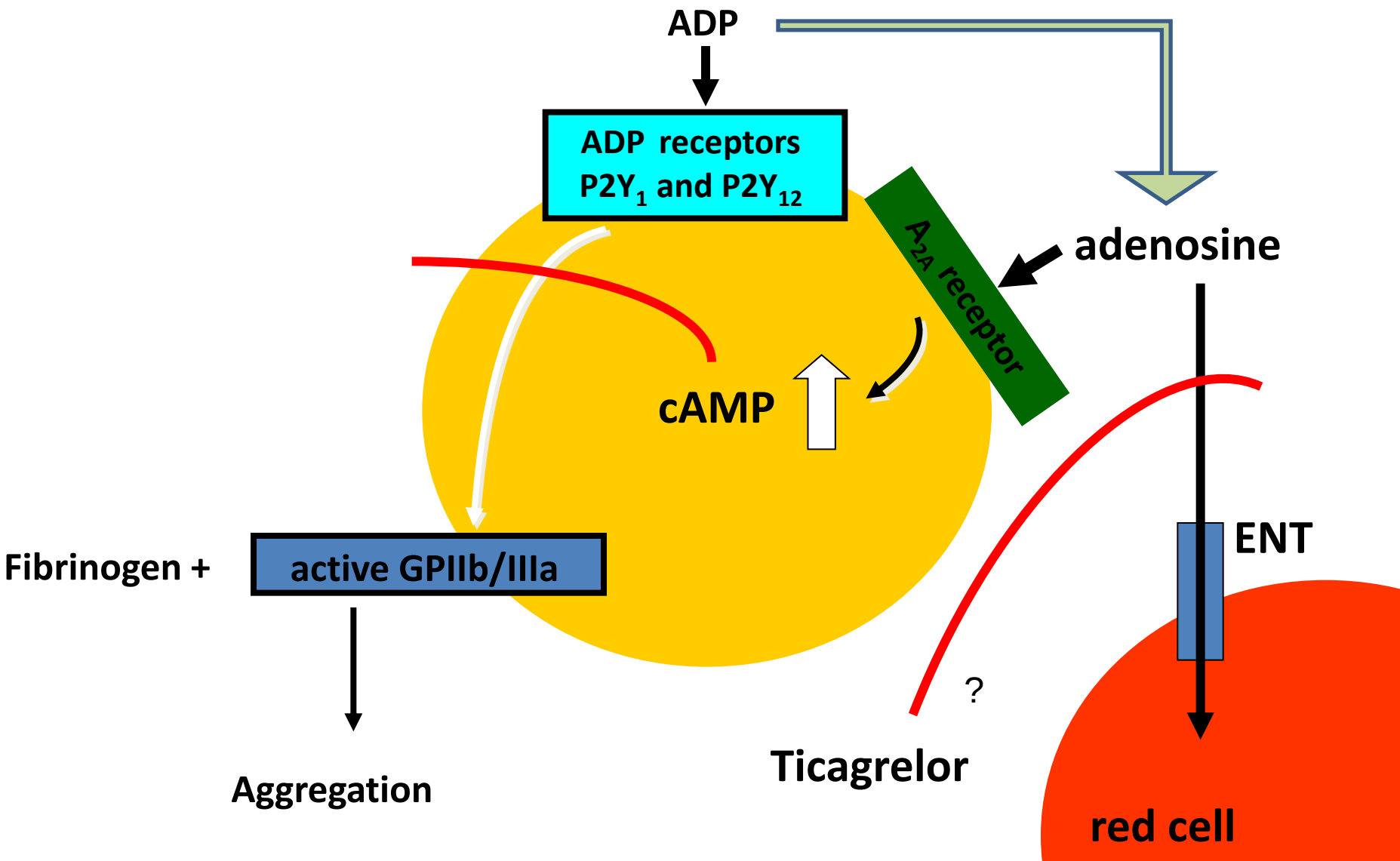

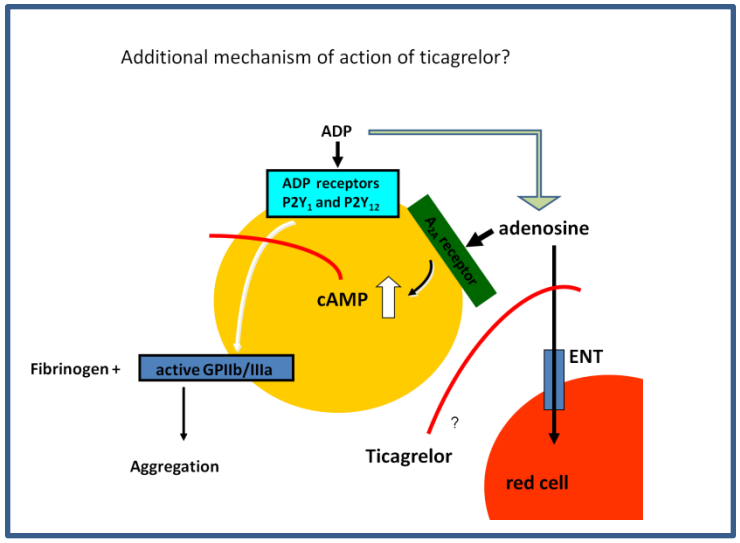

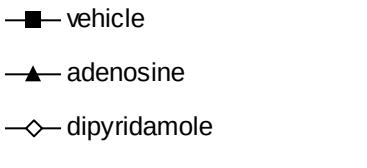

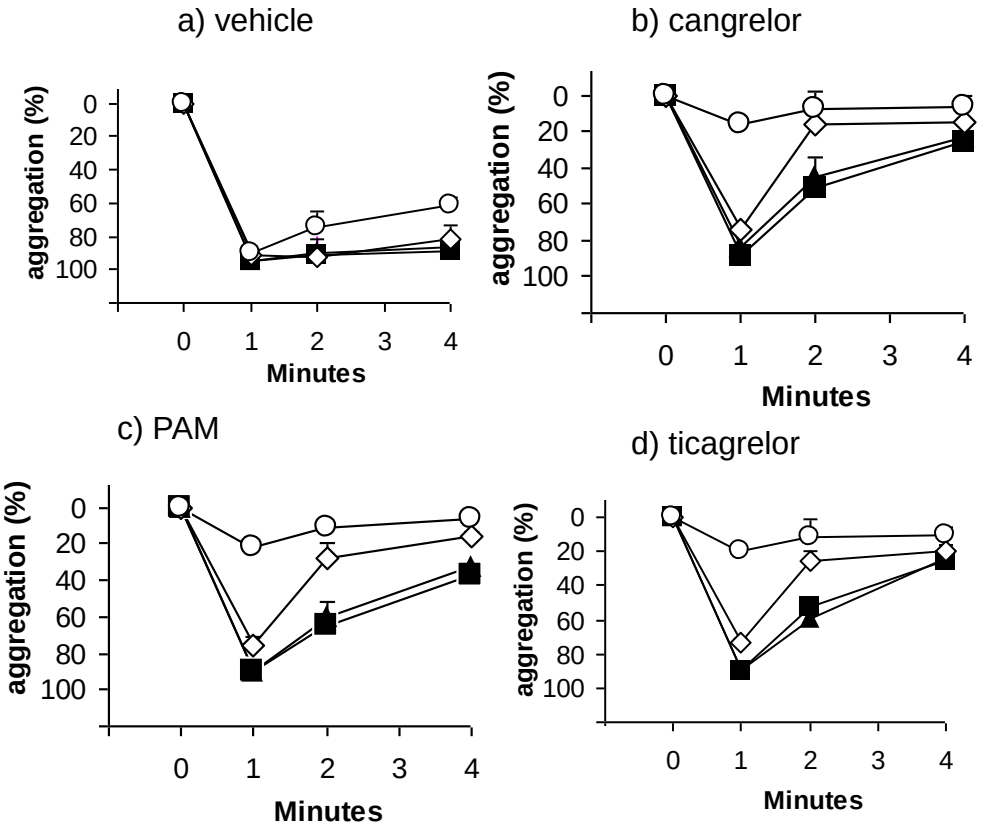

- $P2Y_{12}$ antagonists, including ticagrelor, DO NOT enhance inhibition of platelet aggregation by adenosine when erythrocytes are present
- $P2Y_{12}$ antagonists, including ticagrelor, DO enhance inhibition of platelet aggregation by adenosine when dipyridamole is also present
- Ticagrelor DOES NOT have the ability to further inhibit platelet function via a mechanism involving adenosine

Iyú et al ATVB 2011 ;31:416-422

ADP and $P2Y_{12}$ antagonists - conclusions

- Several $P2Y_{12}$ antagonists are in development or already being used in patients with ACS
- They all differ from each other in several respects with more sustained and less variable inhibition of platelet function by prasugrel and by cangrelor compared with clopidogrel
- The PLATO study (ticagrelor) revealed a “North American Paradox” and dyspnoea as a side-effect
- Studies have revealed a strong enhancement of inhibition of platelet function by PGI_2 in the presence of any $P2Y_{12}$ antagonist
- Studies have NOT demonstrated any additional inhibitory effect of ticagrelor on platelet function via inhibition of adenosine uptake into erythrocytes