Joint meeting of Coronary Revascularization

Busan, Korea. 11-12/12/2015

Pleiotropic effects of ticagrelor

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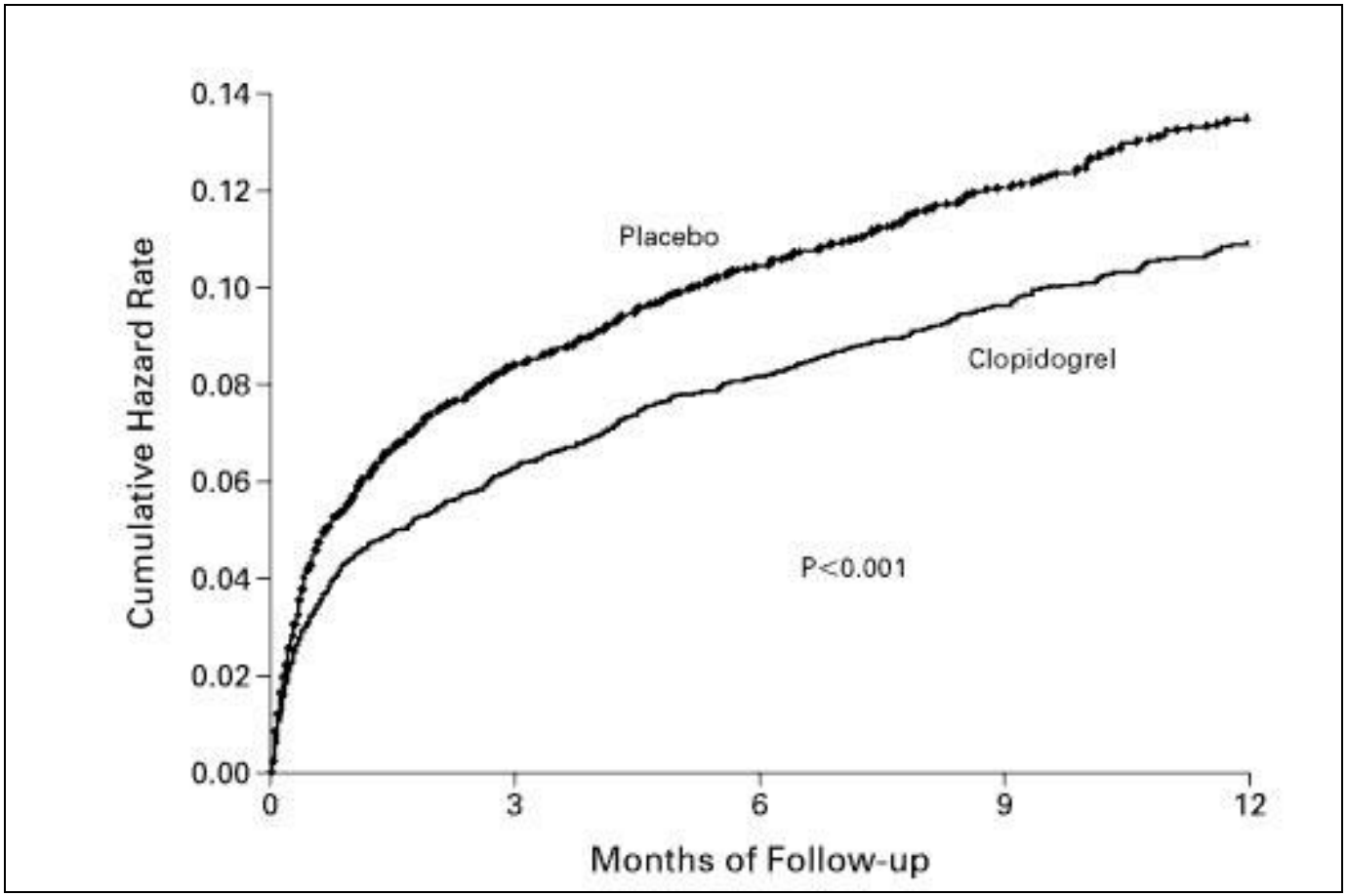
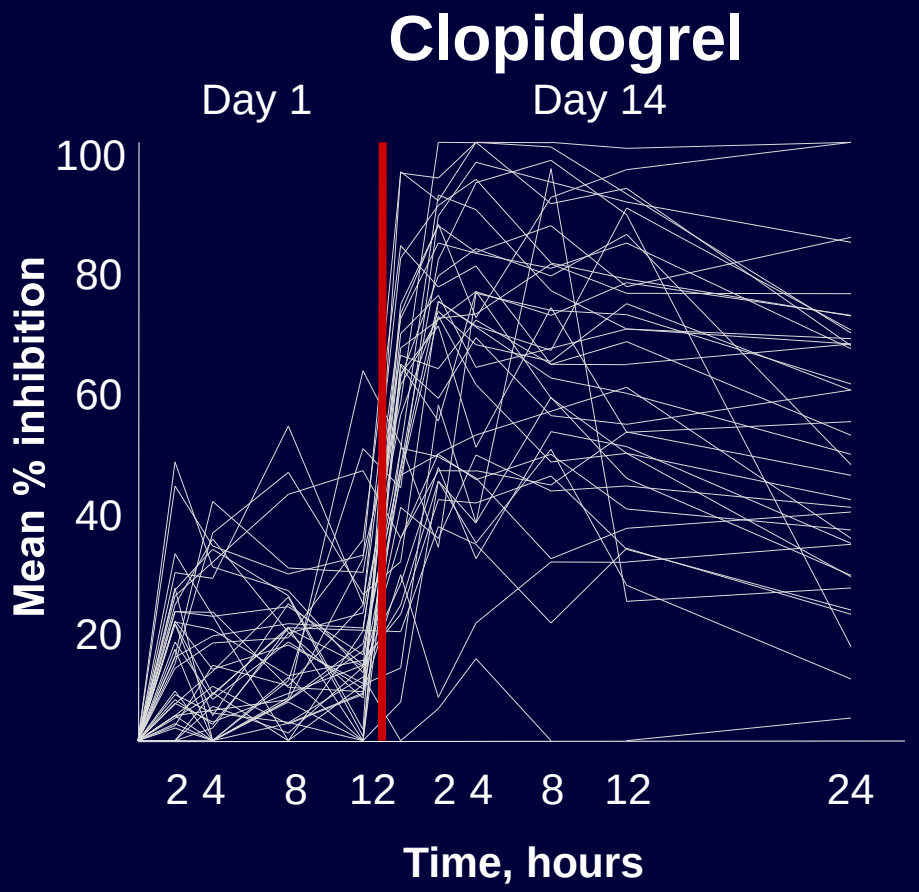
Azienda Ospedaliera SAN PAOLO POLO UNIVERSITARIO

Cumulative Hazard Rates for the First Primary Outcome (Cardiovascular Death, Nonfatal Myocardial Infarction, or Stroke) during the 12 Months of the Study



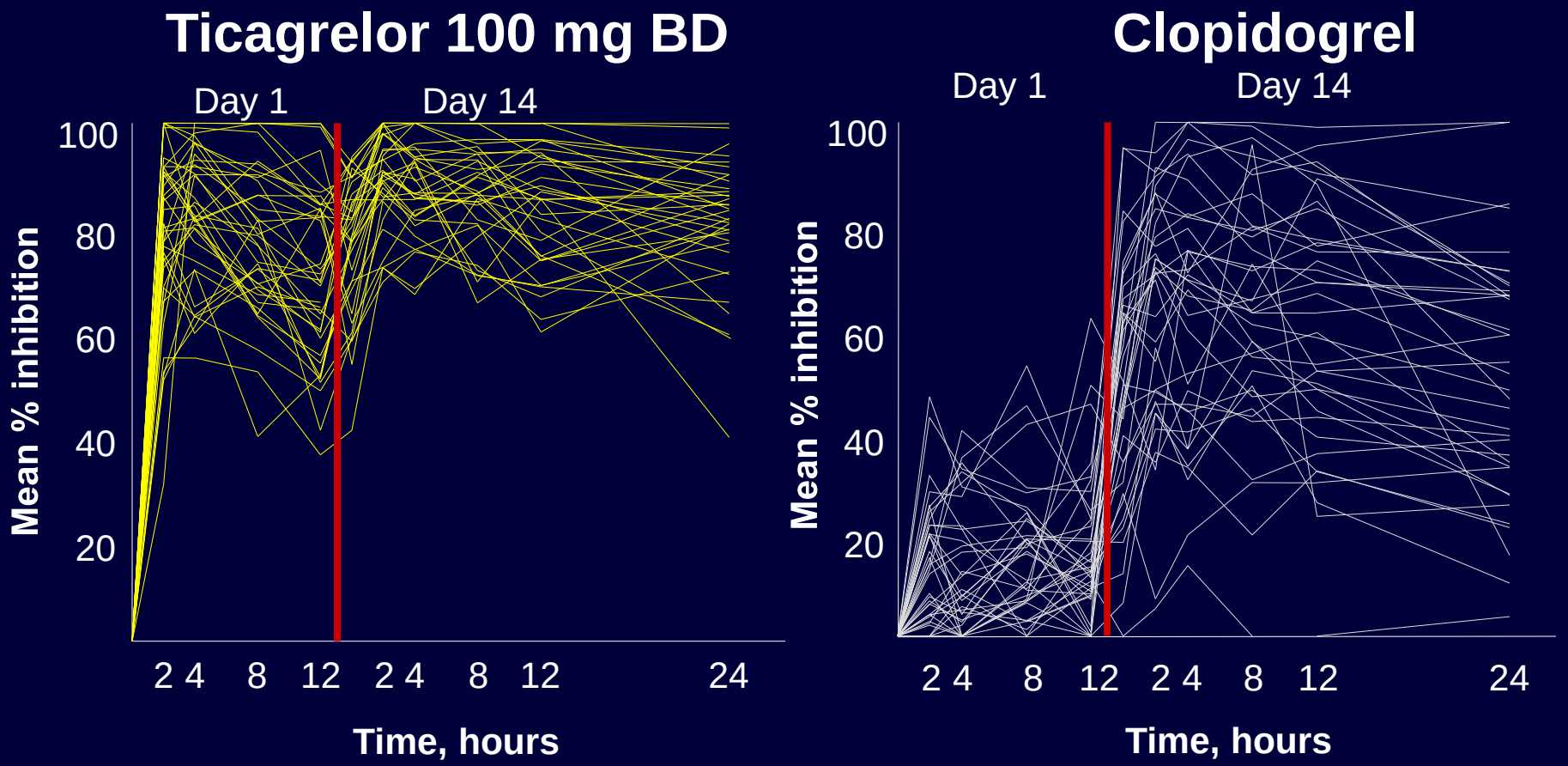
The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. N Engl J Med 2001;345:494-502

The inhibition of platelet aggregation by ticagrelor is faster and less variable than that by clopidogrel



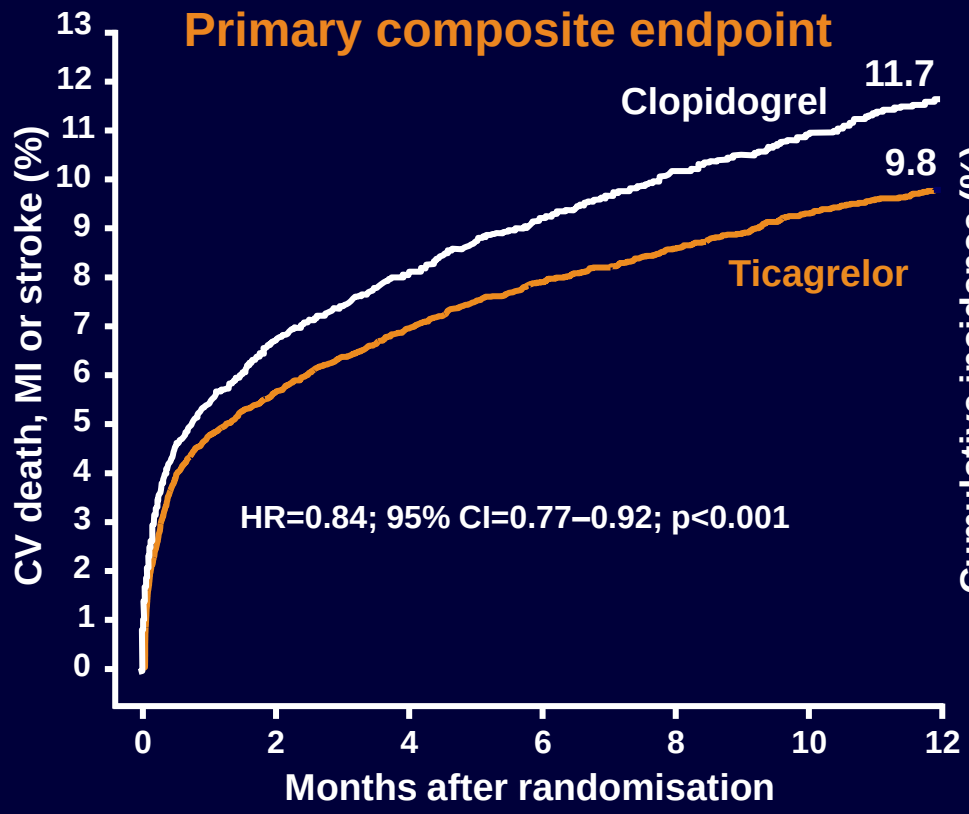
IPA = inhibition of platelet aggregation; od = once daily; bd = twice daily.
Adapted from Husted SE, et al. Presented at: European Society of Cardiology Annual Congress 2005; 3-7 September, 2005; Stockholm, Sweden.

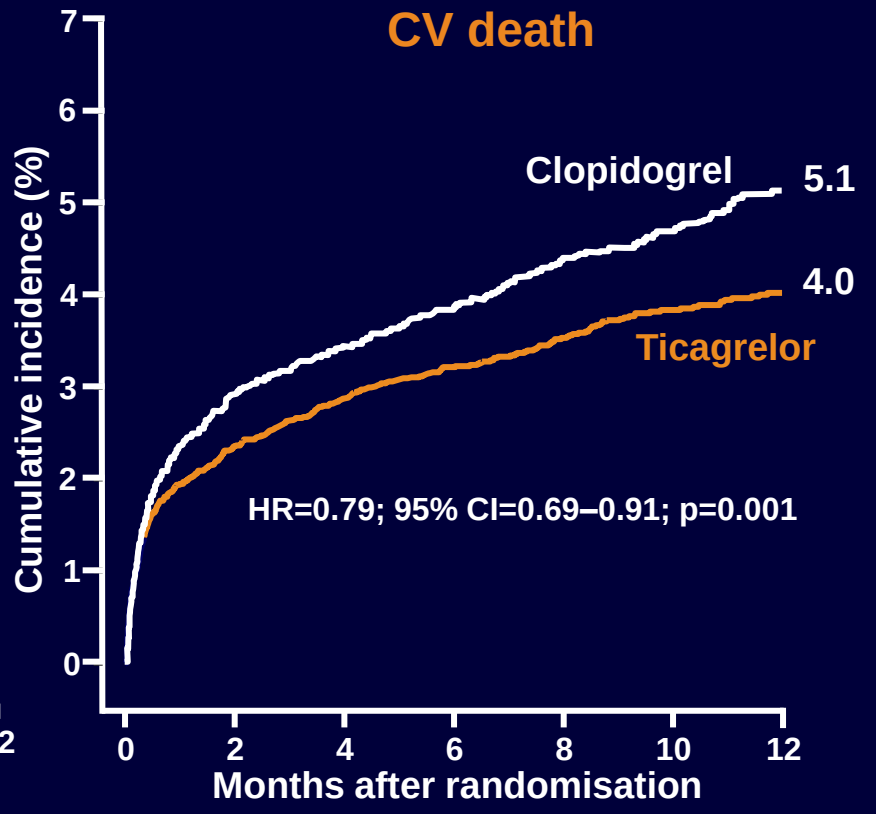
The inhibition of platelet aggregation by ticagrelor is faster and less variable than that by clopidogrel



IPA = inhibition of platelet aggregation; od = once daily; bd = twice daily.
Adapted from Husted SE, et al. Presented at: European Society of Cardiology Annual Congress 2005; 3-7 September, 2005; Stockholm, Sweden.

In PLATO, ticagrelor significantly reduced the risk of the primary composite endpoint and CV death after 12 months, compared with clopidogrel





CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

Wallentin L, et al. *N Engl J Med* 2009;361:1045–1057.

Ticagrelor was associated with significant reductions in CV death and all-cause death in the full PLATO ACS population and patient subgroups

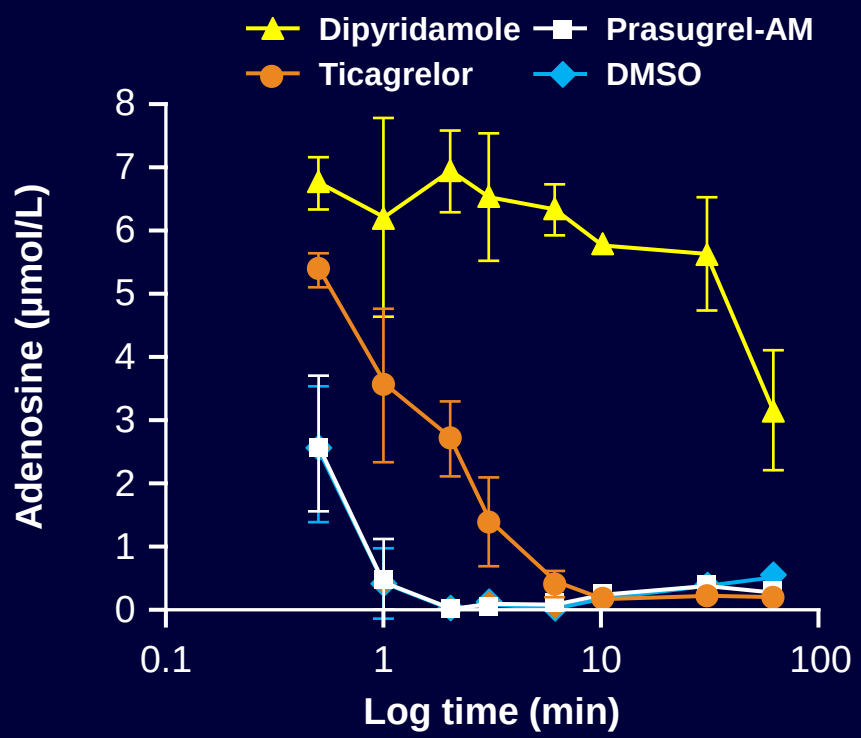
Patient population	CV death			All-cause death		
	Ticagrelor	Clopidogrel	p value	Ticagrelor	Clopidogrel	p value
Total (n=18,624)	4.0%	5.1%	0.001	4.5%	5.9%	<0.001
Intent for invasive (n=13,408)	3.4%	4.3%	0.025	3.9%	5.0%	0.01
Intent for non-invasive (n=5216)	5.5%	7.2%	0.019	6.1%	8.2%	0.01
CABG (n=1258)	4.1%	7.9%	0.009	4.7%	9.7%	0.002

ACS, acute coronary syndromes; CABG, coronary artery bypass grafting; CV, cardiovascular.

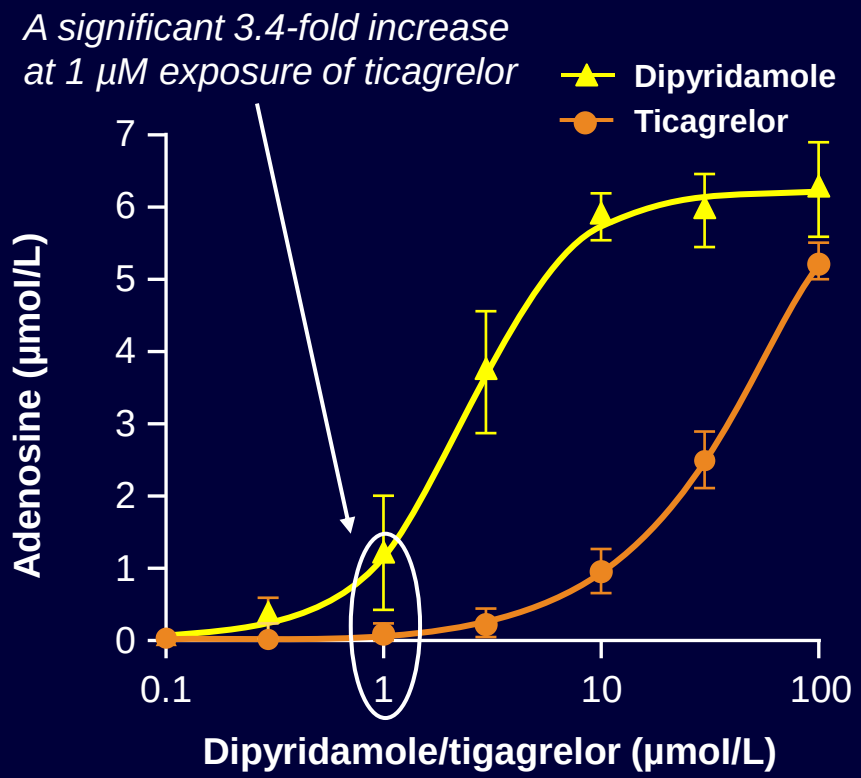
Cannon CP, et al. *Lancet* 2010;375:283–293; Held C, et al. *J Am Coll Cardiol* 2011;57:672–684; James S, et al. *BMJ* 2011;342:d3527; Wallentin L, et al. *N Engl J Med* 2009;361:1045–1057.

Does ticagrelor have additional mechanism(s) of action?

Ticagrelor, but not prasugrel active metabolite, delays adenosine degradation



Extension of adenosine half-life after addition of 7.1 µM to human whole blood in the presence of DMSO, prasugrel-AM, ticagrelor or dipyridamole

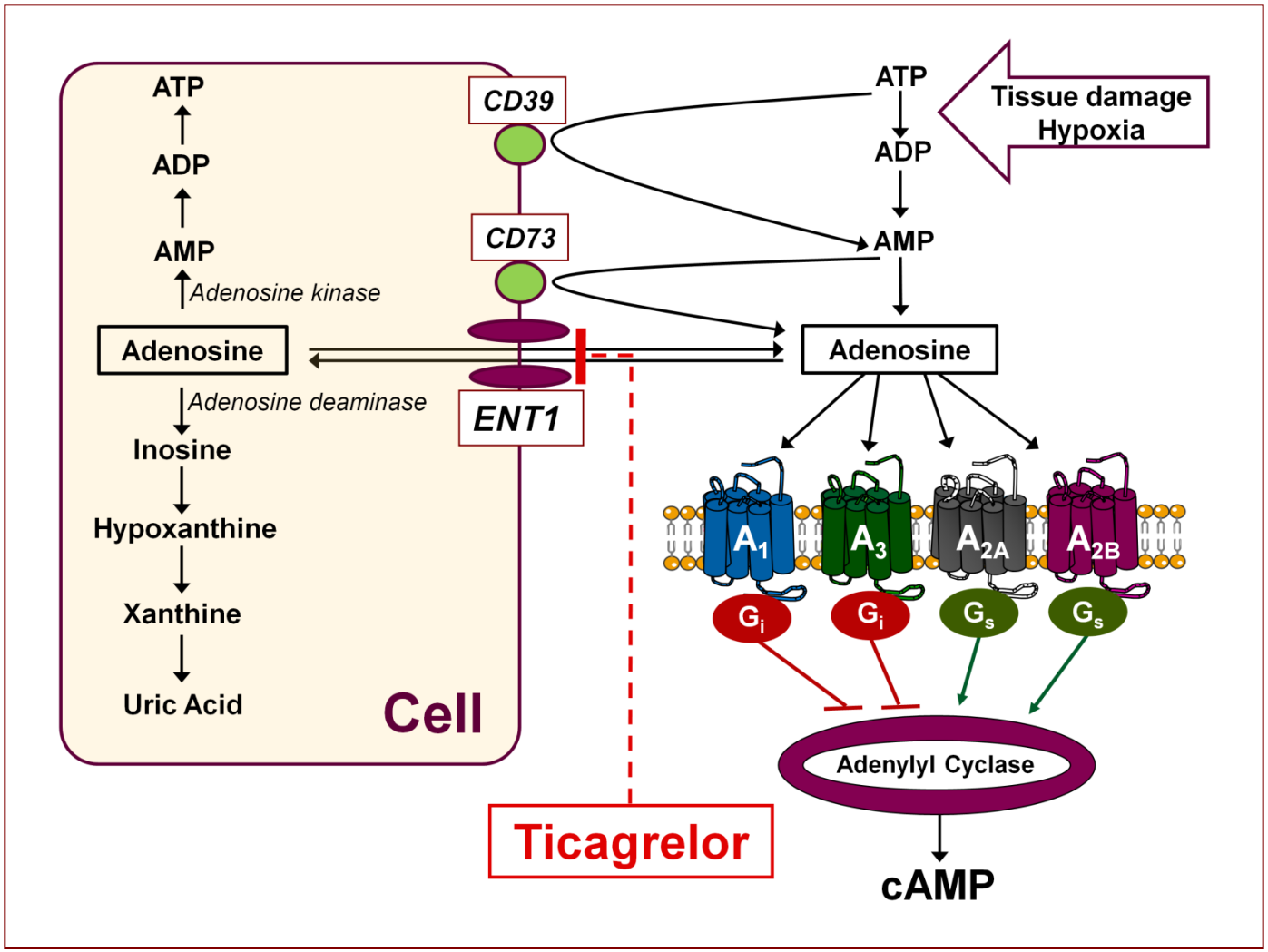


Residual adenosine concentrations in whole blood 1 min after addition of 7.1 µmol/L adenosine, in the presence of a concentration range of dipyridamole or ticagrelor

AM, active metabolite; DMSO, control.

Nylander S, et al. *J Thromb Haemost* 2013;11:1867–1876.

The Equilibrative Nucleoside Transporter 1 (ENT1) is an additional target of Ticagrelor



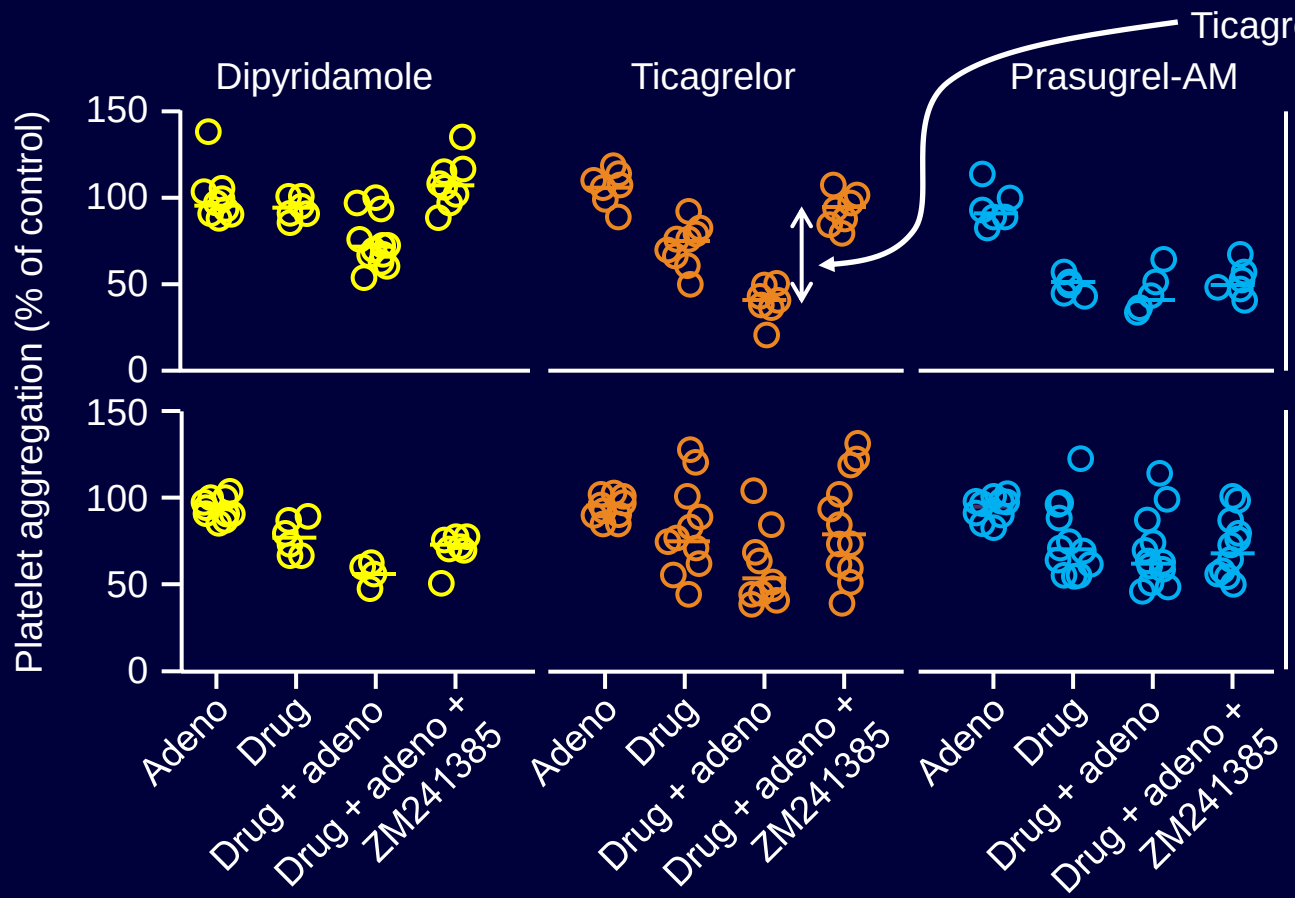
Cattaneo et al, JACC 2014

Main biological effects of adenosine

- Modulation of the vascular tone
- Cardiac electrophysiological effects:
  - negative chronotropic effect (by suppressing the automaticity of cardiac pacemakers)
  - negative dromotropic effect (inhibition of AV-nodal conduction)
- Modulation of the inflammatory responses to a variety of stressful conditions
- Reduction of ischemia/reperfusion injury
- Inhibition of platelet function

Does ticagrelor potentiate the biological effects of exogenous adenosine?

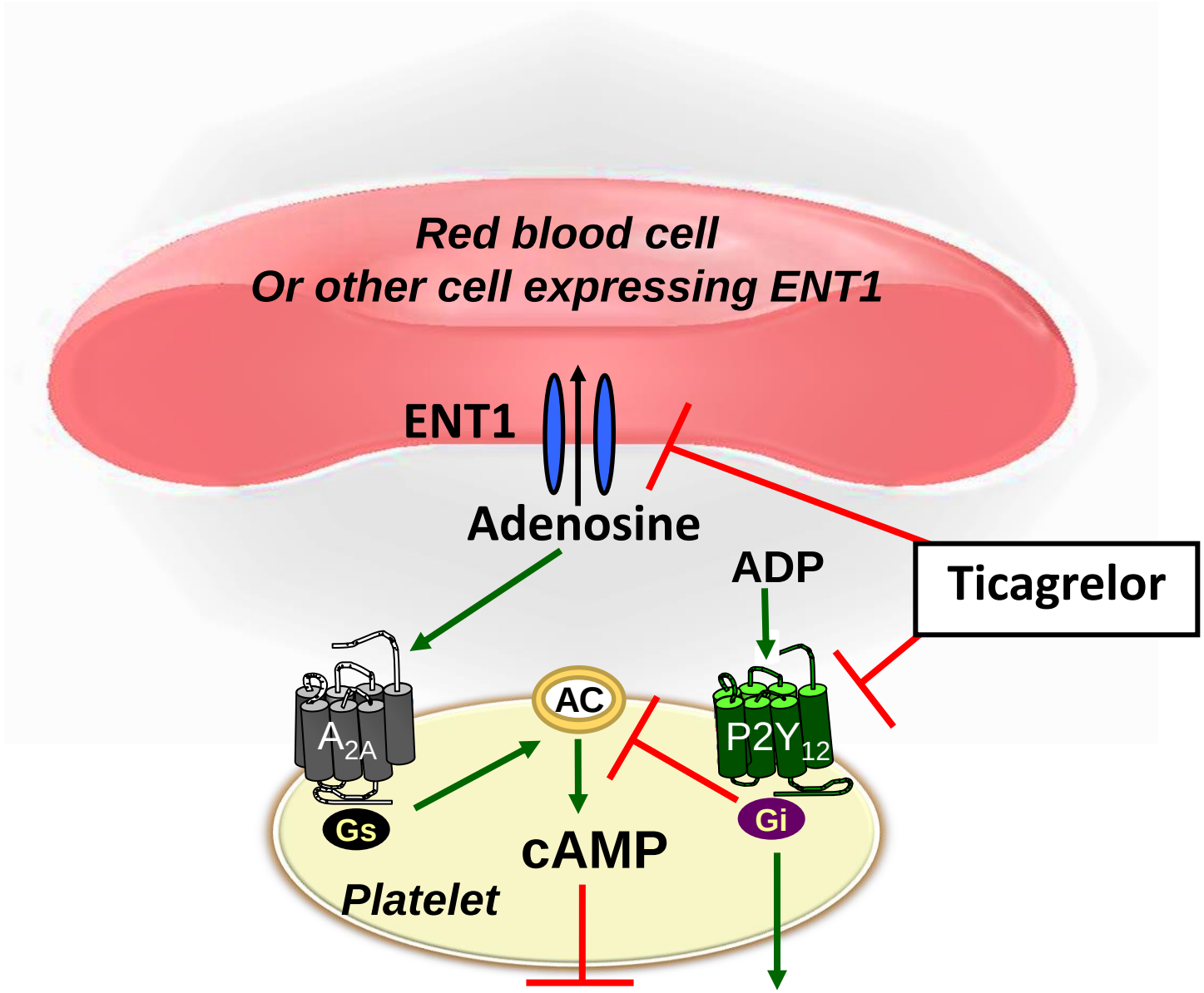
Ticagrelor inhibits human platelet aggregation in whole blood via adenosine in addition to $P2Y_{12}$ antagonism



Residual collagen-induced platelet aggregation in whole blood, in the presence of added compounds alone or in combination. Adenosine 7.1 µmol/L, dipyridamole 14 µmol/L, ticagrelor 14 µmol/L, prasugrel-AM 14 µmol/L and ZM241385 14 µmol/L

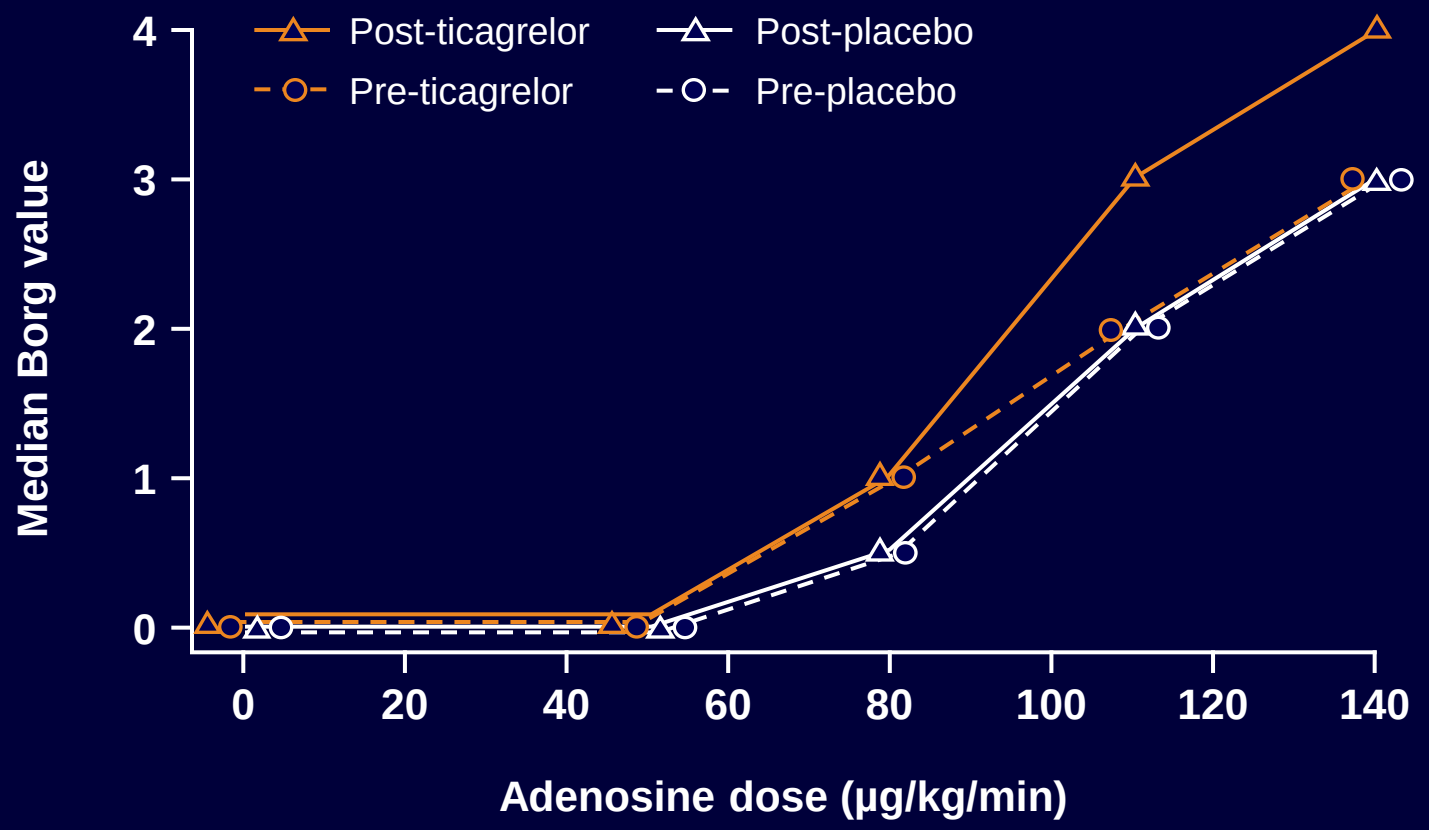
Adeno, adenosine; AM, active metabolite; ZM241385, selective A_{2A} antagonist.

Nylander S, et al. *J Thromb Haemost* 2013;11:1867–1876.



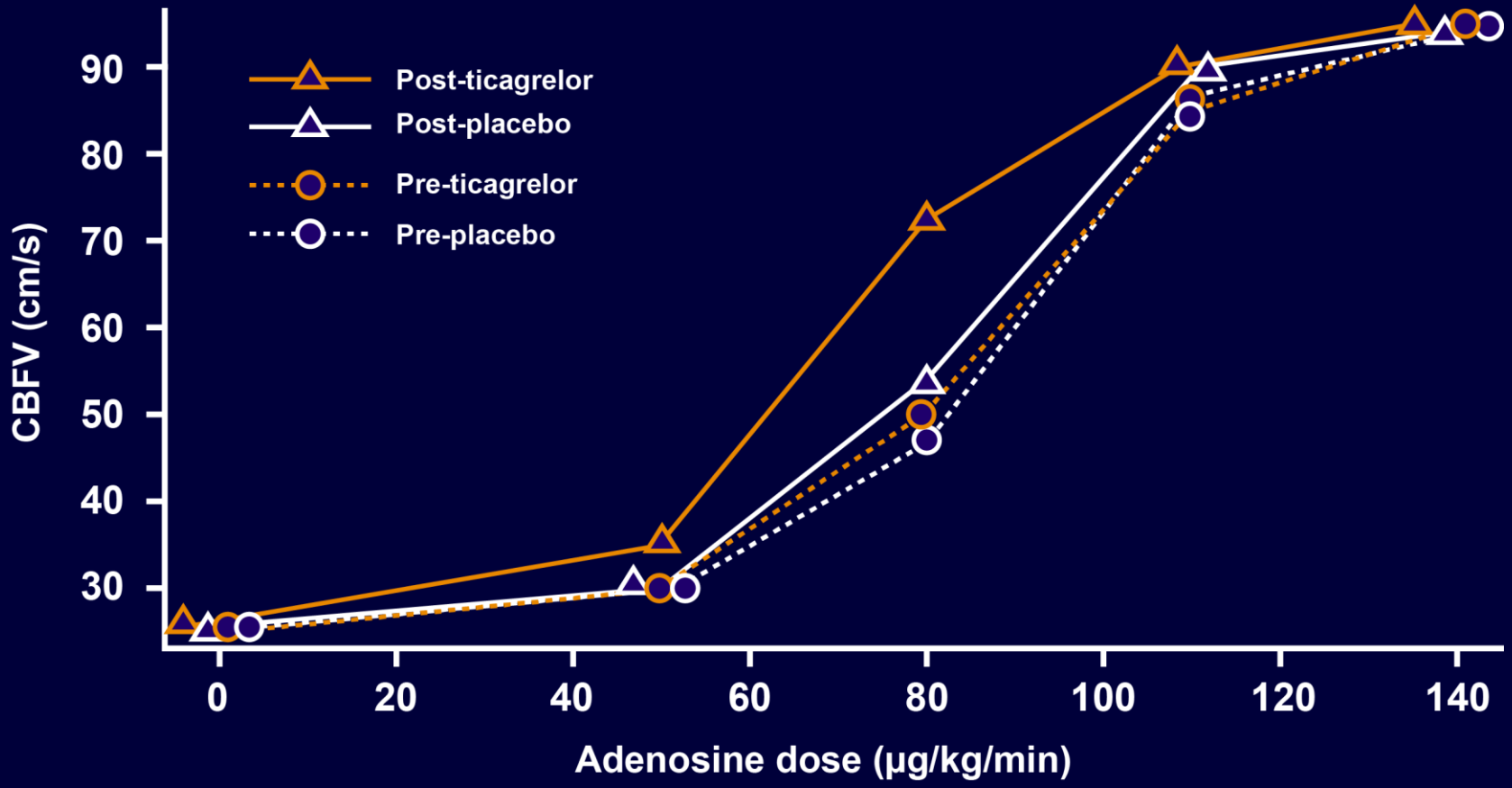
Platelet activation/aggregation

Ticagrelor augments adenosine-induced dyspnea*



*Scored using the Modified Borg Scale, from 0 (no sensation of dyspnoea) to 10 (maximum sensation of dyspnoea).
Wittfeldt A, et al. *J Am Coll Cardiol* 2013;61:723–727.

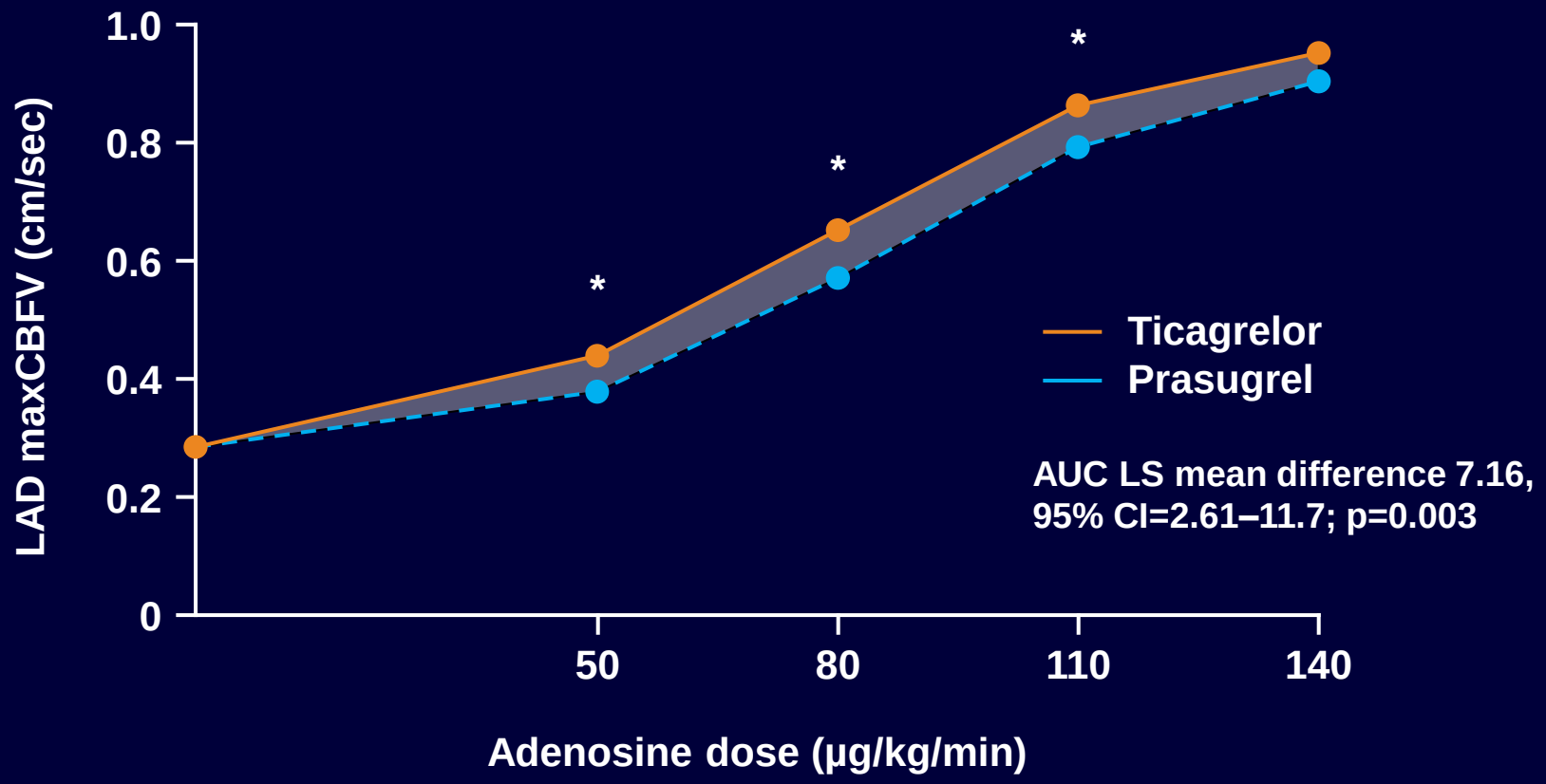
Ticagrelor augments adenosine-induced coronary blood flow velocity in healthy subjects



CBFV, coronary blood flow velocity.

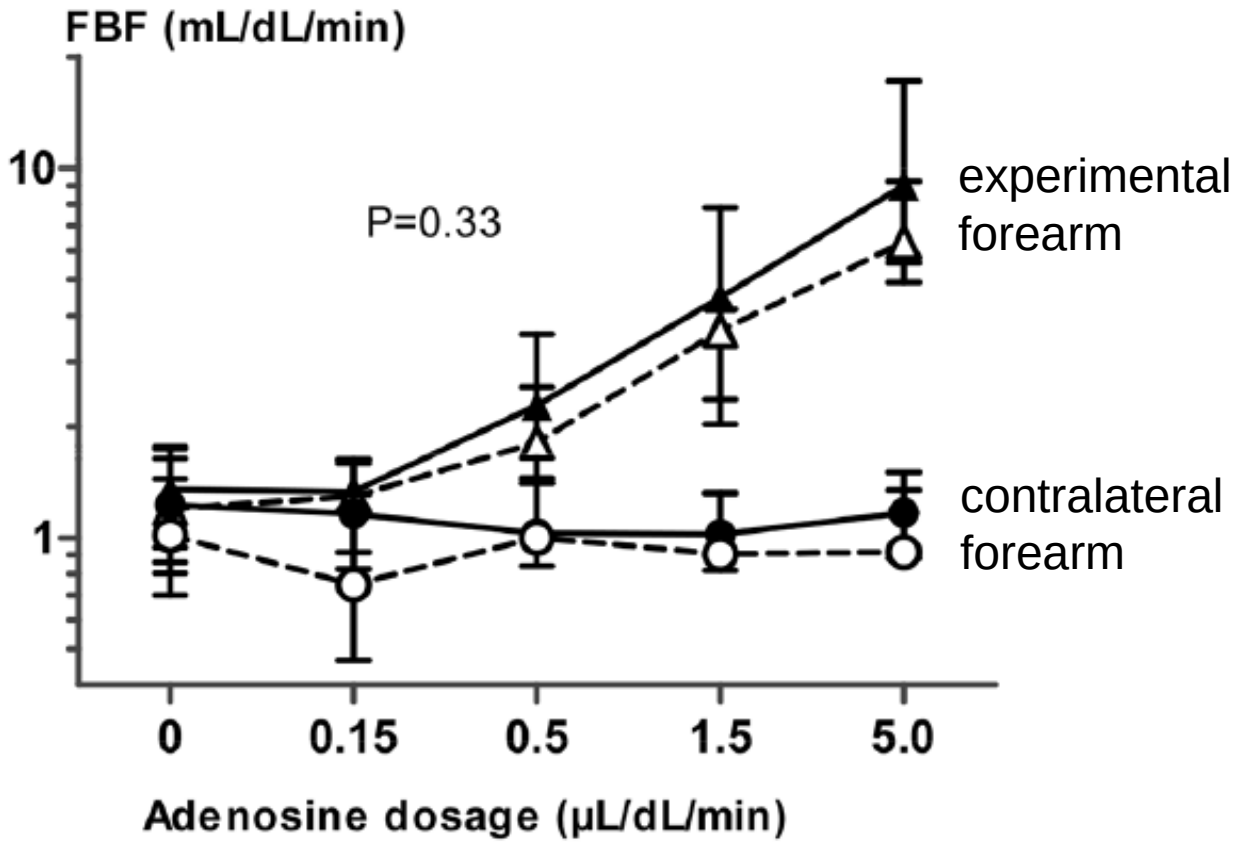
Wittfeldt A, et al. *J Am Coll Cardiol* 2013;61:723–727.

Ticagrelor increases adenosine-induced CBFV in NSTE-ACS patients relative to prasugrel



*Significantly higher ratio of LAD maxCBFV/bCBFV for ticagrelor vs. prasugrel.
AUC, area under the curve; CBFV, coronary blood flow velocity; CI, confidence interval; LAD, left anterior descending artery; LS, least squares; NSTE-ACS, non-ST-segment elevation acute coronary syndromes.
Alexopoulos D, et al. *Circ Cardiovasc Interv* 2013;6:277–283.

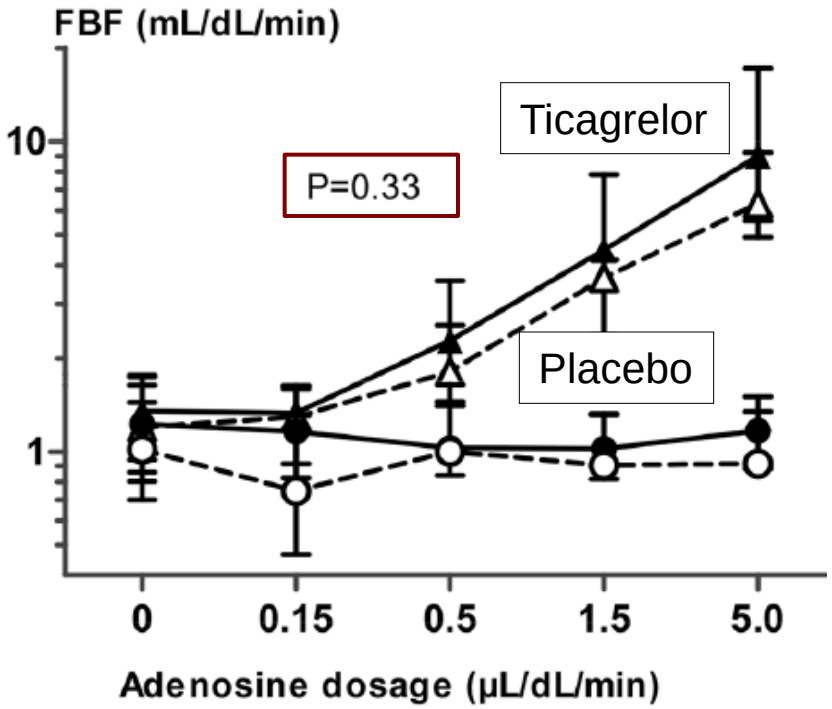
Effect of ticagrelor (●▲) or placebo (○△) on forearm blood flow (FBF) induced by intrabrachial infusion of adenosine



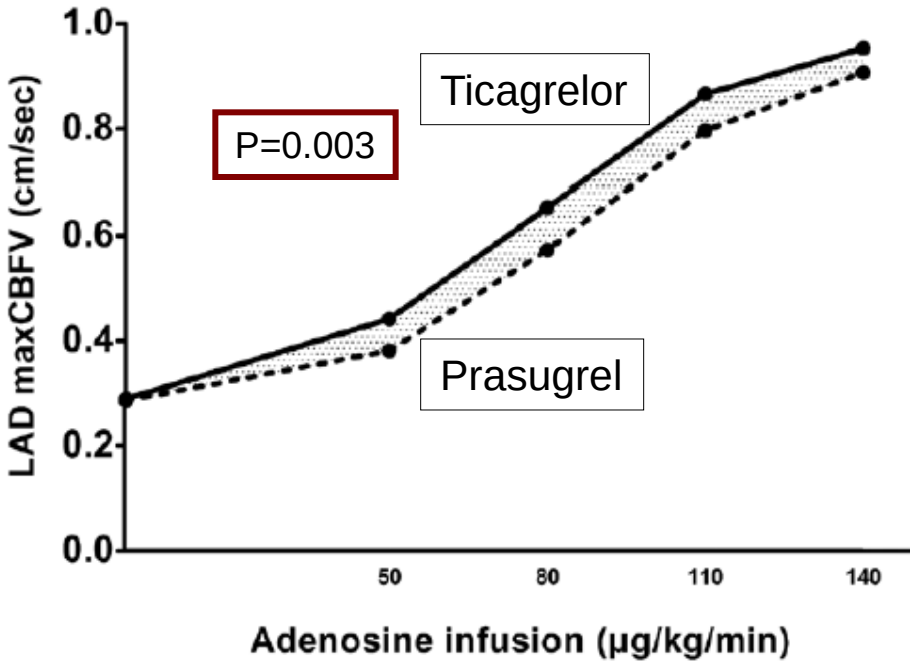
van den Berg TNA et al, PLoS ONE 2015

Comparison of the effect of ticagrelor on adenosine-mediated vasodilation in teo studies

Van den Berg *et al*. 2015, **n=13**

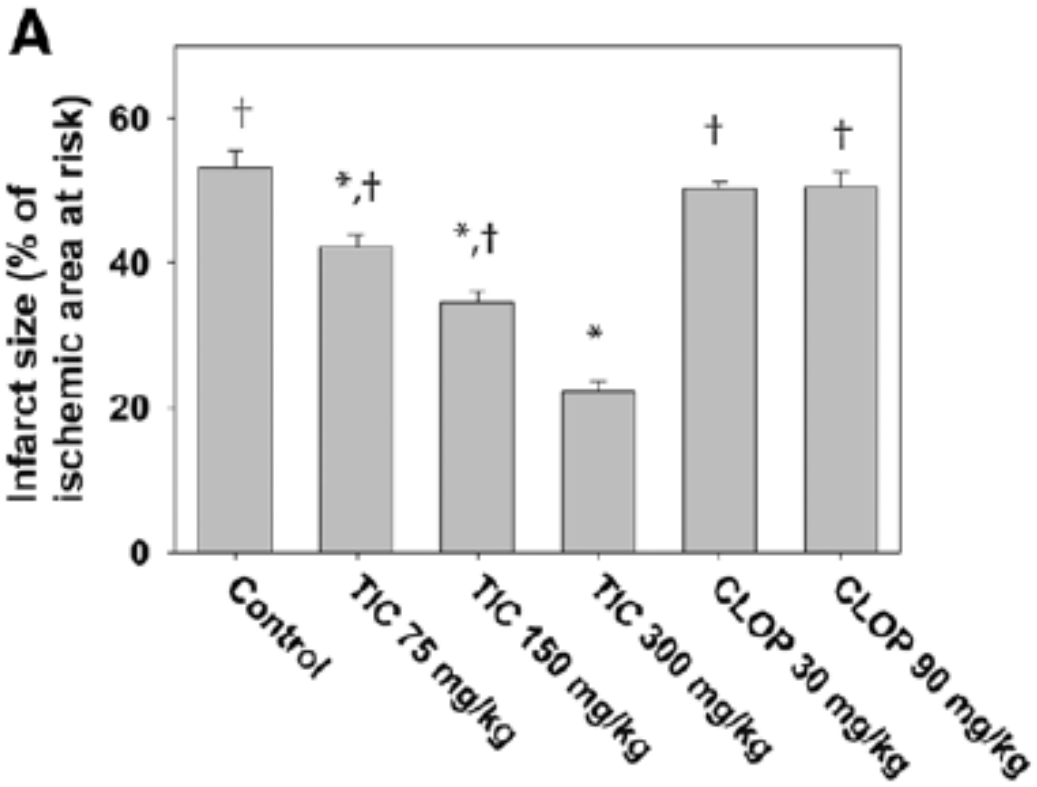


Alexopoulos *et al.* 2013**, n=56**



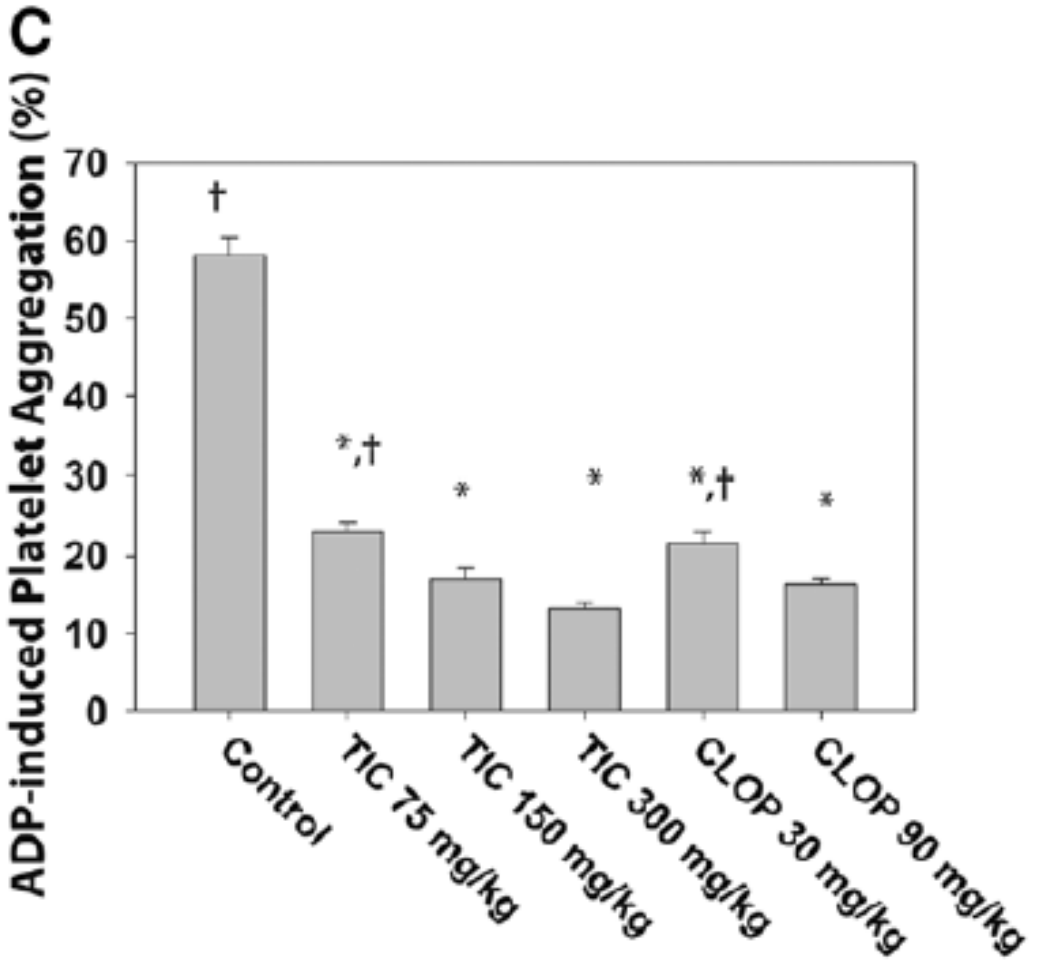
Effects of ticagrelor on the plasma levels of endogenous adenosine and on its biological effects

Effects of ticagrelor and clopidogrel on infarct size in a rat coronary artery ischemia model



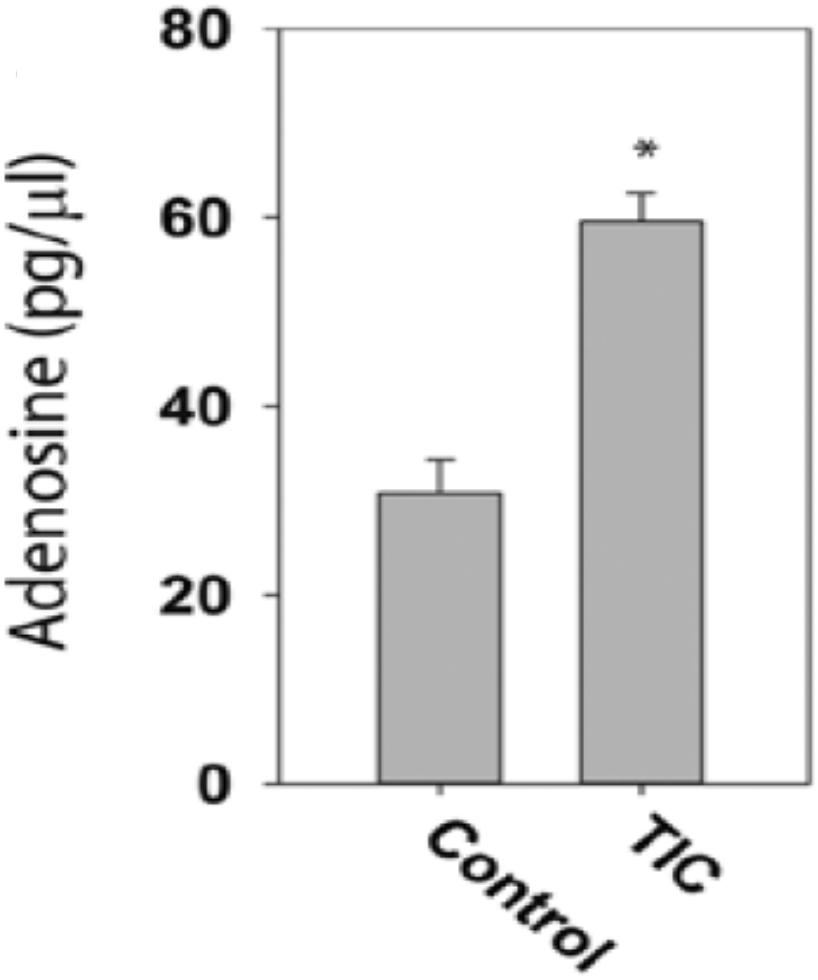
Nanwhan et al, ATVB 2014

Effects of ticagrelor and clopidogrel on platelet aggregation in a rat coronary artery ischemia model



Nanwhan et al, ATVB 2014

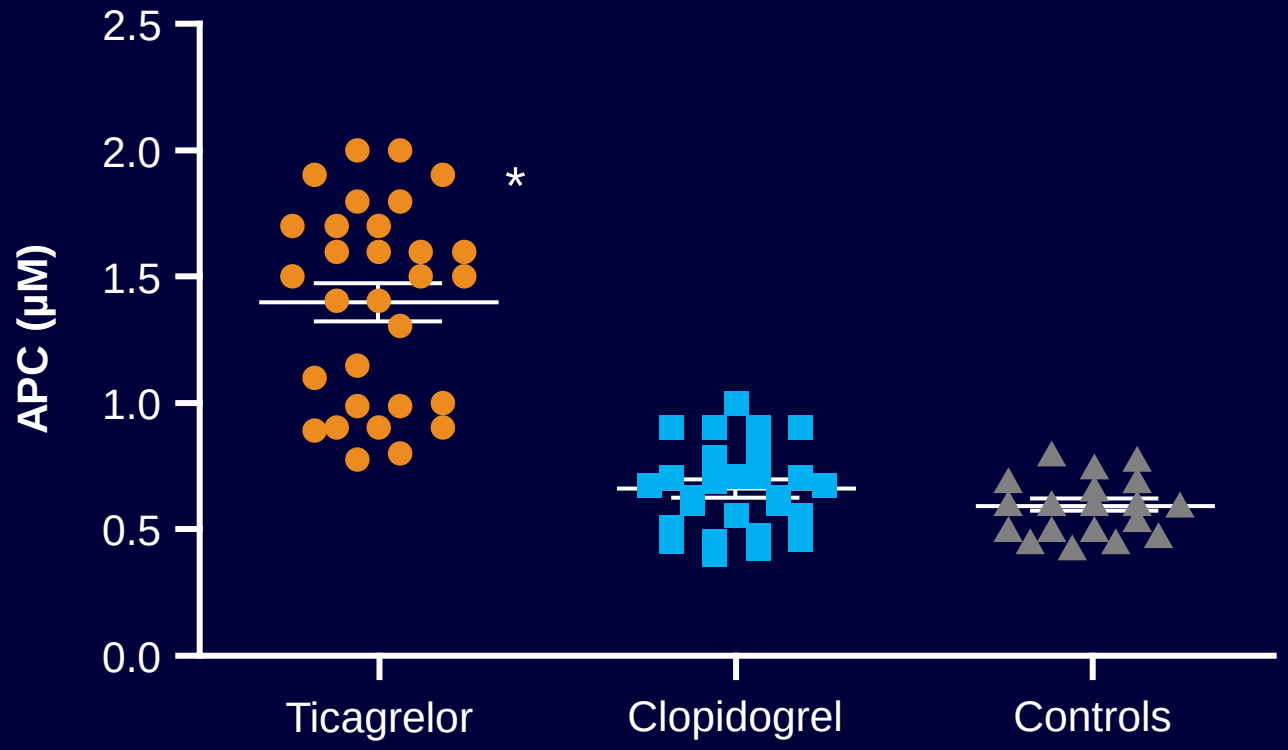
Effects of ticagrelor on myocardial adenosine levels



Nanwhan et al, ATVB 2014

Ticagrelor increases adenosine plasma concentration in medium to high-risk n-STEMI ACS patients

Comparisons of adenosine plasma concentration (APC) in the ticagrelor, clopidogrel, at 6 hrs after loading dose, and control group



***: p<0.01 Ticagrelor group versus control or clopidogrel**

Bonello L, et al. ***J Am Coll Cardiol. 2013 Nov 14***

Ticagrelor and Dyspnea

Comparison of the incidence of dyspnea in patients treated with ticagrelor and patients treated with clopidogrel

Study drug	Patients (n)	Dose	Duration	A. Percent dyspnea in study group	B. Percent dyspnea in clopidogrel group	A/B	Study
Ticagrelor	Atherosler (200)	50-400 mg bid	28 d	10-20	0	∞	DISPERSE
Ticagrelor	ACS (990)	90 mg bid 180 mg bid	12 wk 12 wk	10.5 15.8	6.4 6.4	1.64 2.47	DISPERSE 2
Ticagrelor	Stab. CAD (123)	90 mg bid	6 wk	38.6	9.3	4.15	ONSET/ OFFSET
Ticagrelor	Stab. CAD (98)	90 mg bid	14 d	13	4	3.25	RESPOND
Ticagrelor	ACS (18,624)	90 mg bid	12 mo	13.8	7.8	1.77	PLATO

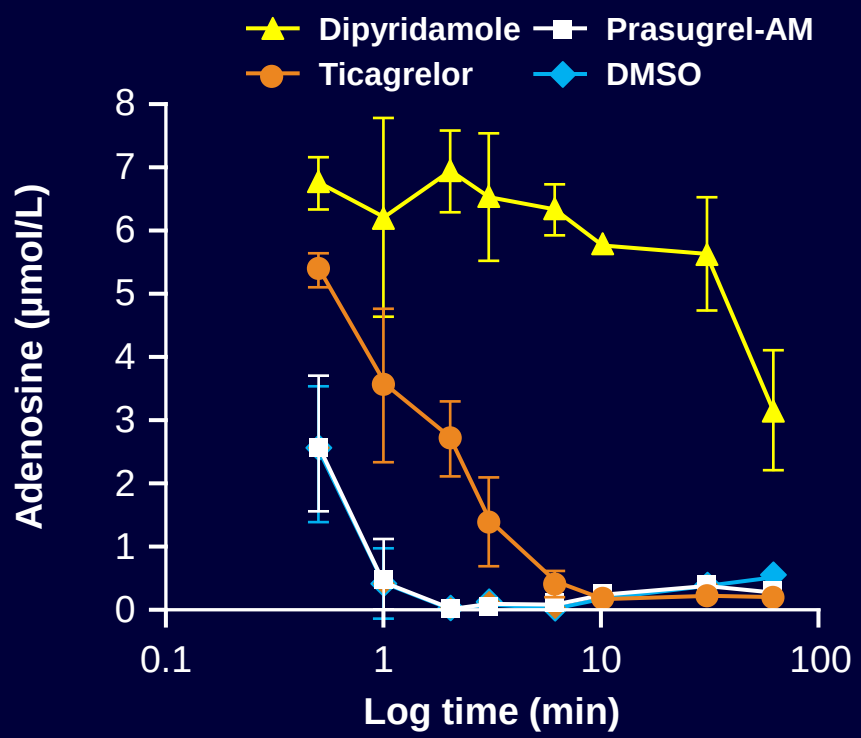
Cattaneo, T&H 2012

Ticagrelor and dyspnea

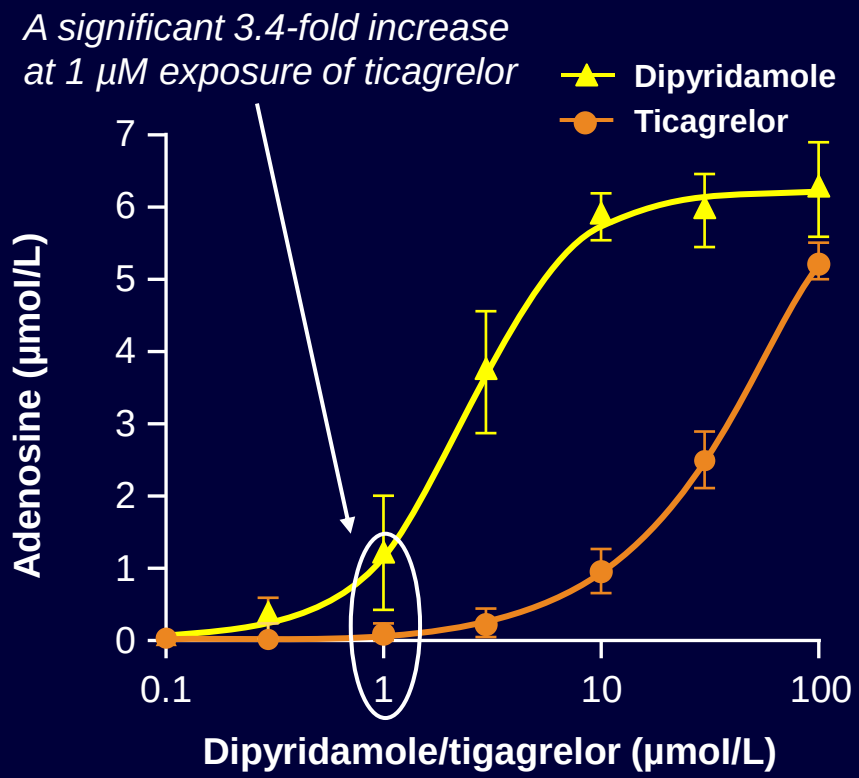
- In most instances, dyspnea started within 1-7 days of drug administration, was mild/moderate, resolved spontaneously
- In depth studies of pulmonary and cardiac function in patients with ACS or stable CAD treated with ticagrelor or clopidogrel concluded that **dyspnea was not associated with drug-induced pulmonary dysfunction, cardiac dysfunction or acidosis**.

Storey et al, JACC 2010; Am J Cardiol 2011; Eur Heart J 2011

Ticagrelor, but not prasugrel active metabolite, delays adenosine degradation



Extension of adenosine half-life after addition of 7.1 µM to human whole blood in the presence of DMSO, prasugrel-AM, ticagrelor or dipyridamole



Residual adenosine concentrations in whole blood 1 min after addition of 7.1 µmol/L adenosine, in the presence of a concentration range of dipyridamole or ticagrelor

AM, active metabolite; DMSO, control.

Nylander S, et al. *J Thromb Haemost* 2013;11:1867–1876.

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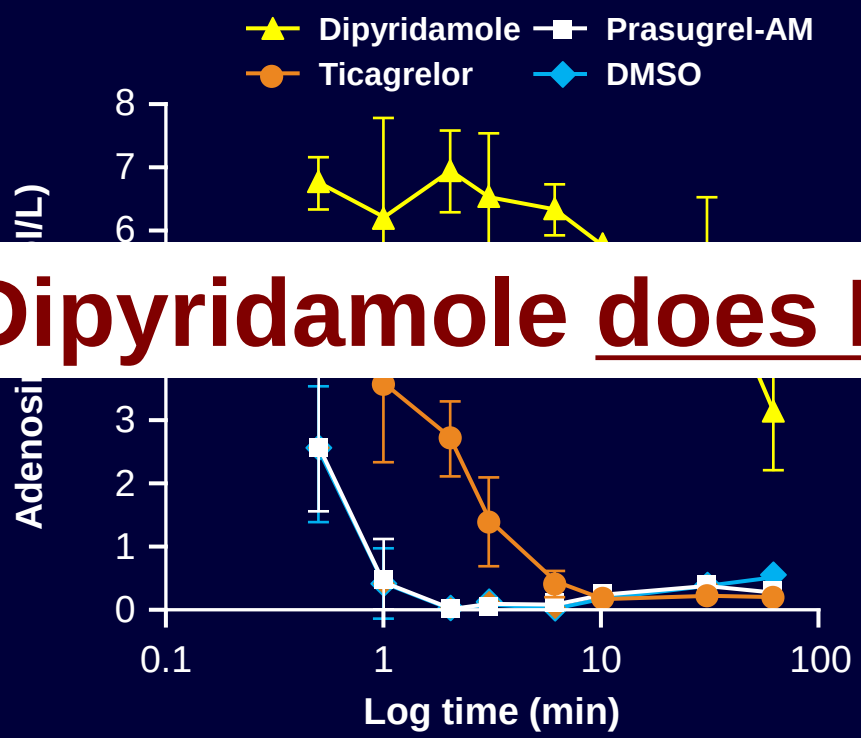
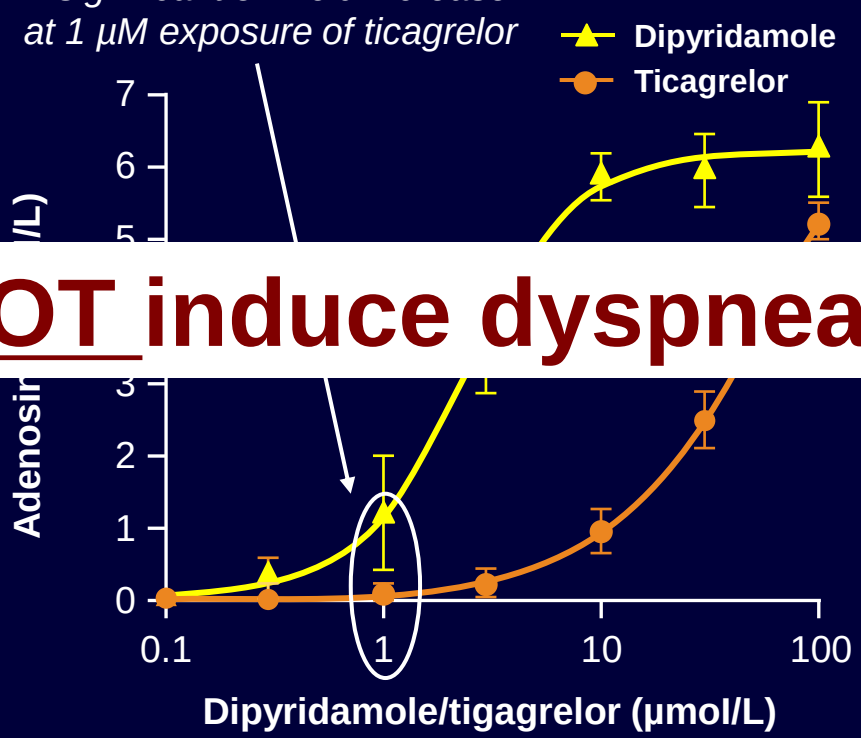


Extension of adenosine half-life after addition of 7.1 µM to human whole blood in the presence of DMSO, prasugrel-AM, ticagrelor or dipyridamole

A significant 3.4-fold increase at 1 µM exposure of ticagrelor



Residual adenosine concentrations in whole blood 1 min after addition of 7.1 µmol/L adenosine, in the presence of a concentration range of dipyridamole or ticagrelor

Dipyridamole does NOT induce dyspnea!

AM, active metabolite; DMSO, control.

Nylander S, et al. *J Thromb Haemost* 2013;11:1867–1876.

Hypothesis

The sensation of dyspnea is increased by pharmacological inhibition of $P2Y_{12}$

Cattaneo, T&H 2012

Frequency of dyspnea in the PLATO Study

	Ticagrelor n/total (%)	Clopidogrel
Number with dyspnea/total number of patients	1339/9235 (14.5%)	798/9186 (8.7%)
Number with «unexplained» dyspnea/total number of patients with dyspnea	366/1339 (27.3%)	160/798 (20.1%)

Storey et al, Eur Heat J 2011

Frequency of dyspnea among 3,719 PCI patients on DAPT (ASA+clopidogrel)

Number with dyspnea	**178/3,719 (4.7%)**
Number with unexplained dyspnea/total number with dyspnea	17/178 (9.6%)

Serebruany et al, T&H 2009

Comparison of the incidence of dyspnea in patients treated with reversible $P2Y_{12}$ inhibitors and patients treated with clopidogrel

Study drug	Patients (n)	Dose	Duration	A. Percent dyspnea in study group	B. Percent dyspnea in clopidogrel group	A/B	Study
Ticagrelor	Atherosler (200)	50-400 mg bid	28 d	10-20	0	∞	DISPERSE
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Ticagrelor	Stab. CAD (98)	90 mg bid	14 d	13	4	3.25	RESPOND
Ticagrelor	ACS (18,624)	90 mg bid	12 mo	13.8	7.8	1.77	PLATO
Cangrelor	ACS (8,877)	4µg/Kg/min IV	2-4 h	1	0.4	2.5	CHAMPION PCI
Elinogrel	Nonurgent PCI (626)	100 mg bid 150 mg bid	120 d 120 d	12.4 12.1	3.8 3.8	3.26 3.18	INNOVATE PCI

Cattaneo, T&H 2012

Table 1 Antiplatelet Agents and Dyspnea

Drug	Inhibition of $P2Y_{12}$	Inhibition of Cellular Uptake of Adenosine	Increased Sensation of Dyspnea
Ticagrelor	Yes (reversible)	Yes (+)	Yes (++)
Cangrelor	Yes (reversible)	No*	Yes (++)
Elinogrel	Yes (reversible)	No	Yes (++)
Clopidogrel	Yes (irreversible)	No	Yes (+/−)†
Dipyridamole‡	No	Yes (++)	No

Cattaneo et al, JACC 2014

Hypothesis

The sensation of dyspnea is increased by pharmacological inhibition of $P2Y_{12}$, particularly when reversible inhibitors are used

Cattaneo, T&H 2012

Why does ticagrelor induce dyspnea?

Marco Cattaneo; Elena M. Faioni

Medicina 3, Ospedale San Paolo, Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy

Thromb Haemost 2012; 108

Viewpoint Article

Viewpoint: Reversible nature of platelet binding causing transfusion-related acute lung injury (TRALI) syndrome may explain dyspnea after ticagrelor and elinogrel

Victor L. Serebruany

HeartDrug™ Research Laboratories, Johns Hopkins University, Towson, Maryland, Maryland, USA

Thromb Haemost 2012; 108

Summary

Several characteristics differentiate ticagrelor from thienopyridines:

- Two pharmacological targets:
  - $P2Y_{12}$ (inhibition of platelet function)
  - ENT1 (inhibition of cellular uptake of adenosine)
- Direct acting (it is NOT a pro-drug)
- Reversible $P2Y_{12}$ inhibition
- 24-h systemic activity

The increased incidence of dyspnea in treated patients is likely attributable to the reversible inhibition of $P2Y_{12}$, rather than to the induced increase in adenosine levels

ENT1, equilibrative nucleoside transporter 1.