Supplemental Material

Platelet $P2Y_{12}$ inhibitors reduce systemic inflammation and its prothrombotic effects in an experimental human model

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Supplemental Results

Residual Platelet $P2Y_{12}$ Reactivity Prior to LPS Correlates with Subsequent Peak Levels of TNFα and D-dimer

TNFα was the first pro-inflammatory cytokine to increase, consistent with its central role in the pathophysiology of systemic inflammation and its prothrombotic effects. Each of the following indices of platelet reactivity to ADP pre-LPS correlated with subsequent peak levels of TNFα after LPS administration: platelet-monocyte aggregate formation ($r=0.55$; $p=0.002$; Fig III in the online supplement), final platelet aggregation ($r=0.54$; $p=0.002$) and platelet P-selectin expression ($r=0.42$; $p=0.023$). Peak levels of TNFα correlated with peak levels of D-dimer ($r=0.60$; $p<0.001$) and fibrin clot maximum absorbance ($r=0.48$; $p=0.01$).

Supplemental Table

Table I Baseline and treatment characteristics

	Control n=10	Clopidogrel n=10	Ticagrelor n=10
Age - median years (interquartile range)	22.5 (21.0 – 24.25)	21.0 (20.50 – 22.50)	21.5 (20.0 – 22.0)
Male sex – no./total no. (%)	10/10 (100)	10/10 (100)	10/10 (100)
Weight (kg) – mean (SEM)	76.4 (2.7)	75.0 (3.2)	74.2 (2.5)
Body mass index (kg/m^2) – mean (SEM)	23.0 (0.6)	22.7 (0.5)	23.2 (0.8)
Race – no./total no.			
White (%)	10/10 (100)	8/10 (80)	9/10 (90)
Black (%)	0/10 (0)	1/10 (10)	0/10 (0)
Asian (%)	0/10 (0)	1/10 (10)	1/10 (10)
Duration of clopidogrel treatment – days (SEM)	0 (0)	7.1 (0.1)	0 (0)
Duration of ticagrelor treatment – days (SEM)	0 (0)	0 (0)	6.7 (0.3)

There were no significant differences in baseline characteristics between groups.

Table II Hemodynamic parameters before treatment, after treatment and 3 hours after LPS administration

	Baseline	Before LPS	3 Hours After LPS
Heart rate (bpm)			
Control	72±4	70±2	94±4*
Clopidogrel	70±5	68±4	94±4*
Ticagrelor	74±2	71±3	93±3*
Mean arterial blood pressure (mm Hg)			
Control	87±2	88±3	84±2
Clopidogrel	89±3	88±3	82±3
Ticagrelor	87±3	87±3	80±2
Temperature °C			
Control	36.1±0.1	35.9±0.1	37.9±0.2*
Clopidogrel	36.0±0.1	36.0±0.1	38.1±0.2*
Ticagrelor	36.0±0.1	36.0±0.1	37.7±0.2*

Data are mean ± SEM. * = $P<0.05$ compared to value before LPS administration.

Supplemental figures

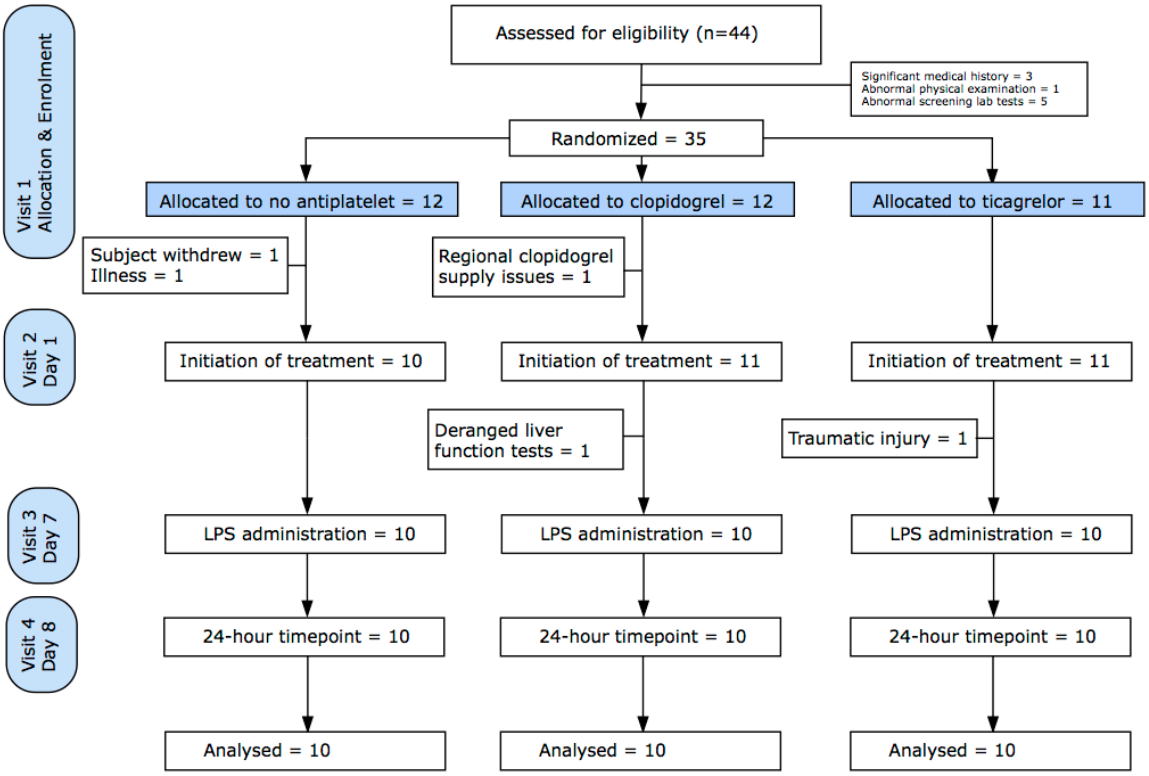

Figure I. CONSORT flow diagram presenting the enrolment, intervention allocation, follow-up and data analysis with number of subjects for each group.

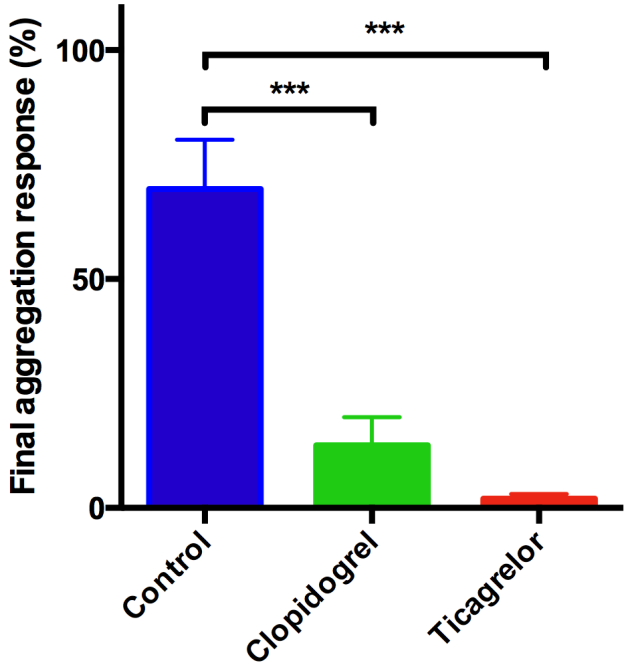

Figure II. Final platelet aggregation response measured after 1 week of ticagrelor, clopidogrel or control. Data expressed as mean ±SEM (n=10 in each group). Effect of ticagrelor and clopidogrel compared to control using ANOVA.

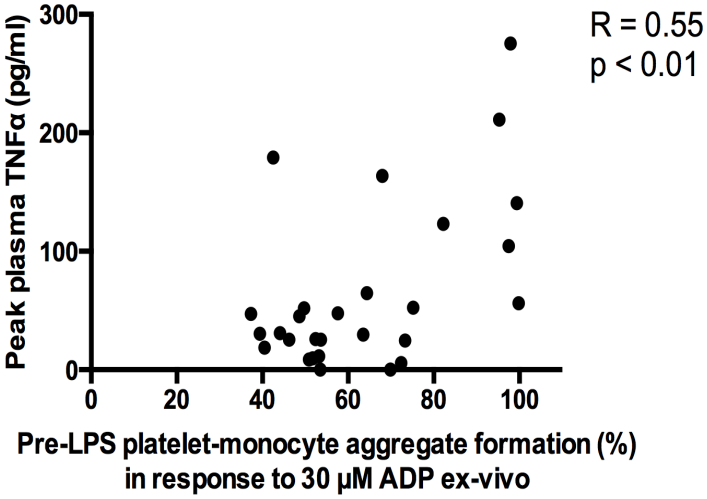

Figure III. Correlation between residual platelet reactivity after 1 week of randomized treatment (as demonstrated by ADP-induced platelet-monocyte aggregate formation) and subsequent TNFα response. Correlation determined by Pearson correlation co-efficient.