Recovery of platelet reactivity following cessation of either aspirin or ticagrelor in patients treated with dual antiplatelet therapy following percutaneous coronary intervention: a GLOBAL LEADERS substudy

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Abstract

Cessation of one component of dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI) has been associated with increased risk of ischaemic events but it is uncertain whether discontinuation of aspirin is preferable to discontinuation of the oral $P2Y_{12}$ inhibitor. The GLOBAL LEADERS study compared two antiplatelet strategies following PCI, cessation of aspirin at 1 month with continued ticagrelor monotherapy for 23 months versus standard DAPT for 12 months followed by aspirin monotherapy for a further 12 months. We assessed recovery of platelet reactivity after withdrawal of either aspirin or ticagrelor at 1 month and 12 months, respectively, in this study. Platelet aggregation (PA) was assessed before cessation of DAPT ('baseline') and after 2, 7 and 14 days post-cessation using Multiplate whole-blood aggregometry with collagen, thrombin-receptor-activating peptide (TRAP), adenosine diphosphate (ADP) and arachidonic acid (AA) as agonists. Following cessation of aspirin at 1 month, there was marked recovery of PA induced by AA (baseline [mean ± SD]: 11.1 ± 7.4 U vs. 14 days: 64.9 ± 19.6 U, p<0.0001) and collagen (37.4 ± 22.9 U vs. 79.8 ± 13.8 U, p<0.0001), whereas PA induced by ADP (18.6 ± 6.6 vs. 69.1 ± 20.5, p<0.0001) and collagen (34.4 ± 18.7 U vs. 43.0 ±21.0, p=0.0018) recovered following cessation of ticagrelor at 12 months. There were no significant changes in TRAP-induced PA in either group. In conclusion, cessation of either component of DAPT leads to substantial increase in platelet reactivity with differential effects on different pathways of platelet activation when aspirin or the $P2Y_{12}$ inhibitor is stopped. Further work is required to determine which patients receive net benefit from long-term continuation of DAPT.

Keywords

Platelet aggregation; aspirin; ticagrelor; percutaneous coronary intervention

Introduction

Dual antiplatelet therapy (DAPT), consisting of the combination of aspirin, a cyclo-oxygenase inhibitor, and an oral platelet $P2Y_{12}$ receptor antagonist ('$P2Y_{12}$ inhibitor') is used after percutaneous coronary intervention (PCI) to reduce rates of stent thrombosis and ischaemic events such as spontaneous myocardial infarction (MI) [1]. However, the optimal duration of DAPT to prevent ischemic events whilst minimizing the risk of bleeding remains uncertain. Current international guidelines support the long-term use of DAPT in patients with previous MI who have a high risk of recurrent ischaemic events related to burden of coronary artery disease and unmodifiable risk factors but no high-bleeding-risk conditions [2]. However, recent studies have also suggested that cessation of aspirin and use of ticagrelor monotherapy leads to reduced bleeding risk without increasing the risk of ischaemic events in a broad population of patients following PCI [1, 3-5]. There have been divergent views in the literature about the impact of cessation of aspirin on platelet reactivity in DAPT-treated patients whereas numerous studies have shown a higher incidence of acute coronary events within 3 months of switching from DAPT to aspirin monotherapy [6-9]. One explanation for this clustering of events is an increase in platelet reactivity leading to higher risk of clinically-evident plaque rupture events and, in the context of malapposed non-endothelialised stent struts, stent thrombosis, an event associated with significant morbidity and mortality [10].

Ticagrelor is a directly-acting and reversible $P2Y_{12}$ inhibitor that provides a consistently high level of receptor $P2Y_{12}$ inhibition during maintenance therapy [11]. In combination with aspirin, it has been shown to be superior to clopidogrel in reducing major adverse cardiovascular events and mortality following an acute coronary syndrome (ACS) [12]. Addition of ticagrelor to aspirin has also been shown to reduce long-term MACE in patients with prior MI who are at increased risk of further ischaemic events [13].

The open-label, multicenter GLOBAL LEADERS study evaluated whether aspirin and ticagrelor for 1 month, followed by ticagrelor monotherapy for 23 months, after PCI with DES was superior to standard treatment of 12 months DAPT followed by long-term aspirin monotherapy with a composite primary endpoint of death or new Q-wave MI [4]. There was no evidence of superiority and rates of major bleeding and stent thrombosis were similar; however, those patients with ACS receiving ticagrelor monotherapy between 1 and 12 months post-ACS had less bleeding and similar rates of ischaemic events compared with those receiving aspirin and ticagrelor [5]. The finding that de-escalation of antithrombotic therapy reduced bleeding is consistent with findings in other groups such as those with atrial fibrillation [14].

In the post-PCI population, the offset profile of aspirin's effect when transitioning from DAPT to ticagrelor monotherapy has not been determined and, furthermore, there are only very limited data available concerning platelet function during the latter regimen [15].

The aim of this substudy was to investigate the pharmacodynamic offset of effects on platelet aggregation over time when participants in the GLOBAL LEADERS study transitioned from DAPT with aspirin and ticagrelor to monotherapy with either agent, in order to provide mechanistic insights into any observed differences in ischaemic or bleeding endpoints in the main study.

Methods

Inclusion/Exclusion Criteria

Patient population inclusion and exclusion criteria were those of the GLOBAL LEADERS study [4]. The principal inclusion criteria were: age ≥18 years, one or more coronary artery stenoses of ≥50% in a native coronary artery or in a saphenous venous

or arterial bypass conduit suitable for stent implantation, and informed consent. Exclusion criteria were: intolerance to aspirin or $P2Y_{12}$ inhibitors, use of bivalirudin, allergy to stainless steel or biolimus, intake of a strong CYP3A4 inhibitor, moderate to severe hepatic impairment, planned surgery, need for anti-coagulation therapy, active major bleeding or major surgery within the last 30 days, history of intracranial haemorrhagic stroke or intra-cranial aneurysm, stroke within the last 30 days, pregnancy or breastfeeding at time of randomisation, and current participation in another trial not yet at its primary endpoint.

In the GLOBAL LEADERS study, participants were randomised to receive one of two open-label antiplatelet regimens after PCI. One half received one month of DAPT with aspirin 75-100 mg once daily and ticagrelor 90 mg twice daily followed by 23 months of ticagrelor 90 mg twice daily, therefore stopping aspirin at one month. The other half received 12 months of DAPT with aspirin 75-100 mg once daily and either ticagrelor 90 mg twice daily (if PCI was for ACS) or clopidogrel 75 mg once daily (if PCI was for stable coronary artery disease [CAD]) , followed by 12 months of aspirin monotherapy, therefore stopping the $P2Y_{12}$ inhibitor at 12 months. Patients were recruited to participate in this substudy either if they were randomised to the ticagrelor monotherapy arm, or if they were receiving DAPT with aspirin and ticagrelor. Participants were enrolled at the time of discontinuation of DAPT when attending routine follow-up as part of the GLOBAL LEADERS study either at 1 month for the group assigned to stop aspirin and continue ticagrelor monotherapy from this timepoint, or 12 months for the group assigned to stop ticagrelor following 12 months treatment after MI and continue aspirin monotherapy. All eligible participants within a single centre were approached. Written consent was obtained in accordance with a protocol approved by National Research Ethics Service Committee West Midlands–Solihull.

Platelet Function Studies

Blood samples were drawn at baseline, prior to discontinuation of DAPT, and 2, 7 and 14 days following discontinuation of DAPT in both groups. Phlebotomy was carried out after the patient had been sitting for 10 minutes with minimal tourniquet time and care given to avoid unnecessary trauma to the vein or agitation of blood sample. The first 3 ml were discarded, then venous blood was collected in hirudin-anticoagulated tubes. Samples were analysed within 60 minutes of sample collection but with the aim of performing assays at 30 minutes post-phlebotomy. Analysis was undertaken by multiple-electrode aggregometry (MEA) using the Multiplate system in concordance with manufacturer's guidelines. MEA assays measure changes in electrical impedance caused by adhesion of platelets to silver-covered electrodes. The degree of platelet aggregation is measured in arbitrary units (U) generated by the area-under-the-curve in a given time (10 AUC*min = 1U). The agonists used were adenosine diphosphate (ADP, final concentration 6.5 μmol/L), arachidonic acid (AA, 0.5 mmol/L), thrombin receptor activating peptide 6 (TRAP, 32 μmol/L) and collagen (3.2 μg/mL).

Statistical Plan

An a priori sample size calculation suggested that a total of 52 participants would have 90% power to detect a clinically relevant increase in collagen-induced platelet aggregation (PA) of 10U in each group between the lowest and highest value. For each group and agonist, within-participant comparisons were made between baseline and each timepoint using paired t-tests. No adjustment was made for multiple testing due to the exploratory, hypothesis-generating nature of the study. All graphical and statistical analyses were carried out using IBM SPSS Statistics 23 and GraphPad Prism v8.4.3.

Results

Patient demographics

Of 36 eligible participants, 34 (94%) consented to take part in the substudy. The two patient groups were similar in sex distribution and age (Table 1).

Platelet aggregation

In the group that discontinued aspirin at 1 month post-PCI and continued to receive ticagrelor, there was significant recovery of AA-induced PA by day 2 after cessation (baseline [mean ± SD]: 11.1 ± 7.4 U vs. day 2: 22.4 ± 16.2 U, p=0.032), which increased to 64.9 ± 19.6 U by day 14 (p<0.0001 vs, baseline) (Figure 1). Similarly, collagen-induced PA was significant greater by day 2 than baseline (37.4 ± 22.9 U vs. 54.5 ± 26.8 U, p=0.033), also increasing further to 79.8 ± 13.8 U by 14 days (p<0.0001 vs. baseline) (Figure 1). There were no significant changes in ADP- or TRAP-induced PA after discontinuation of aspirin.

In those discontinuing ticagrelor at 12 months post-PCI and continuing to receive aspirin, ADP-induced PA had recovered significantly by 2 days after cessation (baseline: 18.6 ± 6.6 U vs. day 2: 48.1 ± 31.3 U, p=0.0005), increasing to 69.1 ± 20.5 U by day 14 (p<0.0001 vs. baseline) (Figure 2). This was accompanied by a modest but significant increase in collagen-induced PA from baseline by day 2 (34.4 ± 18.7 U vs. 40.3 ± 24.9 U, p=0.033), which was also significant at day 14 (43.0 ± 21.0, p=0.0018 vs. baseline) but not day 7 (36.9 ± 13.0, p=0.63 vs. baseline). There were no significant changes in AA- or TRAP-induced PA after discontinuation of ticagrelor.

Stratification by diagnosis in those discontinuing aspirin

In the group discontinuing aspirin, 9 (53%) had stable CAD as the indication for the index PCI, the remaining 8 having had an ACS event (47%). At 7 days and, to a lesser extent, 14 days after discontinuing aspirin, PA responses to AA were significantly greater in those in the ACS subgroup than the stable angina subgroup (Figure 3). Serum C-reactive protein (CRP) was higher in the ACS group compared to the stable CAD group both before and after discontinuation of aspirin (e.g. day 0: mean ± SD 6.21 ± 7.25 mg/L vs. 0.94 ± 0.72 mg/L, p=0.023; day 7 3.44 ± 2.47 mg/L vs.1.38 ± 0.84 mg/L, p=0.015). CRP positively and significantly correlated with AA PA response at day 2 after discontinuation of aspirin (r=0.65 [95% CI 0.25 to 0.86], Pearson test p=0.0045). There were no significant differences between the two groups in post-discontinuation responses to ADP, TRAP or collagen.

Post-hoc power calculation

As the number of participants recruited to the substudy did not meet the target, a post-hoc power calculation was performed to ensure validity (G*Power v3.1.9.6). The power to detect a change of the effect size seen in collagen-induced platelet aggregation from day 0-2 in those discontinuing ticagrelor was 89.7%, and 99.9% for day 0-14. Values for those discontinuing aspirin were 89.7% and >99.9% respectively. The calculated power to detect changes in AA- and ADP-induced platelet aggregation in those discontinuing aspirin or ticagrelor respectively between days 0-2 and 0-14 was >90%.

Discussion

In the GLOBAL LEADERS study, there was no significant reduction in death or Q-wave MI in patients randomized to a very short duration of DAPT and long-term ticagrelor monotherapy compared with a standard-of-care strategy of 12-months DAPT followed by 12-months aspirin monotherapy. In an exploratory analysis, those patients with ACS receiving ticagrelor monotherapy between 1 and 12 months post-ACS had less bleeding and similar ischaemic events compared with those receiving aspirin and ticagrelor [5]. The TWILIGHT study similarly demonstrated a significant reduction in bleeding events and no obvious penalty in terms of ischaemic events in patients treated with ticagrelor alone for 12 months compared with ticagrelor plus aspirin after three months uncomplicated DAPT following PCI [3]. In this sub-study of the GLOBAL LEADERS trial, we demonstrated that, in patients who have been receiving DAPT with aspirin and ticagrelor after PCI, there is a detectable and statistically significant increase in platelet aggregation upon cessation of either drug.

These differences are likely to underpin the reduced incidence of major bleeding seen when receiving ticagrelor monotherapy as opposed to DAPT in TWILIGHT and the ACS subgroup of GLOBAL LEADERS, although other factors such as gastroduodenal ulceration caused by aspirin, but not ticagrelor, may also play a role [15].

The effects of reduced inhibition of AA- and collagen-induced PA when receiving ticagrelor monotherapy rather than DAPT on risk of ischaemic events after PCI remains uncertain, and adequately powered studies to definitively assess these, in contrast to bleeding events, have not yet been performed. On the one hand, contemporary stent design with ultra-thin struts and biocompatible materials has reduced the risk of stent thrombosis over previous-generation devices [16]. Similarly, improvements in understanding and management of modifiable risk factors such as

hyperlipidaemia and hypertension have further reduced atherothrombotic risk [2]. On the other hand, some events are associated with release of very high levels of pro-thrombotic factors and significant disruption of flow, such as ST-elevation MI or acute thrombotic stroke, and therefore in individuals at particularly high risk of such events, a greater degree of multi-pathway platelet inhibition may be optimal in patients who do not have conditions associated with high bleeding risk [17, 18]. Novel dose regimens of aspirin, such as 20-mg twice daily, in conjunction with ticagrelor might improve haemostasis without relevant loss of platelet inhibition and offer an alternative approach to aspirin cessation in such individuals [19]. Conversely, in those with high bleeding risk, there is growing evidence that, with current generations of drug eluting stents, just one month of DAPT may be sufficient to keep stent thrombosis risk acceptably low [20, 21].

As would be expected from their respective mechanisms of action, stopping aspirin leads primarily to an increase in AA-induced PA and stopping ticagrelor increases primarily ADP-induced PA. Stopping either aspirin or ticagrelor led to increase in collagen-induced PA, reflecting the contribution of both ADP and TXA_2 to collagen-induced platelet activation [22]. Accordingly, our data offer evidence of a significant additive inhibitory effect of aspirin and ticagrelor on multi-pathway PA in patients who have undergone PCI, also supported by another platelet function study of patients receiving DAPT vs. ticagrelor alone in the TWILIGHT study [23].

We observed a more rapid offset of aspirin's effect in those with ACS than stable CAD. This is consistent with higher platelet turnover in the former group, likely driven by higher levels of inflammation, underlined by the correlation between CRP and AA-

induced PA response from day 2 after discontinuation [24], which may be consistent with previous studies linking platelet function to inflammation [25].

There already exists evidence of comparable profiles of effect of ticagrelor in patients with stable angina, ACS and prior MI [11, 26, 27], and it was reassuring in our study that there were no differences in the responses to ADP, collagen or TRAP between the clinical groups when receiving ticagrelor monotherapy.

Limitations: We were unable to compare PA responses during or after treatment with pre-treatment or pre-PCI measurements because these data were not available. Similarly, because discontinuation of aspirin occurred at a different timepoint after PCI compared to discontinuation of ticagrelor, direct comparisons between the groups may not be reliable and so were not undertaken. Furthermore, because of the design of the main study, all the participants who discontinued ticagrelor had an index diagnosis of ACS, whereas there was a mix of ACS and stable CAD patients in those discontinuing aspirin, and the potential for unidentified confounders means that the comparison between ACS and stable angina groups should be treated with caution. The subanalysis by clinical group and subsequent correlation with CRP, whilst being performed in a logical hypothesis-driven fashion and not accompanied by any other subgroup analyses, was post-hoc and therefore its findings can only be interpreted as exploratory. Further measures of platelet function or more timepoints may have enhanced the insight and applicability of the study.

Conclusions

When receiving DAPT with aspirin and ticagrelor after PCI, either drug leads to detectable increases in platelet aggregation responses. Cessation of ticagrelor leads to a substantial increase in ADP-induced PA and a modest increase in collagen-induced PA, whilst AA-induced PA remains unchanged. Cessation of aspirin leads to a substantial increase in both AA- and collagen-induced PA whilst ADP-induced PA

remains unchanged. Stopping either agent has no effect on responses to TRAP. These findings are likely to underpin the lower bleeding rates seen when receiving antiplatelet monotherapy over DAPT but may hypothetically increase ischaemic risk. Further work is required to compare antiplatelet monotherapy options and DAPT in patients at particularly high risk of atherothrombotic events.

Author roles

Conceived, designed and set up the study: B. W. Hennigan, R. Good, K. G. Oldroyd, L. Anderson, M. Campbell. Data collection and analysis: B. W. Hennigan, L. Martin, C. Adamson, W.A.E. Parker. Wrote the paper: B. W. Hennigan, R. Good, C. Adamson, W.A.E. Parker, R.F. Storey, K. G. Oldroyd.

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Declaration of Interest

B. W. Hennigan, R. Good, C. Adamson, L. Martin, L. Anderson, M. Campbell, and W.A.E. Parker declare no conflicts of interest. R.F. Storey reports institutional research grants/support from AstraZeneca, GlyCardial Diagnostics and Thromboserin; consultancy fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb/Pfizer, Cytosorbents, GlyCardial Diagnostics, Haemonetics, HengRui, Portola, Sanofi Aventis and Thromboserin; and honoraria from AstraZeneca, Bayer, Bristol Myers Squibb/Pfizer, Intas Pharmaceuticals and Medscape. K. G. Oldroyd is Chief Medical Officer of Biosensor International, which provided funding for the GLOBAL LEADERS study.

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TABLES

Table 1. Baseline demographics for participants in each randomized treatment group.

	Aspirin monotherapy (n=17)	Ticagrelor monotherapy (n=17)
Age - median (IQR)	62 (56, 66)	59 (56, 68)
Female sex	5 (29%)	5 (29%)
Indication for PCI		
Stable angina	0 (0%)	9 (53%)
NSTEMI	16 (94%)	6 (35%)
STEMI	1 (6%)	2 (12%)
Smoker	6 (35%)	4 (24%)
Ex-smoker	2 (12%)	1 (6%)
Positive family history	3 (18%)	5 (29%)
BMI >30	5 (29%)	9 (53%)
Medical history		
Hypertension	9 (53%)	11 (65%)
Diabetes	1 (6%)	4 (24%)
Dyslipidaemia	8 (47%)	4 (24%)
Myocardial infarction	9 (53%)	3 (18%)
Heart failure	0 (0%)	0 (0%)
Previous PCI	5 (29%)	8 (47%)
CVA/TIA	2 (12%)	3 (18%)
CABG	1 (6%)	0 (0%)
Peripheral arterial disease	0 (0%)	1 (6%)
Treatment		
Insulin	0 (0%)	1 (6%)
Oral hypoglycaemic	1 (6%)	3 (18%)
Statin	16 (94%)	16 (94%)
Beta blocker	15 (88%)	14 (82%)
Calcium channel antagonist	2 (b12%)	4 (24%)
ACE or ARB	15 (88%)	12 (71%)

ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; IQR, interquartile range; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIA, transient ischaemic attack.

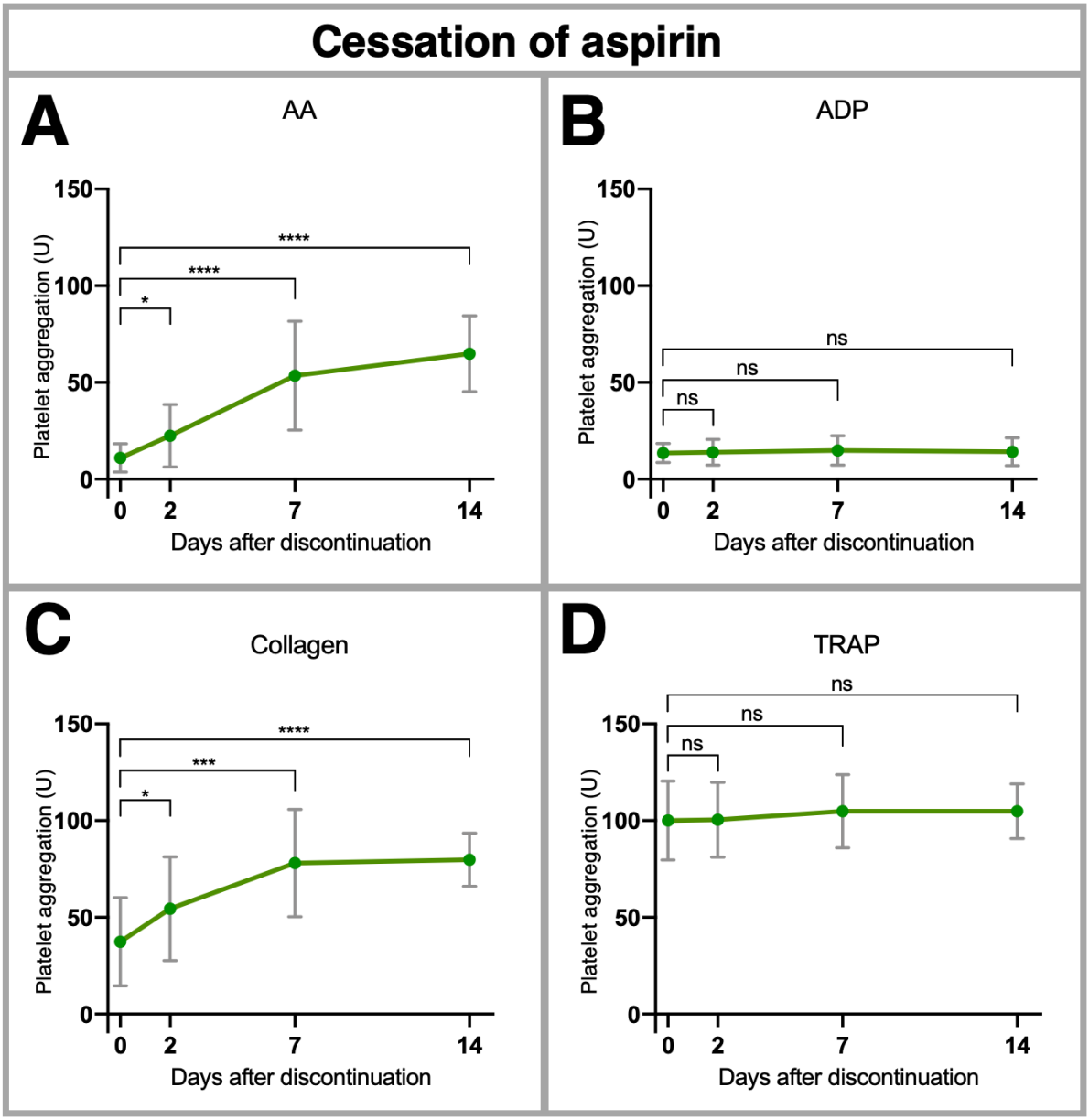

Figure 1. Platelet aggregation responses determined by Multiplate analysis using as agonists AA (panel A), ADP (panel B), collagen (panel C) and TRAP (panel D) in patients ceasing aspirin treatment but continuing ticagrelor. Bars represent mean ± SD. Brackets represent within-participant comparisons with baseline using two-tailed paired t-tests. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$; ****, $p<0.0001$; AA, arachidonic acid; ADP, adenosine diphosphate; AUC, area under the curve (Multiplate® test); ns, not significant ($p>0.05$); TRAP, thrombin receptor activating peptide.

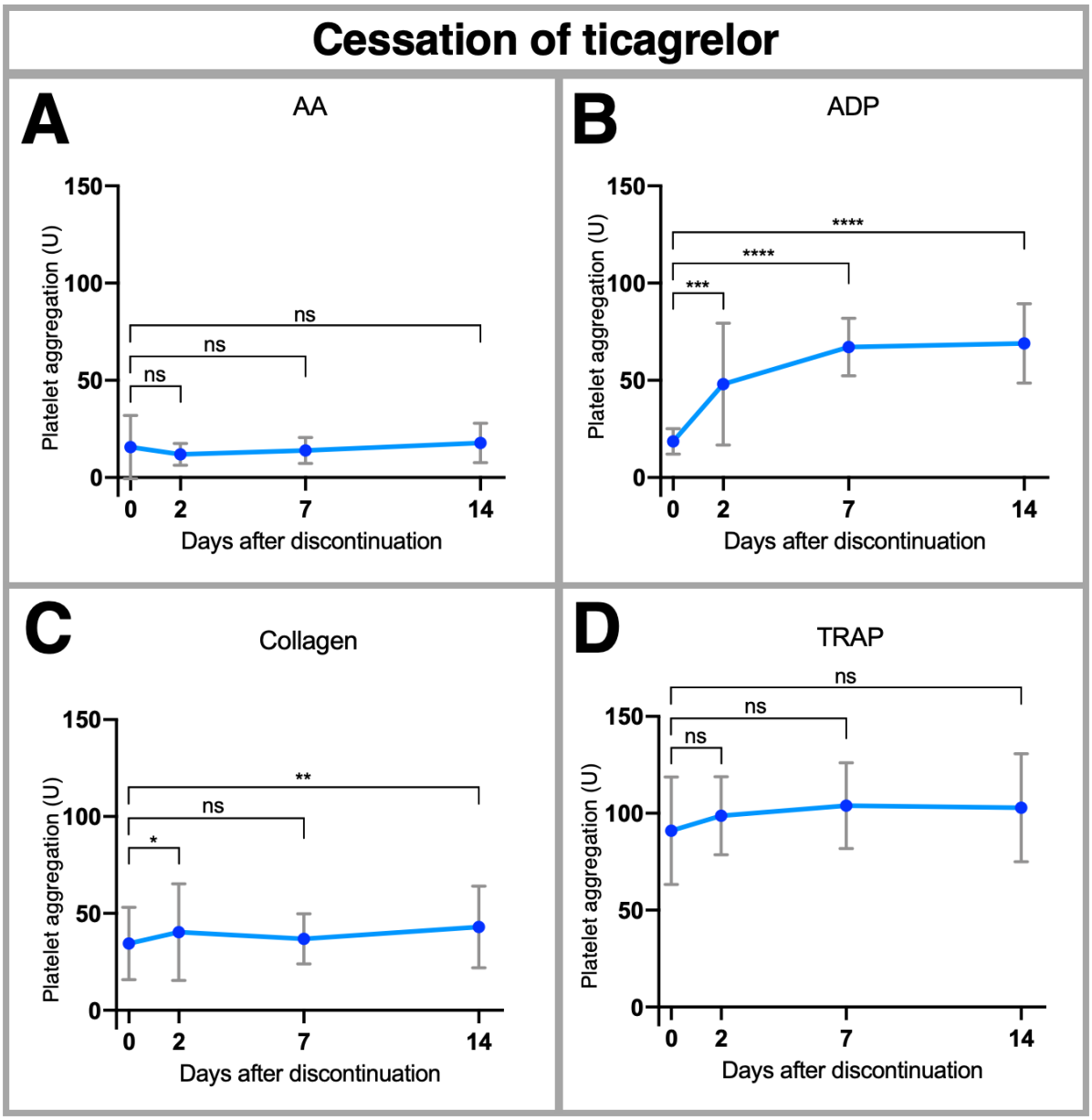

Figure 2. Platelet aggregation responses determined by Multiplate analysis using as agonists AA (panel A), ADP (panel B), collagen (panel C) and TRAP (panel D) in patients ceasing ticagrelor treatment but continuing aspirin. Bars represent mean ± SD. Brackets represent within-participant comparisons with baseline using two-tailed paired t-tests. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$; ****, $p<0.0001$; AA, arachidonic acid; ADP, adenosine diphosphate; ns, not significant ($p>0.05$); TRAP, thrombin receptor activating peptide.

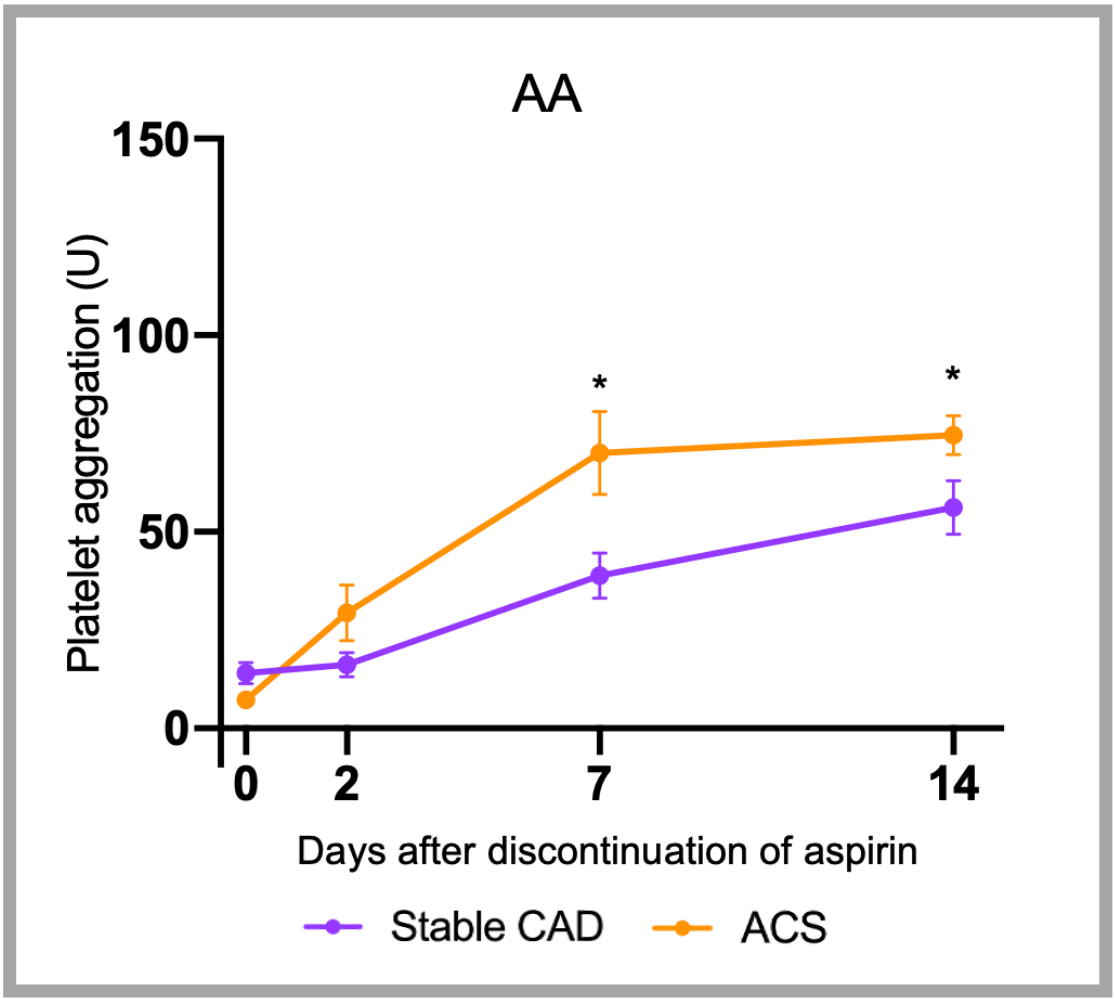

Figure 3. Platelet aggregation responses determined by Multiplate analysis using AA as an agonist. Bars represent mean ± SEM. *, p<0.05 (stable CAD vs ACS at timepoint); AA, arachidonic acid; ACS, acute coronary syndrome; CAD, coronary artery disease; U, units.