

A case report of absolute thrombocytopenia with ticagrelor

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Background

We report a rare case of absolute thrombocytopenia with ticagrelor after 6 h of single loading dose of ticagrelor.

Case summary

A 68-year-old male with ischaemic cardiomyopathy, hypertension, and dyslipidaemia presented with chest pain. He was found to be in new-onset atrial flutter and ruled in for a non-ST-segment elevation myocardial infarction. An echocardiogram showed decreased left ventricular ejection fraction, estimated at 15–20% and serum troponin peaked at 0.2 ng/dL, baseline platelet count was $203 \times 10^3/\mu\text{L}$. He underwent a drug-eluting stent placement to the right coronary artery with excellent angiographic results. He received 3000 units of unfractionated heparin and 180 mg of ticagrelor during the procedure. About 6 h after the procedure, he had coffee ground emesis. A complete blood count revealed a platelet count of 2×10^3 and $0 \times 10^3/\mu\text{L}$ on repeat testing. Peripheral smear did not show any evidence of platelet clumping and schistocytes, serum haptoglobin and lactate dehydrogenase were normal. Ticagrelor and heparin were discontinued, while the aspirin was continued. Five units of platelet were transfused. The platelet count improved to $200 \times 10^3/\mu\text{L}$. Since his CHADS₂VASC score was 3, he was discharged on apixaban and clopidogrel in addition to other medication. No thrombocytopenia was seen on outpatient follow-up.

Discussion

The common side effects of ticagrelor include bleeding, dyspnoea, gynaecomastia, and rarely thrombotic thrombocytopenic purpura. Although extremely rare, absolute or profound thrombocytopenia can occur with ticagrelor, hours after administration and should be considered when other potential causes of thrombocytopenia have been ruled out.

Keywords

Thrombocytopenia • Antiplatelet • Ticagrelor • Case report

Learning points

- The common causes of post-percutaneous coronary intervention (PCI) thrombocytopenia include pseudo-thrombocytopenia, glycoprotein IIb/IIIa inhibitors, unfractionated heparin and low-molecular-weight heparin, thienopyridines, intra-aortic balloon pumps, cardiogenic shock, cardiopulmonary bypass, and extracorporeal membrane oxygenation.
- Profound thrombocytopenia with ticagrelor is rare but should be considered in the differential diagnosis of post-PCI thrombocytopenia.
- A single loading dose of ticagrelor can cause absolute thrombocytopenia.

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Introduction

Ticagrelor reversibly to the P2Y12 receptor at a site distinct from the adenosine diphosphate (ADP)-binding site and inhibits ADP signalling and receptor conformational change by ‘locking’ the receptor in an inactive state,¹ it dissociates from the receptor and leaves the receptor intact, which shows its dose-dependent and reversible ability to inhibit platelets.^{1,2} In contrast to thienopyridine derivatives (ticlopidine, clopidogrel), ticagrelor does not require metabolic activation for inhibition of platelet activity and has rapid onset and offset of anti-platelet activity. Reported side effects of ticagrelor include increased incidence of asymptomatic ventricular pauses in the first week of treatment, elevated creatinine and uric acid levels, gynaecomastia, bleeding, and dyspnoea.² We report a rare case of absolute thrombocytopenia after 6 h of administration of loading dose of ticagrelor.

Timeline

Day 1		Hospitalization for new-onset atrial flutter, non-ST-elevation myocardial infarction, and worsening left ventricle ejection fraction Platelet count $203 \times 10^3/\mu\text{L}$ Treatment with intravenous heparin, aspirin, beta-blockers, and atorvastatin started
Day 3	18:48	Percutaneous coronary intervention of the right coronary artery and administration of 180 mg of ticagrelor
	23:00	Coffee ground emesis Platelet count $2 \times 10^3/\mu\text{L}$ Ticagrelor and heparin held
	04:00	Emesis improved Platelet count $0 \times 10^3/\mu\text{L}$
	15:25	Platelet count $5 \times 10^3/\mu\text{L}$ Platelets transfused
Day 4		Platelet count $29 \times 10^3/\mu\text{L}$ Clopidogrel initiated in addition to aspirin
Day 6		Platelet count $104 \times 10^3/\mu\text{L}$ Discharged home on clopidogrel and apixaban
Follow-up (Month 7)		Platelet count $200 \times 10^3/\mu\text{L}$

Case presentation

A 68-year-old Caucasian male with hypertension, dyslipidaemia, coronary artery disease, myocardial infarction, and ischaemic cardiomyopathy presented with jaw pain and palpitations associated with progressive dyspnoea for 3 days. Ten years ago, he underwent a drug-eluting stent placement to the left anterior descending (LAD) and ramus-intermedius arteries (RI). Biventricular pacemaker-implantable cardioverter-defibrillator was placed for decreased ejection fraction of 25–30% along with left bundle branch block with

QRS-duration of 154 ms. His left ventricular ejection fraction (LVEF) had later improved to 40–45%. On current hospitalization, he had a normal physical examination. He was found to be in atrial flutter with 3:1 block, LVEF was now 15–20% with global hypokinesis. High sensitivity troponin-I peaked at 0.2 ng/mL, haemoglobin (Hb): 14.4 g/dL, platelet count: $203 \times 10^3/\mu\text{L}$, activated partial-thromboplastin time: 58 s, and serum creatinine: 1.35 mg/dL, other laboratory values were within normal limits and no ST-segment or T-wave changes were noted on the electrocardiogram. Treatment with IV heparin, aspirin, beta-blockers, and atorvastatin was initiated. He reverted to normal sinus rhythm and reported improvement in symptoms.

On coronary angiography (Day 3), the prior stent in the LAD was patent with 30% ostial stenosis, 30% distal in-segment stenosis followed by sequential lesions of 40–50% in the mid-LAD. The RI stent was patent with a distal 50% in-segment stenosis (Figure 1). The right coronary artery (RCA) had a 20–30% ostial lesion, an eccentric 10–20% stenosis in the distal RCA, and an 85% tapering eccentric stenosis in mid-RCA that was stented with a 4.0×15 and a 4.0×12 mm drug eluting stent (DES) (Figure 1). Intra-procedurally, he received 3000 units of IV heparin and 180 mg of PO ticagrelor at 18:48, prior to stent deployment. No glycoprotein IIb/IIIa inhibitors (GPIs) were used during the procedure. The procedure was uneventful without complications.

At around 23:00, the patient experienced coffee ground emesis. A subsequent complete blood count (CBC) showed: Hb 13 g/dL, platelet count $2 \times 10^3/\mu\text{L}$, and decreased platelet sufficiency. To rule out error in sampling and lab processing, repeat CBC showed a platelet count of $0 \times 10^3/\mu\text{L}$. Peripheral smear showed mild normochromic anaemia with no schistocytes, marked thrombocytopenia with rare and morphologically unremarkable platelets, ruling out pseudo-thrombocytopenia. Direct and indirect Coomb’s test were negative, serum haptoglobin and lactate dehydrogenase were normal. Heparin-induced thrombocytopenia (HIT) was less likely in view of low index of suspicion (4T-score: 1) and a HIT antibody panel was not tested (Table 1).

Ticagrelor was held whereas aspirin was continued. The patient received 5 units of platelets and his platelet count improved to 29×10^3 and $55 \times 10^3/\mu\text{L}$ on the following days. At this point, clopidogrel 75 mg once daily was initiated along with aspirin. The patient did not have any repeat coffee ground emesis. On discharge, he was switched to a combination of clopidogrel 75 mg once daily and apixaban 5 mg twice a day since his CHADS₂VASC score was 3, warranting thromboembolic prophylaxis for atrial fibrillation/flutter in addition to other medication. After discharge, the patient was back to his baseline and on subsequent follow-up visits, his platelet count returned to his baseline of $200 \times 10^3/\mu\text{L}$ (Figure 2). Last follow-up was 7 months after the above-mentioned hospitalization where the patient was seen in the hospital for atrial flutter ablation, there was a minimal improvement in his LVEF to 25% from 15% to 20% on echocardiography. After a successful atrial flutter ablation, he was then discharged to home.

Discussion

Post-percutaneous coronary intervention (PCI) thrombocytopenia is independently associated with significantly higher rates of major

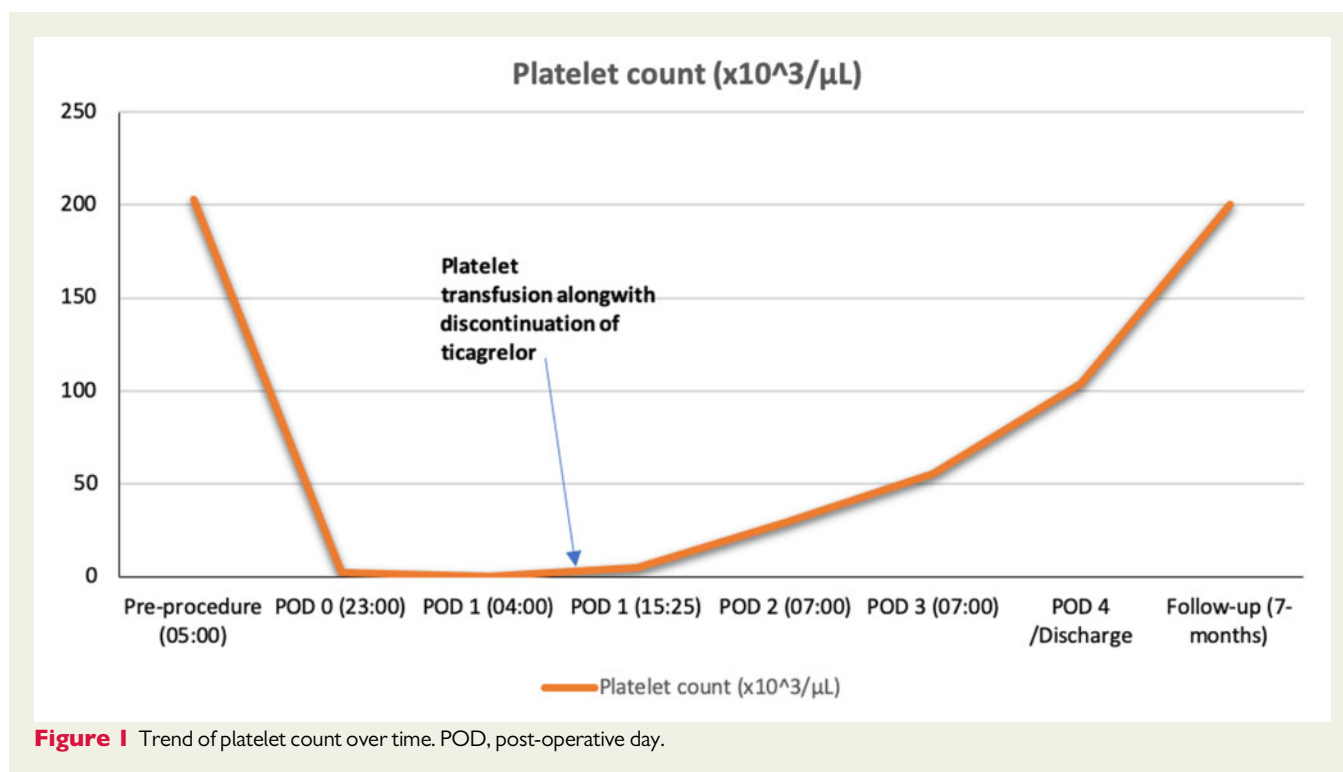


Table 1 Serial platelet count, haemoglobin, haematocrit, blood urea nitrogen, and creatinine pre- and post-percutaneous coronary intervention

Date	21 September	21 September	22 September	22 September	22 September	23 September	24 September	25 September	26 September
Time	7:02	23:08	4:15	11:00	15:25	7:34	6:35	7:35	7:05
Platelet count ($N \times 10^3/\mu\text{L}$)	203	2	0	1	5	29	55	104	
Haemoglobin (g/dL)	14.4	13	12.4	12.5	12	12.3	13	14.1	
Haematocrit (%)	45.4	40.5	39.2	39.3	38.1	39.1	40.1	43.3	
Blood urea nitrogen (mg/dL)	18		21			23	23	27	
Serum creatinine (mg/dL)	1.35		1.27			1.38	1.43	1.32	

adverse cardiovascular events.^{3,4} The common causes of post-PCI thrombocytopenia include pseudo-thrombocytopenia, GPIs, heparin, thienopyridines, intra-aortic balloon pumps, cardiogenic shock, cardiopulmonary bypass, and extracorporeal membrane oxygenation (Table 2). Angiotensin-converting enzyme inhibitors and statins are the other rare causes of post-PCI thrombocytopenia.⁴

Pseudo-thrombocytopenia is a benign condition caused by platelet aggregation, platelet clumping on peripheral blood smear can confirm the presence of pseudo-thrombocytopenia.⁵ Thrombocytopenia due to heparin can be either heparin-associated thrombocytopenia (HAT) or HIT. HAT is a benign entity that occurs within 48–72 h of exposure heparin, results in mild thrombocytopenia and resolves

despite continued heparin therapy. On the other hand, HIT typically leads to a platelet drop of >50%,⁶ occurs 5–14 days after heparin administration but can be early (within 24 h in patient who received heparin within past 100 days), or delayed (after 7–40 days).^{4,6,7} It is associated with arterial and venous thrombosis. HIT was less likely in our patient in view of the degree of thrombocytopenia, time of onset of thrombocytopenia of several hours with no prior exposure to unfractionated heparin in past 10 years. The 4T-score of our patient was 1 (4T-score <4 has a negative predictive value of 97–99%). Testing for HIT, including HIT antibody panel or anti-PF4-heparin enzyme immunoassays have a high negative predictive value and a low positive predictive value, and unnecessary testing should be avoided

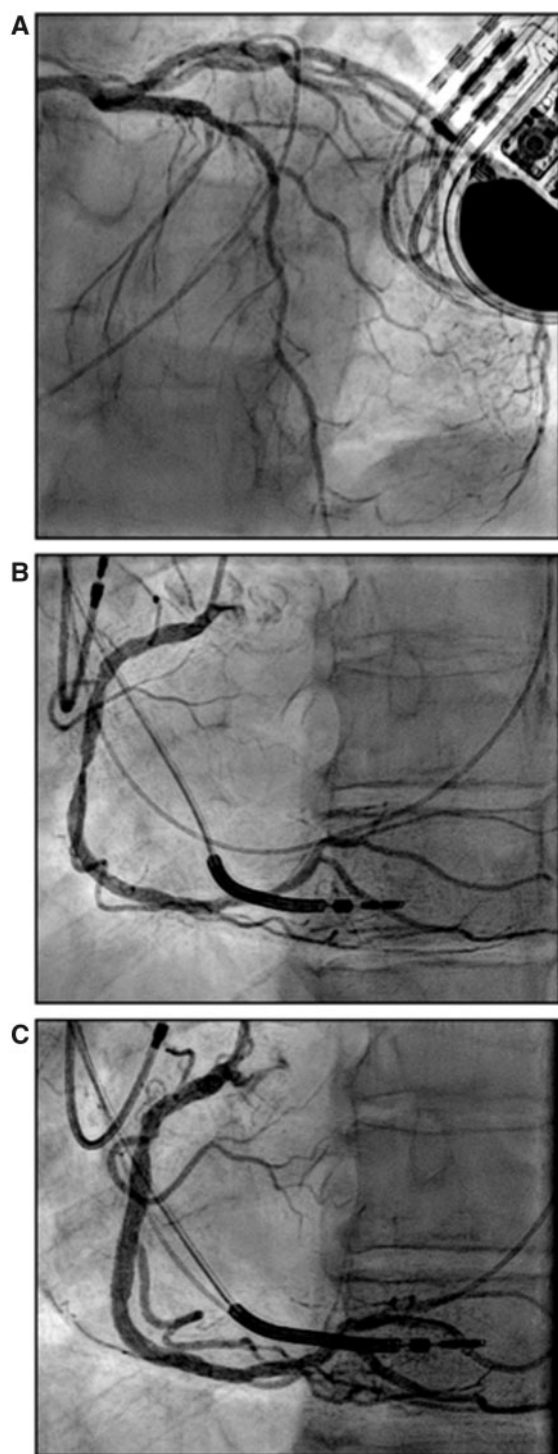


Figure 2 (A) Left anterior oblique—cranial projection of left coronary system. (B) Left anterior oblique projection of the right coronary artery, pre-intervention. (C) Left anterior oblique projection of the right coronary artery after stent placement.

by combining the HIT antibody testing with pre-test probability scores, i.e. testing for HIT antibodies in patients at intermediate-high probability of HIT to avoid false positives.⁶ GPI-induced

thrombocytopenia often occurs rapidly within first few hours of drug administration and can be severe (platelet $<20 \times 10^3/\mu\text{L}$),⁴ whereas thienopyridines usually cause thrombotic thrombocytopenic purpura (TTP) characterized by severe thrombocytopenia, microangiopathic haemolytic anaemia, fever, renal, and neurologic abnormalities,⁷ none of which were present in our patient. Our patient received intravenous heparin for atrial flutter ablation 7 months after the above-mentioned hospitalization and did not have thrombocytopenia, ruling out HIT. In addition, the rapid improvement and maintenance of platelet count after discontinuation of ticagrelor, point to ticagrelor being the most likely cause of our patient's profound thrombocytopenia.

Prior published cases have shown thrombocytopenia as a very rare side effect associated with ticagrelor. In the cases reported by Doğan et al.⁸ and Wang et al.,⁹ the mechanism of development of thrombocytopenia was TTP, which was ruled out in our patient. Siao et al.¹⁰ also reported severe thrombocytopenia with ticagrelor administration through unclear mechanisms that were probably similar to our patient. However, it is important to note that the patient reported by Siao et al.¹⁰ developed thrombocytopenia 2 weeks after continued administration of ticagrelor as opposed to our patient who developed absolute thrombocytopenia within hours of a single dose of ticagrelor administration. To the best of our knowledge, our case is the first case of profound thrombocytopenia hours after administration of a single loading dose of ticagrelor and resolution with drug discontinuation.

Conclusion

Ticagrelor has potential to cause profound thrombocytopenia even with a single loading dose. Our case points to an extremely rare but important severe side effect of ticagrelor that should be considered in the differential diagnosis of post-PCI thrombocytopenia that can have important therapeutic implications.

Lead author biography



Mahin R. Khan, MD, is currently a general cardiology fellow at McLaren-Flint/Michigan State University and attained his medical degree from King Edward Medical University, Pakistan in 2014. His areas of interest include percutaneous interventions in complex patient populations including patients with unprotected left-main coronary artery disease, older adults, and patients with left ventricular systolic dysfunction.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Table 2 Common causes, mechanism, and management of post-percutaneous coronary intervention thrombocytopenia

Causes	Mechanism	Management
Pseudo-thrombocytopenia	EDTA in the specimen tube or the low temperature of the laboratory specimen causing platelet aggregation	Platelet clumping on PBS Recollect blood sample with citrate/heparin, maintain the specimen at 37°C
GPIs	Immune-mediated thrombocytopenia	Often rapid onset severe thrombocytopenia Discontinue GPIs
Heparin-associated thrombocytopenia	Direct interaction between heparin and circulating platelets causing platelet clumping (non-immune mediated)	Mild thrombocytopenia ($>100 \times 10^9/L$) within 48–72 h of exposure Resolves within few days despite continued heparin
Heparin-induced thrombocytopenia	Antibodies to platelet factor four-heparin complex (immune mediated)	Clinical diagnosis, 4Ts scoring system helpful ELISA, serotonin release assay supportive Discontinue heparin products immediately
Thienopyridines	Immune mediated	Usually cause TTP Discontinue drug
Intra-aortic balloon pumps	Mechanical destruction of platelets	Platelet count usually stabilizes over 4 days
Cardiogenic shock	Decreased bone marrow production	Manage cardiogenic shock
Cardiopulmonary bypass and ECMO	Platelet dysfunction from artificial membrane oxygenators/mechanical destruction	Usually spontaneous platelet recovery, must rule out other causes (especially HIT)

ECMO, extracorporeal membrane oxygenation; EDTA, ethylenediaminetetraacetic acid; GPIs, glycoprotein IIb/IIIa inhibitors; HIT, heparin-induced thrombocytopenia; PBS, peripheral blood smear; TTP, thrombotic thrombocytopenic purpura.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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