ESC European Society of Cardiology

European Heart Journal - Case Reports (2023) **7**, 1–4
https://doi.org/10.1093/ehjcr/ytad051

**GRAND ROUND**
*Coronary intervention*

# Can platelet count be controlled with ticagrelor in patients with essential thrombocythaemia? A case series

**Samet Yılmaz [1]*, Yakup Çetinkaya [1], Hasan Akkaya [2], and Arif Arısoy [3]**

[1]Cardiology Department, Nigde Omer Halisdemir University Research and Training Hospital, Aşağı Kayabaşı Mahallesi Hastaneler Cad 51100, Niğde Merkez, Nigde, Turkey; [2]Cardiology Department, Nigde Omer Halisdemir University Medicine Faculty Education and Research Hospital, Aşağı Kayabaşı Mahallesi Hastaneler Cad 51100, Niğde Merkez, Nigde, Turkey; and [3]Department of Cardiology, Medical Park Hospital, Yeşilırmak, Vali Zekai Gümüşdiş Blv. No: 29, 60230 Tokat Merkez, Tokat, Turkey

*Received 11 July 2022; first decision 22 August 2022; accepted 25 January 2023; online publish-ahead-of-print 14 February 2023*

**Background** Essential thrombocythaemia (ET) is defined as a myeloproliferative neoplasm with a tendency to haemorrhage and thrombosis. Acute coronary thrombosis can be observed in 1 out of 10 patients. The management of ET patients with acute coronary syndrome (ACS) is a complex clinical condition that requires close follow-up.

**Case summary** **Case-1**: a 52-year-old female patient with a diagnosis of ET with Janus kinase (JAK)–2 mutation, despite using cytoreductive agents, platelet counts could not be controlled. Platelet counts started to follow a normal course with the ticagrelor treatment given after ACS. **Case-2**: a 49-year-old female patient who was given ticagrelor treatment after ACS was found to have JAK-2+ ET. The patient whose platelet count returned to normal after ticagrelor treatment was using a cytoreductive agent before the index event. **Case-3**: a 54-year-old female patient with ET without any genetic mutation. In the patient whose platelet count did not decrease despite ticagrelor treatment and cytoreductive agents given after ACS, platelet counts returned to normal with interferon therapy.

**Discussion** Platelet counts returned to the normal range with ticagrelor treatment given after ACS in patients with JAK+ ET. Monitoring platelet reduction in JAK+ patients with P2Y12 inhibition is thought to be important for new treatment options.

**Keywords** Essential thrombocythaemia • Acute coronary syndrome • Ticagrelor • JAK-STAT pathway • P2Y12 receptor • Case series

**ESC Curriculum** 3.1 Coronary artery disease • 9.9 Cardiological consultations • 3.2 Acute coronary syndrome

## Learning points

- It should be kept in mind that the incidence of acute coronary syndrome (ACS) related to platelet count and functions is substantial in patients with essential thrombocythaemia (ET).
- Conditions that may cause ACS, other than atherosclerosis, should be considered and a multidisciplinary approach should be adopted.
- Patients with ET, given antiaggregant therapy, especially those with Janus kinase mutations, should be followed closely as thrombocytopenia may be seen in the acute or chronic phases.

## Primary specialities involved other than cardiology

Hematology-protection of patients with essential thrombocythaemia from thrombogenic events and new treatment options.

## Introduction

Essential thrombocythaemia (ET) has been defined as Philadelphia-negative myeloproliferative neoplasm (MPN), in the World Health Organization classification, which can progress with

* Corresponding author. Tel: +905428455708, Fax: +903882121411, Email: sametyilmaz.dr@gmail.com
Handling Editor: Silvia Castelletti
Peer-reviewers: Georgios A. Christou; Rafael Vidal-Perez
Compliance Editor: Anas Mohamad Hashem
Supplementary Material Editor: Rafaella Siang

vascular complications, including thrombosis and bleeding.[1] Studies have shown that thrombogenic complications are more common in ET than haemorrhagic complications and the incidence of acute coronary syndrome (ACS) in these patients is 9.4%.[2] Dual antiplatelet therapy (DAPT) is provided after medical follow-up/percutaneous coronary intervention (PCI) in the ACS.[3] Ticagrelor reversibly inhibits the adenosine diphosphate P2Y12 receptor more strongly and rapidly than clopidogrel without the need for metabolic activation.[4] Common side effects include major bleeding, shortness of breath and hyperuricaemia, and ticagrelor-associated thrombocytopenia, which has been reported in several cases.[5] When the literature is examined, there is no case study reporting thrombocyte reduction with ticagrelor in patients with ET. We plan to present an ET case series of two Janus kinase (JAK)-2 (+) patients with a decrease in platelet count and one JAK-2 (−) patient without a decrease in platelet count who had ticagrelor treatment after an ACS diagnosis.

## Timeline

| Timeline | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Until the index event | Essential thrombocythaemia (ET) diagnosis with JAK mutation, for 2 years | ET diagnosis with JAK mutation, for 6 months | ET without JAK mutation, for 1 year |
| ET treatment | ASA+ Anegrelide+Hydroxyurea | ASA+ Anegrelide+Hydroxyurea | ASA+ Anegrelide+Hydroxyurea |
| Index event | A 52-year-old female patient with a 2 year diagnosis of ET was diagnosed with acute anterior myocardial infarction with anterior upper segment elevation in the emergency department, and a percutaneous coronary intervention (PCI) with dual antiplatelet therapy (DAPT) containing ticagrelor was performed | A 49-year-old female patient with a 6 month diagnosis ofET, was diagnosed with acute anterior myocardial infarction with anterior upper segment elevation in the emergency department and PCI was performed with DAPT containing ticagrelor | A 54 years old female patient with a 1 year diagnosis of ET was diagnosed with acute anterior myocardial infarction with anterior upper segment elevation in the emergency room and PCI is was performed with DAPT containing ticagrelor |
| Pre-discharge | Platelet count 700 000 | Platelet count 600 000 | Platelet count 700 000 |
| Month 1 | Referral of the patient with a platelet count of 170 000 to the haematology clinic and reducing the cytoreductive treatment doses | Referral of the patient with 500 000 platelet count to the haematology clinic and continuing without reducing the cytoreductive treatment doses | Referral of the patient with 600 000 platelet count to the haematology clinic and adding anagrelide to cytoreductive therapy |
| Month 6 | The treatment of the patient, whose platelet count was noted as 450 000, continues | The treatment of the patient, whose platelet count was noted as 465 000, continues | The treatment of the patient, whose platelet count was noted as 750 000, continues |
| 9 Month | — | Discontinuation of anagrelide treatment of the patient whose platelet count was followed as 390 000 | — |
| 12 Month | Ticagrelor was removed from the treatment of the patient whose DAPT period had been completed | Ticagrelor was removed from the treatment of the patient whose DAPT period had been completed. (platelet count measured before discontinuation of treatment 440 000) | Ticagrelor was removed from the treatment of the patient whose DAPT period had been completed |
| 18. Month | After ticagrelor treatment was stopped, the patient's platelet count increased, anagrelide and hydroxyurea doses were increased and platelet count was between 630 and 750 000 | *-the follow-up period has not expired yet-* | Interferon treatment was added for the patient whose ticagrelor treatment was discontinued, and the platelet count was observed as 400 000 |

## Case presentation

### Case-1

The platelet count of a 52-year-old female patient diagnosed with ET, without a history of thrombogenic complications, was between 700 × 103/μL (normal range: 150R400) and 1.100 × 103/μL, under treatment with acetylsalicylic acid (ASA) (100 mg 1 × 1), anagrelide (3 × 0.5 mg) and hydroxyurea (2 × 500 mg). JAK-2 mutation was observed in the examinations. After the patient presented to the emergency department with ACS and was given loading doses containing ticagrelor, a left anterior descending artery (LAD) PCI was performed. Since the platelet count of the patient, who was assessed regularly after ACS, was lowered to between 170 and 400 × 103/μL, the dose of the patient's existing haematological drugs was reduced. In the follow-up of the patient who received DAPT for 1 year, a platelet count over 500 × 103/μL was not detected. It was observed that the thrombocyte count of the patient whose DAPT period expired, had increased. Hydroxyurea and anagrelide doses were revised, and platelet counts were between 630 and 750 × 103/μL.

### Case-2

A 49-year-old female patient was diagnosed with JAK-2 (+) ET, with no decrease in platelet count under hydroxyurea (2 × 500 mg) and ASA 1 × 100 mg treatment observed. Despite the initiation of anagrelide (2 × 0.5 mg) treatment, the number of platelets was between 550 and 750 × 103/μL, in the patient to whom interferon treatment was given but who could not tolerate this treatment. Dual antiplatelet therapy treatment containing ticagrelor was initiated after LAD PCI in the patient who presented to the emergency department with ACS in the sixth month after diagnosis. In the follow-up, a decrease was observed in the thrombocyte count. The platelet count of the patient

whose DAPT period continued was between 390 and 500 × 103/μL. When the DAPT period expired, ticagrelor was discontinued, and the platelet count was 440 × 103/μL at the last visit. Although anagrelide treatment was discontinued in the patient with a decrease in platelet count, no increase in platelet count was observed, and no haemorrhagic and thrombogenic complications were observed.

### Case-3

A 54-year-old female patient, who was not found to have a genetic mutation and reactive thrombocytosis during the examination, was diagnosed with ET and treatment of ASA 1 × 100 mg and hydroxyurea (2 × 0.500 mg) was initiated. During the treatment, the patient's platelet count was between 600 and 750 × 103/μL and LAD artery PCI was performed with ACS. No decrease in platelet count was observed in the follow-up of the patient who received DAPT treatment containing ticagrelor. Despite the addition of anagrelide, platelet counts hovered between 550 and 800 × 103/μL. Ticagrelor was removed from the treatment of the patient whose DAPT ended, and a decrease in platelet count of up to 400 × 103/μL was observed with interferon treatment.

## Discussion

In the case series we presented, the decrease in platelet count with ticagrelor treatment in patients with ET and the JAK mutation raised considerable interest in terms of the relationship between the JAK/signal transducer and activator of transcription proteins (STAT) pathway and the P2Y12 receptor family. In addition, the fact that there was no decrease in platelet count with ticagrelor in the case without a JAK mutation could be considered as data that would strengthen the relationship between these pathways. The fact that there were no complications in terms of bleeding in patients whose platelet counts decreased after ticagrelor treatment was important in terms of treatment options for the patient group who were already prone to bleeding.

The production of platelets in bone marrow, their participation in peripheral circulation, and the regulation of their functions are performed through complex intracellular secondary communication pathways. Members of the JAK protein family mediate a series of complex intracellular activations that include homologous units, such as JAK homology domain (JH)-1, which causes phosphorylation-mediated activation, and JH-2, which is normally inactive, blocks the binding of adenosine triphosphate and/or substrates when regulating the JH-1 subdomain.[6,7] JAK-2 receptors and mutations in the stat protein family that mediate intracellular phosphorylation and over-activation of the JAK/STAT pathway are the main factors for MPN.[8]

The P2Y receptor family, which plays a major role in platelet functions, haemostasis, and thrombogenicity, is located on the platelet surface and acts as a chemoreceptor for adenosine diphosphate. P2Y12 receptors, which mediate platelet aggregation with cyclic adenosine monophosphate-mediated activation, are the target of thienopyridine group drugs used as antiplatelet agents as a result of this mechanism. Interestingly, when the literature is examined, it is found that it has been suggested that P2Y12 receptor inhibition or hereditary absence reduces cancer development and prevents metastasis *in vivo* rat models.[9,10] When the pilot study conducted by Chang *et al.*[11] in 2013 was examined, it was suggested that the defective P2Y12 pathway in MPNs may have been associated with the bleeding tendency in this patient group. For the possible connection between P2Y12 and JAK/STAT pathways in MPN patients, more comprehensive studies would be needed in line with the study examined at the molecular level and the cases we presented clinically.

Finally, clopidogrel and heparin-associated thrombocytopenia (HIT) cases after ACS were observed in our clinical practice, but ticagrelor-associated thrombocytopenia had rarely been reported in the literature.[12–14] Common side effects of ticagrelor include bleeding, dyspnoea, gynaecomastia, and rarely thrombotic thrombocytopenic purpura. Although extremely rare, deep thrombocytopenia may occur within hours of having had ticagrelor.[15] Other causes (such as HIT, ASA, viral infections, cardiogenic shock, use of intra-aortic balloon pump) that may cause platelet decrease in JAK-2 (+) patients with norm thrombocytosis in platelet count were excluded and no pathology was detected in other haematological series during follow-up.[14,15]

## Conclusion

With ticagrelor treatment after ACS, a decrease in platelet count was observed in JAK (+) patients, and although anagrelide and hydroxyurea doses were reduced, platelet count was observed to be within normal limits. Whether the ticagrelor molecule could be a treatment option in ET or whether it could replace ASA in prophylaxis in terms of thrombogenic events has aroused interest after these cases. Future studies would shed light on clinical practice, in terms of the connection between the JAK-2 mutation and the P2Y receptor family with these mechanisms.

## Lead author biography

Samet Yılmaz. I am 31 years old. In 2014, I graduated from Kocaeli University Medical School and continued my studies in clinical residency in Cardiology at Gaziosmanpaşa University. I graduated in 2020 as a cardiologist. Since my residency years, I have participated in clinical studies and prepared oral/poster papers. Currently, I have been assigned by the Ministry of Health of the Republic of Turkey to work at the Kyrgyzstan-Turkish Friendship Hospital and to transfer my knowledge. In my free time I like to play electric guitar and snowboard.

## Supplementary material

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


### Acknowledgements

For his contribution in the evaluation of haematological parameters, our thanks to Dr Ahmet Emre Eşkazan.


**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

**Consent:** The authors confirm that written consent for the submission and publication of this case series, including images and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** None declared.


**Funding :** None declared.


### References


1. Rumi E, Cazzola M. How I treat essential thrombocythemia. *Blood* 2016;**128**: 2403–2414.
2. Camacho FJ, Hernández N, Díaz E, Vázquez R. Essential thrombocythemia and acute myocardial infarction. *Rev Esp Cardiol* 2009;**62**:583–585.
3. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, *et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease

of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;**39**:213–260.
4. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, *et al.* Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 2010;**375**:283–293.
5. Granger CB, Berger PB. Understanding the adverse effects of ticagrelor in practice. *JAMA Cardiol* 2016;**1**:381–383.
6. Tamiya T, Kashiwagi I, Takahashi R, Yasukawa H, Yoshimura A. Suppressors of cytokine signaling (SOCS) proteins and JAK/STAT pathways: regulation of T-cell inflammation by SOCS1 and SOCS3. *Arterioscler Thromb Vasc Biol* 2011;**31**:980–985.
7. de Freitas RM, da Costa Maranduba CM. Myeloproliferative neoplasms and the JAK/STAT signaling pathway: an overview. *Rev Bras Hematol Hemoter* 2015;**37**:348–353.
8. Gari M. The role of Janus Kinase 2 (JAK2) in the pathologenesis of myeloproliferative disorders. *J King Abdulaziz Univ Med Sci* 2009;**16**:3–19.
9. Mezouar S, Darbousset R, Dignat-George F, Panicot-Dubois L, Dubois C. Inhibition of platelet activation prevents the P-selectin and integrin-dependent accumulation of cancer cell microparticles and reduces tumor growth and metastasis in vivo. *Int J Cancer* 2015;**136**:462–475.
10. Gebremeskel S, LeVatte T, Liwski RS, Johnston B, Bezuhly M. The reversible P2Y12 inhibitor ticagrelor inhibits metastasis and improves survival in mouse models of cancer. *Int J Cancer* 2015;**136**:234–240.
11. Chang H, Shih LY, Michelson AD, Dunn P, Frelinger AL, Wang PN, *et al.* Clinical and laboratory significance of defective P2Y(12) pathway function in patients with myeloproliferative neoplasms: a pilot study. *Acta Haematol* 2013;**130**:181–187.
12. Siao WZ, Chuang WY, Su CH, Huang SF, Tu WK, Chan KC. A rare case of ticagrelor-induced profound isolated thrombocytopenia. *Acta Cardiol Sin* 2017;**33**:556–558.
13. Doğan A, Özdemir B, Bal H, Özdemir E, Kurtoğlu N. Ticagrelor-associated thrombotic thrombocytopenic purpura. *Anatol J Cardiol* 2017;**17**:73–74.
14. Wang X, Zhang S, Li L, Hua J, Zhu L, Li L, *et al.* Ticagrelor-induced thrombotic thrombocytopenic purpura: a case report and review of the literature. *Medicine* 2018;**97**: e11206.
15. Khan MR, Adhikari G, Khan H, Changezi HU. A case report of absolute thrombocytopenia with ticagrelor. *Eur Heart J Case Rep* 2020;**4**:1–5.