

A rare but serious complication of ticagrelor therapy: a case report

Manfredi Arioti *, Giovanni Sirianni , Maria Luisa Laudisa , and Nicoletta Bianca De Cesare 

Dipartimento di Cardiologia, Policlinico San Marco, Zingonia, Gruppo San Donato

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Background

Ticagrelor is a widely used P2Y₁₂ inhibitor and represents a fundamental therapeutic agent in acute coronary syndrome treatment and selected post-percutaneous coronary intervention (PCI) cases. Dyspnoea and bradycardia are the most common side effects but the latter has been reported to be of trivial clinical significance

Case summary

A 51-year-old gentleman underwent PCI to left anterior descending and obtuse marginal for unstable angina receiving a loading dose of ticagrelor (180 mg). During hospital stay, whilst on telemetry monitoring, a 16 s long, symptomatic, asystolic ventricular standstill was recorded prompting ticagrelor interruption and a switch to prasugrel.

Discussion

Despite ventricular pauses have been reported in dedicated analyses of Phase III trials, no apparent clinical consequences were documented. However, several reports have shown that significant brady-arrhythmic events might be linked to ticagrelor administration presenting both as sino-atrial and atrio-ventricular conduction disturbances. We report a case of asystole occurring 36 h after the administration of a loading dose.

Keywords

Ticagrelor • Side effect • Acute coronary syndrome • Asystole • Case report

Learning points

- Despite being generally safe, rare but potentially serious side effects of a common use drug, as ticagrelor, should be acknowledged.
- Although asymptomatic ventricular pauses have been described, we report a long, symptomatic, ventricular asystolic standstill occurring 36 h following ticagrelor loading dose administration.
- Drug interruption leads to the absence of further episodes.

Introduction

P2Y₁₂ inhibitors are a mainstay of acute coronary syndrome (ACS) management and more in general of post-percutaneous coronary intervention (PCI) therapy nowadays. Clopidogrel, once the only option, has now been joined and largely substituted in the acute

coronary syndrome setting, by more potent medications such as ticagrelor and prasugrel as indicated in the guidelines.¹ Ticagrelor, in contrast to the other agents, is a direct and reversible inhibitor of platelet activation through P2Y₁₂ receptor.² Despite everyday use, rare but potentially significant side effects of such medication should be always kept in mind.

*Corresponding author. Tel: +39 347 1680527, Email: manfredi.arioti@gmail.com

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We present a case of ticagrelor induced asystole in a 51-year-old gentleman who underwent PCI for unstable angina.

Timeline

Admission to cardiology ward	Electrocardiogram showing widespread subendocardial ischaemia, in light of unstable symptoms patient loaded with ticagrelor 180 mg
1 h after admission	Urgent coronary angiogram for recurrent angina at rest. Coronary angiogram showed severe narrowing in mid-left anterior descending (LAD) with TIMI 1 flow downstream and severe OM1 stenosis
2 1/2 h after admission	Percutaneous coronary intervention to LAD and OM1 with drug-eluting stent implantation
36 h after admission	Patient complained of lightheadness and sweating, telemetry monitoring showed a 16 s asystolic ventricular pause. Ticagrelor halted and switched to prasugrel. A temporary pacing line was inserted.
5 days after admission	Patient dismissed home without further brady-arrhythmic episodes registered

Case presentation

XS, a 51-year-old gentleman, came to our attention complaining of several weeks of worsening angina now occurring upon minimal exertion. Hypertension was his only cardiovascular risk factor actively treated with an angiotensin converting enzyme (ACE) inhibitor. No other relevant past medical history was noted. Physical examination was unremarkable highlighting clear heart sounds with no added murmurs and normal lung sounds. His blood pressure was 140/85 mmHg whilst his electrocardiogram (ECG), upon presentation, showed normal sinus rhythm (98 b.p.m.) with widespread ST segment depression consistent with diffuse subendocardial ischaemia (*Figure 1*) and a first troponin sample was below the limit of significance. Given the presentation with progressively worsening angina (unstable angina) and the ECG which suggested a large area of myocardium at jeopardy the patient was loaded with aspirin 300 mg and ticagrelor 180 mg and, following a new anginal episode at rest, a decision was made to undergo urgent invasive coronary angiography. The investigation highlighted a left dominant circulation with a severe mid-left anterior descending narrowing with reduced distal coronaryflow [thrombolysis in myocardial infarction (TIMI) 1] and a severe, large, first obtuse marginal (OM1) stenosis which were both treated with drug-eluting stents implantation with excellent angiographic result, no complications and resolution of ECG anomalies (*Figures 2 and 3*). A statin (atorvastatin 40 mg) was started as part of standard ACS therapy on top of dual antiplatelet therapy (DAPT) and ramipril, of interest no beta-blocker or other rate limiting drugs were commenced. The first 24 h a free of complications, no arrhythmic episode was registered by telemetry monitoring, a routine echocardiogram was unremarkable showing normal ejection fraction in the absence of regional wall motion

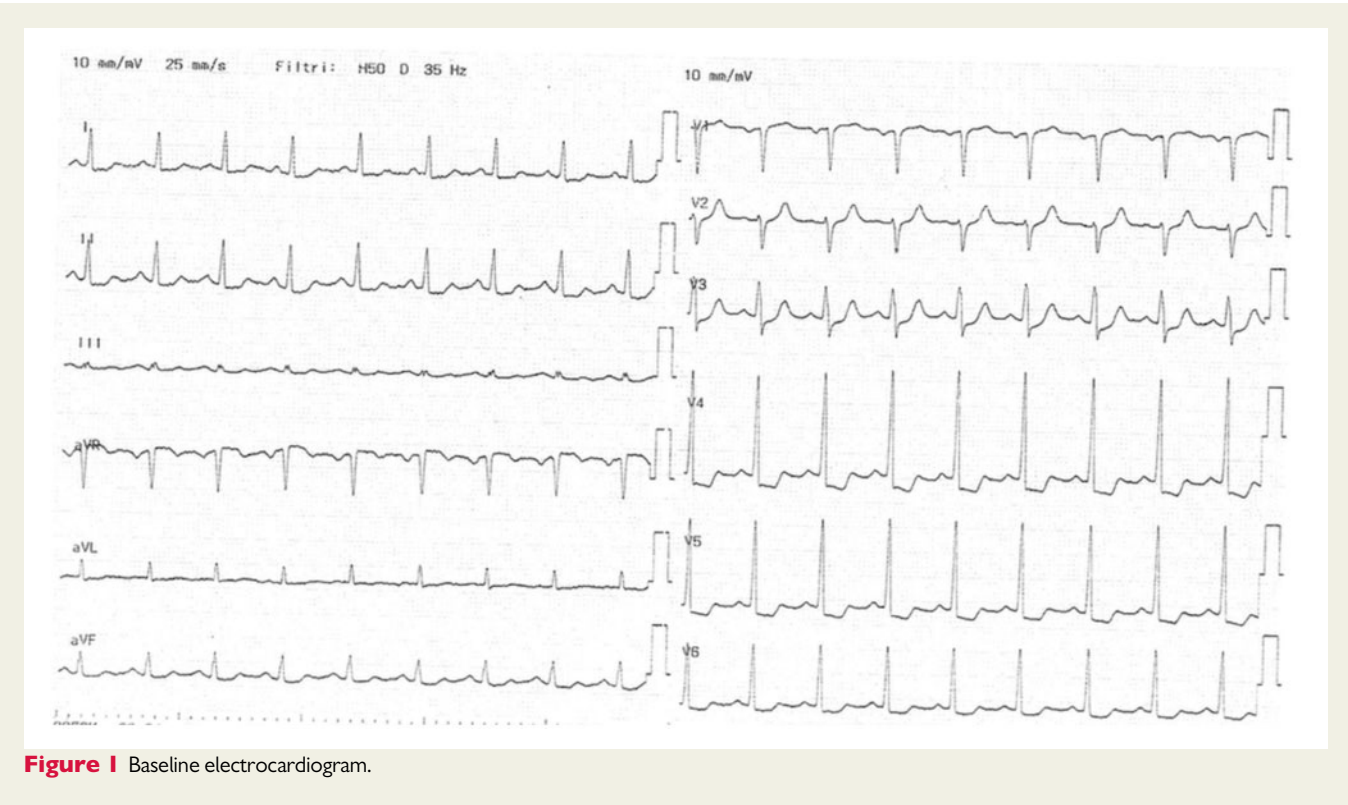


Figure 1 Baseline electrocardiogram.

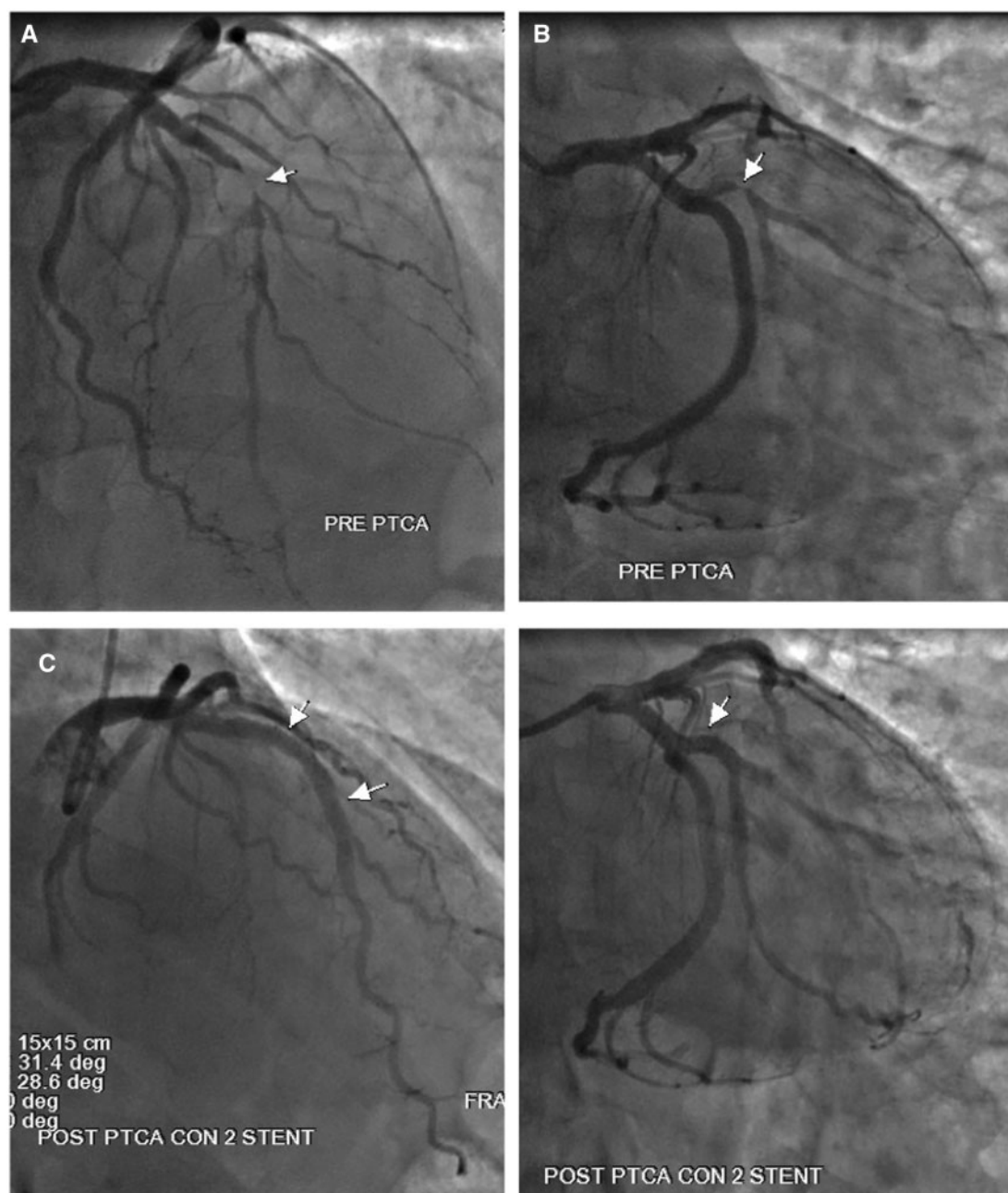


Figure 2 (A) Left anterior descending stenosis; (B) OM1 stenosis; (C) post-percutaneous coronary intervention left anterior descending; (D) post-percutaneous coronary intervention OM1.

abnormalities or major valvular dysfunctions, and the patient received two standard doses of ticagrelor (8 a.m. and 6 p.m.). On the second night of hospital stay, whilst lying in bed, the patient complained of the sudden feeling of lightheadness and profound sweating and called out for medical assistance. Upon medical review the patient denied any other symptoms, in particular any pain or angina, no ischaemic changes were noted on the ECG whilst telemetry monitoring review highlighted a 16 s long asystolic pause (Figure 4). The episode was self-limited with return of sinus rhythm thereafter. Electrolytes were checked and found to be within normal limits. Hence, new

medications were investigated looking for a possible explanation to the unexpected asystole given also the patient had no history of syncope. Ticagrelor, due to its brady-arrhythmic effect was suspected to be involved and was therefore halted shifting the patient to prasugrel following the administration of a 60 mg loading dose. A temporary pacing line (TPL) was inserted fearing possible further episodes. However, no new brady-arrhythmic episodes were noted on telemetry monitoring and the unused TPL was removed 24 h later. After 2 further days of monitoring, the patient was discharged home on Day 5 post-PCI in excellent general conditions.

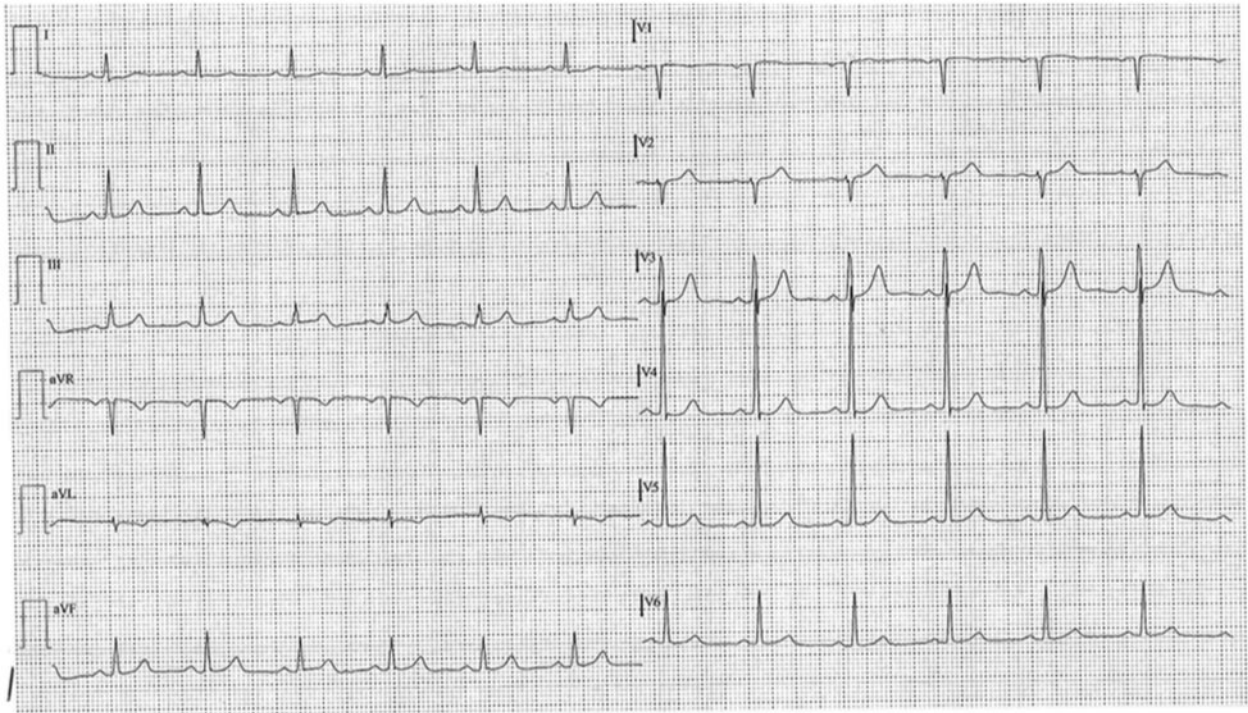


Figure 3 Electrocardiogram post-percutaneous coronary intervention.



Figure 4 Asystole registered on telemetry.

Discussion

Ticagrelor is currently part of every cardiologist's armamentarium being used in most ACS patients as adjunctive therapy with aspirin in DAPT regimens. Notwithstanding its efficacy and safety,³ the drug has some side effects with dyspnoea being the most common and well-known occurring in approximately 10–15% of patients and generally being mild or moderate and fully reversible. Bradycardia is another described side effect with ventricular pauses over 3 s occurring in around 6% of patients during the first week of treatment and ventricular pauses over 5 s occurring in around 2% of patients.³ Such pauses have been reported to be rarely, if at all, symptomatic and clinically relevant.⁴ On the other hand, however, several case reports have emerged over the past years showing the possibility of ticagrelor induced, serious brady-arrhythmic side effects, both as an early effect, following a loading dose or in a delayed fashion.^{5–8} Moreover, such events are reported in both patients with and without baseline conduction abnormalities, although the presence of the latter has been associated with a higher incidence of brady-arrhythmias⁹ and patients at risk of bradycardia were actually excluded from the PLATO trial.³

The mechanism underlying ticagrelor induced bradycardia is incompletely understood and has been related both to its capability in increasing adenosine levels by inhibiting cellular adenosine uptake through the ENT1 transporter¹⁰ and to a possible, direct, cardioinhibitory effect on both automaticity and conduction.

Despite uncertainty in determining the mechanism and previous reports of low clinical significance of ticagrelor induced ventricular pauses, we hereby document a case of symptomatic asystole in a man with no baseline ECG conduction disturbances, a low likelihood for brady-arrhythmic complications, treated with ticagrelor following PCI for unstable angina. The fact that, in the present case, drug cessation resulted in the absence of further brady-arrhythmic episodes, makes it possible to establish a clear causality link. Interestingly, it should be noted that no other side effect, and in particular dyspnoea was reported by our patient.

Expanding on previous literature, our case manifested with asystolic ventricular standstill occurring 36 h following the administration of the loading dose and following the administration of two further standard (90 mg) doses. Such 'intermediate' time frame for ticagrelor-related asystole has not yet been reported to our knowledge with previous publications documenting ventricular asystolic pauses seen close after the administration of a loading dose.

Conclusions

In conclusion, the present case report highlights the need to maintain a high level of awareness towards a rare but potentially serious side effect of ticagrelor therapy.

Lead author biography



Manfredi Ariotti was born in Rome in 1989, he achieved his medical degree in 2014 from Università di Roma La Sapienza. From 2015 to 2019, he completed his cardiology residency program at the Catholic University of the Sacred Heart in Rome. After working as an Interventional Cardiology Fellow at Hairmyres University Hospital in Glasgow UK from April to November 2019, he was appointed as full time Interventional Cardiology Consultant at Policlinico San Marco.

Supplementary material

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

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 submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidelines.

Conflict of interest: none declared.

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