

Ticagrelor-Associated Urticaria

To the Editor:

Dual antiplatelet therapy (DAPT) with potent P2Y₁₂ inhibitor (ticagrelor and prasugrel) is recommended as a class I indication in the European Society of Cardiology after primary percutaneous coronary intervention (PPCI).¹ Furthermore, DAPT is beneficial for patients with high-risk PCI (contemporary criteria defined by the Interventional Council of American College of Cardiology).² Ticagrelor is a well-tolerated P2Y₁₂ inhibitor, with an established safety profile, and hypersensitivity to this adenosine diphosphate receptor blocker is rarely reported in the literature. We report a case of ticagrelor hypersensitivity and conducted a systematic review on the incidence of this rare occurrence.

A 62-year-old man underwent PCI from proximal to the middle right coronary artery with 2 drug-eluting stents. He was loaded with 300 mg of aspirin and 180 mg of ticagrelor before PCI. He developed a progressive rash on his body with urticaria and hives the next day, but there were no respiratory symptoms (Figure 1). He was previously taking aspirin (75 mg qDay); rosuvastatin (20 mg qHS); bisoprolol (5 mg qDay), for stable angina; and tamsulosin (0.4 mg qDay), for benign prostatic hyperplasia. There was no history of allergy and asthma or other relevant diseases. On the third day, he developed a cough and shortness of breath. His chest had an end-expiratory wheeze. He was only treated with loratadine (10 mg qDay) and prednisolone (0.5 mg/kg) for a 6-day taper. Ticagrelor was stopped, and he was loaded with 300 mg of clopidogrel which was maintained at 75 mg qDay. After 2 days, the rash started settling, and by the tenth day, his rash was gone.

This systematic review was guided by the Preferred Reporting Items for Systematic reviews and Meta-analyses (see **Figure S1, Supplemental Digital Content**, <http://links.lww.com/AJT/A115>).³ Data were obtained from PubMed, Scopus, and CINAHL with various Medical Subject Headings (MeSH) keywords. No language or time filters were placed, and the MeSH comprised "Ticagrelor" AND "Hypersensitivity" OR "Allergy" OR "Angioedema" OR "Rash" OR "Urticaria" OR "Hives." The extracted articles were reviewed by 2 investigators (J.M. and S.M.J.Z.), and abstracts, reviews, and conference proceedings were excluded. The final search ended on April 4, 2022. The baseline study and patient-level characteristics

were extracted for age, gender, type of hypersensitivity, and substituted drug. National Heart, Lung, and Blood Institute quality assessment tools were used for case reports/case series and observational studies, and statistical analysis was performed on Statistical Package for Social Sciences version 26 (IBM Corp, Armonk, NY).⁴

This systematic review identified 6 case reports (n = 6) and 1 case series (n = 1/156) of patients with ticagrelor hypersensitivity who were subsequently treated with an alternative P2Y₁₂ inhibitor. Table 1 summarizes the clinical features of these patients.^{5–11} All 7 patients were male who were 44–73 years of age; 4 presented with acute coronary syndrome, whereas 2 had stable angina, and 5 of 6 patients in the case reports had undergone a PCI with a drug-eluting stent. Hypersensitivity manifestations included rash (n = 4), urticaria (n = 1), angioedema (n = 2), periorbital edema (n = 1), and hemorrhagic bullae (n = 2). Clopidogrel was successfully used without cross-reactivity in all patients.

Hypersensitivity reaction to ticagrelor is relatively rare ($\leq 1/1000$) as mentioned in the Drug Information Portal (U.S. Library of Medicine), and the first case of hypersensitive reaction was reported by Quinn et al⁵. In the present case, the patient suffered from rash and urticaria after the first loading dose of ticagrelor. The rash improved after discontinuation of the drug and switching it with clopidogrel.



FIGURE 1. Rash after the first dose of ticagrelor (24 hours).

Table 1. Study characteristics.

Author (yr)	Study type	Age (yrs)	Gender	Cardiac presentation	Type of stent placed	Type of reaction	Time to reaction (h)	Time to resolution (d)	Follow-up/ outcome
Quinn (2014) ⁵	Case report	65	M	NSTEMI	1*DES (everolimus)	Diffuse, pruritic, exanthematous rash	24	7	Resolved by switching to clopidogrel
Ikram (2016) ⁶	Case report	73	M	CCS	1*DES (everolimus)	Progressive, multiple, painful, hemorrhagic, bullae on the palms of both hands	24	12	Resolved by switching to clopidogrel
Dai (2017) ⁷	Case report	68	M	CCS	3*DES (2*paclitaxel and 1*sirolimus)	Pruritic, exanthematous rash	48	10	Resolved by switching to prasugrel
Seechean (2017) ⁸	Case report	69	M	NSTEMI	—	Worsening chest pain, sudden-onset respiratory distress, generalized urticaria, periorbital edema, and angioedema	1	1	Resolved by switching to clopidogrel
Pirnavan (2018) ⁹	Case report	66	M	Unstable angina	1*DES (type not reported)	Angioedema	4	—	Resolved by switching to clopidogrel
Namazi (2020) ¹⁰	Case series	—	—	Acute coronary syndromes	—	Skin rash (1/156)	—	—	—
Kavali (2021) ¹¹	Case report	44	M	STEMI	1*DES (type not reported)	Translucent bullous lesions with surrounding erythema on the distal flexor aspect of the right forearm	—	14	Resolved by switching to clopidogrel

DES, drug eluting stent; CCS, chronic coronary syndrome.

Clopidogrel and ticagrelor are both P2Y₁₂ inhibitors; however, the chemical structures and site of action of the 2 drugs differ.⁷ In patients with ticagrelor hypersensitivity, cross-reactivity among other P2Y₁ inhibitors (clopidogrel, ticlopidine, and prasugrel) might be less likely as they are derivatives of thienopyridines. Ticagrelor is a direct-acting, reversible P2Y₁₂ receptor antagonist, whereas clopidogrel's mechanism of action depends on the activation of an active metabolite by the cytochrome P450 system.⁷ Therefore, the chance of cross-reactivity is low between the 2 drugs. Likewise, prasugrel can be substituted for ticagrelor, as it is a prodrug, which is rapidly metabolized, and is effective in most individuals. However, this is not available in our country, so we substituted ticagrelor with clopidogrel, obtaining a favorable outcome.

In conclusion, clopidogrel represents a viable treatment option in the management of ticagrelor hypersensitivity. While prasugrel can also be used successfully in most patients with ticagrelor hypersensitivity, clinicians should be aware that cross-reactivity between various thienopyridines may occur occasionally. Our systematic search revealed that only 7 cases of ticagrelor hypersensitivity have been published in the literature; however, US Food and Drug Administration has reported ticagrelor hypersensitivity in 34 patients. These reports are either not published or are present as abstracts. Therefore, they did not meet the inclusion criteria for this systematic review.

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REFERENCES

1. Valgimigli M, Bueno H, Byrne RA, et al. ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 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.
2. Atkinson TM, Ohman EM, O'Neill WW, et al. Interventional Scientific Council of the American College of Cardiology. A practical approach to mechanical circulatory support in patients undergoing percutaneous coronary intervention: an interventional perspective. *JACC Cardiovasc Interv*. 2016;9:871–883.
3. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
4. National Institutes of Health. Quality assessment tool for observational cohort and cross-Sectional studies; 2021. Available at: <https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort>. Accessed April 2, 2022.
5. Quinn KL, Connelly KA. First report of hypersensitivity to ticagrelor. *Can J Cardiol*. 2014;30:957.e3–e4.
6. Ikram S, Veerappan Kandasamy V. Ticagrelor-induced sweet syndrome: an unusual dermatologic complication after percutaneous coronary intervention. *Cardiovasc Interv Ther*. 2017;32:244–246.
7. Dai J, Lyu S, Ge C. Hypersensitivity to ticagrelor and low response to clopidogrel: a case report. *Asia Pac Allergy*. 2017;7:51–53.
8. Seecheran R, Seecheran V, Persad S, et al. Ticagrelor-Induced angioedema: a rare and unexpected phenomenon. *Case Rep Cardiol*. 2017;2017:7612713.
9. Piranavan P, Kaur NJ, Marmoush F, et al. Ticagrelor-induced angioedema after percutaneous coronary intervention in a patient with a history of ischemic stroke and low response to clopidogrel: a rare dilemma. *Cureus*. 2018;10:e3720.
10. Namazi MH, Saemifard F, Pishgahi M. One-month outcomes of cases receiving ticagrelor after percutaneous coronary intervention; a case series. *Arch Acad Emerg Med*. 2020;8:e42.
11. Kawall T, Seecheran R, Seecheran V, et al. Suspected ticagrelor-induced bullous fixed drug eruption. *Cureus*. 2021;13:e13890.