RESEARCH LETTER

Impact of psoriasis on ticagrelor platelet activity versus clopidogrel in patients with chronic coronary syndromes treated via percutaneous coronary intervention

Rafał Januszek[1,2], Michał Zabojszcz[3], Sylwia Cyran-Stemplewska[3], Beata Kręcisz[3], Stanisław Bartuś[1,4], Zbigniew Siudak[3]

1 Department of Cardiology and Cardiovascular Interventions, University Hospital, Kraków, Poland
2 Department of Clinical Rehabilitation, University of Physical Education, Kraków, Poland
3 Collegium Medicum, Jan Kochanowski University, Kielce, Poland
4 Department of Cardiology and Cardiovascular Interventions, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland

Correspondence to:
Rafał Januszek, MD, PhD, Department of Cardiology and Cardiovascular Interventions, University Hospital in Kraków, ul. Jakubowskiego 2, 30-688 Kraków, Poland, phone: +48 12 400 22 50, email: jaanraf@interia.pl
Received: July 26, 2021.
Revision accepted: August 13, 2021.
Published online: October 6, 2021.
Pol Arch Intern Med. 2021; 131 (10): 16105
doi:10.20452/pamw.16105

Introduction The link between severe psoriasis and increased risk of cardiovascular mortality, independent of traditional risk factors, has been proven in the literature.[1] One of the major mechanisms attributed to an increased risk of atherosclerosis progression in patients with severe psoriasis is an elevated level of systemic inflammation.[2] Psoriasis is also associated with noncalcified coronary plaque burden and the prevalance of high-risk coronary plaque.[3] The differences between ticagrelor and clopidogrel with regard to the effect on platelet activity assessed by $P2Y_{12}$ reaction units (PRU) have been demonstrated among patients with acute coronary syndromes (ACSs), with ticagrelor showing a significantly better inhibitory effect.[4] It has been further proven that certain concomitant diseases, such as diabetes mellitus, additionally reduce the inhibitory effect of clopidogrel, but not ticagrelor.[5] In the current guidelines of the European Society of Cardiology on antiplatelet therapy, clopidogrel is considered the default $P2Y_{12}$ inhibitor for patients with chronic coronary syndrome (CCS) and treated with percutaneous coronary intervention (PCI).[6] However, ticagrelor or prasugrel therapy is often applied in patients with CCS after elective PCIs who are at a very high risk of in-stent thrombosis or restenosis.

In the current study, we aimed to assess the impact of psoriasis on antiplatelet activity of ticagrelor versus clopidogrel among patients with CCS treated with PCI.

Patients and methods **Patient selection, intervention, and outcome measures** Patients with CCS and treated with elective PCI were included in the current cohort study. The recruitment time was from September to December 2019. Study participants were assessed based on the presence of psoriasis as shown in the patient flow chart (Supplementary material, *Figure S1*). The presence of psoriasis was defined according to the medical history, as reported by the patient at the time of enrolment. Patients were randomized (1:1) to receive ticagrelor 90 mg twice a day and clopidogrel 75 mg once a day, with a preceding loading dose of 180 mg in the ticagrelor group and 600 mg in the clopidogrel group. We collected consecutive patients with and without psoriasis assuming that the proportion of patients without psoriasis would be twice as high. Randomization was not stratified according to the presence of psoriasis. Platelet reactivity was measured before saturation with a loading dose and a month after treatment with ticagrelor or clopidogrel. PRU levels were compared between 4 selected groups of patients (ticagrelor + psoriasis, ticagrelor + no psoriasis, clopidogrel + psoriasis, and clopidogrel + no psoriasis). The methodology for quality of life assessment, severity of psoriasis, and measurement of platelet activity is included in Supplementary material, the *Patients and methods* section (references M1–M6). The research was preliminary with the purpose of generating a hypothesis, therefore, no minimum sample size was established. The study complied with the Declaration of Helsinki. The institutional review board as well as the local bioethical committee approved the study. All patients provided their written informed consent to participate in the trial.

Study end points The primary end point regarded PRU levels on treatment with a $P2Y_{12}$ inhibitor for at least 30 days and the percentage PRU reduction from baseline. Additionally, we assessed PRU levels at baseline in order to exclude any potential baseline differences in PRU.

Statistical analysis Continuous variables were reported as medians (interquartile ranges [IQRs]) in the case of asymmetrical distribution, and categorical variables were given as frequencies and percentages. Due to small sample size, differences between groups were compared using the Mann–Whitney test. Ordinal variables were also compared using the Mann–Whitney test. Nominal variables were compared by the χ^2 test or the Fisher exact test if 20% of cells had an expected count of less than 5. *P* values were adjusted to control multiple comparison problem using the Steel–Dwass method for continuous parameters and the Bonferroni correction for categorical parameters. Statistical analyses were performed with JMP, version 16.0.0 (SAS Institute Inc, Cary, North Carolina, United States).

Results Data on baseline characteristics and parameters characterizing patients with psoriasis are presented in Supplementary material, *Tables S1* and *S2*.

Overall group The median (IQR) PRU value did not differ between the clopidogrel and ticagrelor groups at baseline (212.5 [198.4–230.7] vs 193 [174–222]; $P = 0.13$). After 30 days of treatment with a $P2Y_{12}$ inhibitor, the median (IQR) PRU values were greater in the clopidogrel group when compared with the ticagrelor group (121 [81.5–180.5] vs 5 [2–8]; $P < 0.001$). The median (IQR) percentage inhibition from baseline in PRU was greater in the ticagrelor group when compared with the clopidogrel group (97 [96–99] vs 40 [14.2–57.5]; $P < 0.001$) (FIGURE 1A and 1B).

Psoriatic group The median (IQR) PRU value at baseline was comparable among patients treated with clopidogrel and ticagrelor (205 [174–215] vs 190.5 [152–239.2]; $P = 0.89$). After 30-day treatment with a $P2Y_{12}$ inhibitor, the median (IQR) PRU value was greater in the clopidogrel group when compared with the ticagrelor group (155.5 [105.2–205.2] vs 6 [4–9.7]; $P = 0.004$). The median (IQR) percentage inhibition from baseline in PRU was greater in the ticagrelor group when compared with the clopidogrel group (97 [93.2–97.7] vs 19 [6.7–41.2]; $P < 0.001$) (FIGURE 1A and 1B).

Ticagrelor group The median (IQR) PRU value at baseline was comparable between psoriatic and nonpsoriatic patients (190.5 [152–239.2] vs 193 [180–218]; $P = 0.73$). After 30 days of treatment with a $P2Y_{12}$ inhibitor, the median (IQR) PRU value was similar in psoriatic and nonpsoriatic patients (6 [4–9.7] vs 4 [2–8]; $P = 0.21$). The median (IQR) percentage inhibition from baseline in PRU did not differ between the psoriatic and nonpsoriatic patients (97 [93.2–97.7] vs 97 [96–99]; $P = 0.15$) (FIGURE 1A and 1B).

Clopidogrel group The median (IQR) PRU value at baseline was comparable between psoriatic and nonpsoriatic patients (205 [174–215] vs 219 [198.7–233]; $P = 0.18$). After the 30-day treatment with the $P2Y_{12}$ inhibitor, the median (IQR) PRU value was greater in psoriatic compared with nonpsoriatic patients (155.5 [105.2–205.2] vs 109.5 [59.7–149.7]; $P = 0.051$). The mean percentage inhibition at baseline in PRU was lower in psoriatic compared with nonpsoriatic patients (19 [6.7–41.2] vs 49 [20.7–70.7]; $P = 0.01$) (FIGURE 1A and 1B).

Discussion The data from available analyses confirm that the use of ticagrelor and prasugrel in Poland is low. In fact, it is much lower than it would appear from the number of patients undergoing PCI in ACSs.[7] Nevertheless, the use of new $P2Y_{12}$ inhibitors has increased in the recent years among patients with ACS. Conversely, the use of conventional $P2Y_{12}$ inhibitors is very rare in CCS patients undergoing elective PCI, and limited to those at very high risk of thrombosis or restenosis, which remains in line with the current guidelines.[6] The differences in the antiplatelet activity of ticagrelor and clopidogrel are mainly due to the different mechanisms of action. Because ticagrelor does not follow the same metabolic pathway as clopidogrel, there is also a proportion of patients who respond poorly to treatment with that drug.[8] Differences in the effectiveness of ticagrelor and clopidogrel were shown in patients with CCS as well as in subgroups with comorbidities, such as diabetes.[9] A number of available randomized trials showed better effectiveness of ticagrelor compared with clopidogrel with regard to inhibition of $P2Y_{12}$ in patients with ACS. It has also been demonstrated by Bhatt et al[10] that in patients with diabetes, stable coronary artery disease, and previous PCI, ticagrelor added to aspirin reduced cardiovascular death, myocardial infarction, and stroke, although with increased rates of major bleeding. It was also concluded that long-term therapy with ticagrelor—in addition to aspirin—should be considered among patients with diabetes and with a history of PCI who have tolerated antiplatelet therapy, are at high ischemic risk and low risk of bleeding. By contrast, in the recently published results of a large randomized trial by Silvain et al,[11] it has been demonstrated that ticagrelor was not superior to clopidogrel in reducing periprocedural myocardial necrosis after elective PCI in patients with CCS. The results of that study support the use of clopidogrel as the standard of care for elective PCI.

Considering the study limitations, the main weakness of the presented research is the small group of patients, which allows only to consider this study as preliminary, with the purpose of

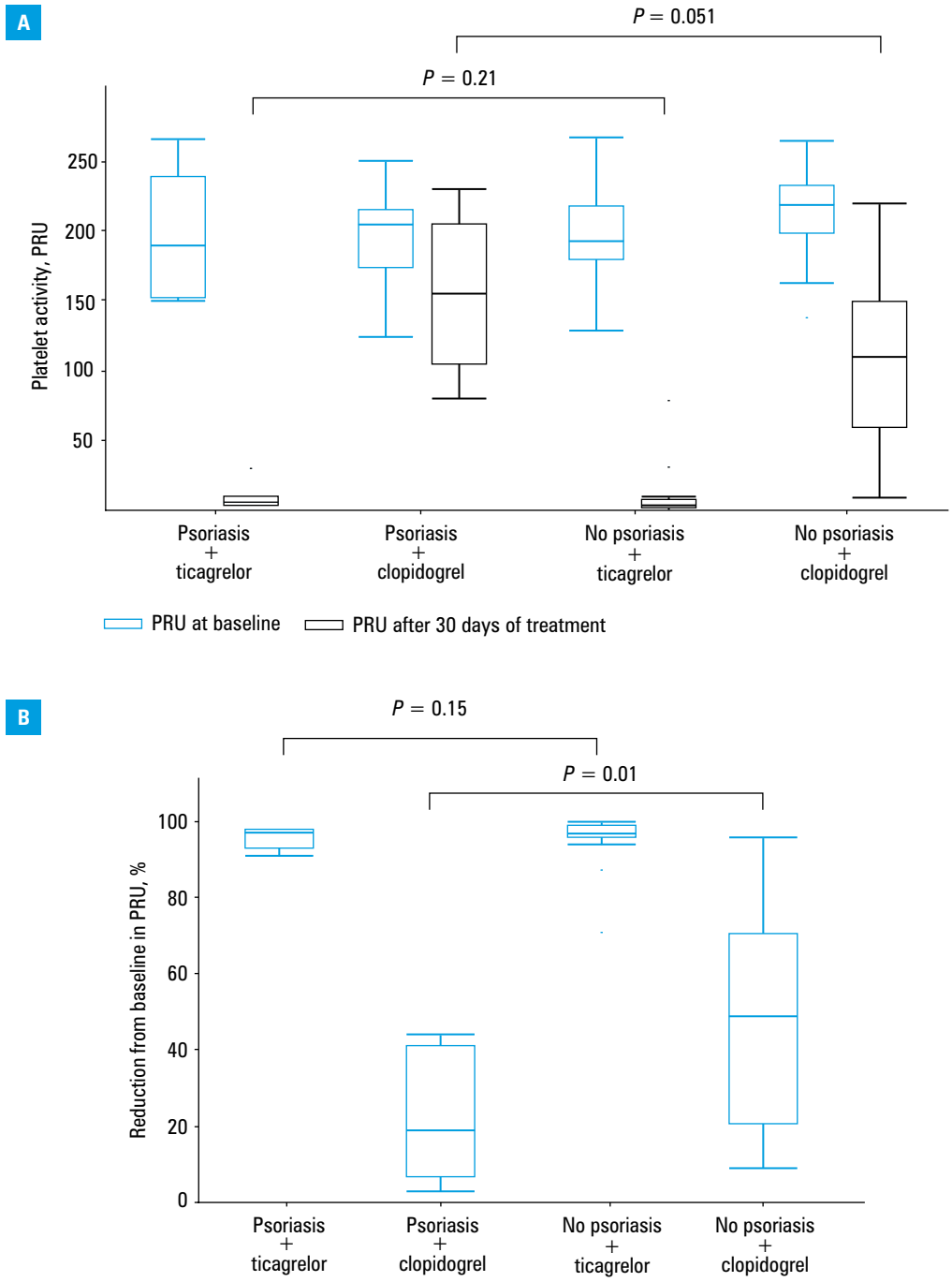

FIGURE 1 **A** – platelet activity expressed in $P2Y_{12}$ reaction units (PRU) among 4 selected groups of patients at baseline and after treatment with a $P2Y_{12}$ inhibitor; **B** – percentage of reduction in PRU at baseline and after treatment with a $P2Y_{12}$ inhibitor in 4 selected group of patients. The horizontal line within the box represents the median sample value. The ends of the box represent the first and third quartiles. The whiskers extend from the ends of the box to the outermost data point that falls within these distances: first quartile – 1.5 × (interquartile range) and third quartile + 1.5 × (interquartile range). If the data points do not reach the computed ranges, then the whiskers are determined by the upper and lower data point values (not including outliers).

generating a hypothesis. Another important aspect is the lack of long-term follow-up to show whether the lower platelet inhibition when using clopidogrel in this particular population is associated with a higher risk of major cardiovascular events.

Conclusions Based on the results of the presented study, psoriasis seems to have no effect on the extent of platelet inhibition by ticagrelor in patients with CCS treated with PCI; however, when treated with clopidogrel, psoriasis could limit its antiplatelet activity.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

ACKNOWLEDGMENTS The study was supported by an Unrestricted Scientific Grant of 2018 by Polish Cardiac Society and Adamed company.

CONFLICT OF INTEREST None declared.

HOW TO CITE Januszek R, Zabojszcz M, Cyran-Stemplewska S, et al. Impact of psoriasis on ticagrelor platelet activity versus clopidogrel in patients with chronic coronary syndromes treated via percutaneous coronary intervention. Pol Arch Intern Med. 2021; 131: 16105. doi:10.20452/pamw.16105

REFERENCES

1 Mehta NN, Azfar RS, Shin DB, et al. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J. 2010; 31: 1000-1006.

2 Lerman JB, Joshi AA, Chaturvedi A, Mehta NN. Coronary plaque characterization in psoriasis reveals high-risk features that improve after treatment in a prospective observational study. Circulation. 2017; 136: 263-276.

3 Späh F. Inflammation in atherosclerosis and psoriasis: common pathogenic mechanisms and the potential for an integrated treatment approach. Br J Dermatol. 2008; 159: 10-17.

4 Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Nat Rev Cardiol. 2015; 12: 30-47.

5 Sweeny JM, Angiolillo DJ, Franchi F, et al. Impact of diabetes mellitus on the pharmacodynamic effects of ticagrelor versus clopidogrel in troponin-negative acute coronary syndrome patients undergoing ad hoc percutaneous coronary intervention. J Am Heart Assoc. 2017; 6: e005650.

6 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.

7 Rakowski T, Siudak Z, Dziewierz A, et al. Contemporary use of $P2Y_{12}$ inhibitors in patients with ST-segment elevation myocardial infarction referred to primary percutaneous coronary interventions in Poland: data from ORPKI national registry. J Thromb Thrombolysis. 2018; 45: 151-157.

8 Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA. 2010; 304: 1821-1830.

9 Clavijo LC, Maya J, Carlson G, et al. Platelet inhibition with ticagrelor versus clopidogrel in Hispanic patients with stable coronary artery disease with or without diabetes mellitus. Cardiovasc Revasc Med. 2015; 16: 450-454.

10 Bhatt DL, Steg PG, Mehta SR, et al; THEMIS Steering Committee and Investigators. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. Lancet. 2019; 394: 1169-1180.

11 Silvain J, Lattuca B, Beygui F, et al; ALPHEUS investigators. Ticagrelor versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS): a randomised, open-label, phase 3b trial. Lancet. 2020; 396: 1737-1744.