

Jacek Kubica¹, Wiktor Kuliczkowski²

on behalf of the authors of the recommendations for medical emergency teams

¹Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

²Institute of Heart Diseases, Wrocław Medical University, Wrocław, Poland

Prehospital treatment of patients with acute coronary syndrome

Previous recommendations from Polish experts in cardiology and emergency medicine regarding pre-hospital treatment of patients with acute coronary syndrome [ACS] were published in 2017 [1] and updated in 2018 [2]. Their purpose was the practical application of the ESC guidelines in Polish reality. The third, successive version of the recommendations, published in this issue of the Medical Research Journal [3] was developed taking into account the 2020 ESC guidelines for the management of ACSs in patients presenting without persistent ST-segment elevation (NSTEMI-ACS) [4] and requires some additional comment as it does not fully comply with the latter. We feel obliged to point out the differences in our position in relation to the ESC guidelines, emphasizing the sources of our criticism.

According to the guidelines, prasugrel should be considered in preference to ticagrelor for NSTEMI-ACS patients who proceed to PCI. This recommendation is solely based on the results of the ISAR-REACT 5 study [5]. Leaving aside serious objections regarding the methodology of this study, the authors of the ESC guidelines do not notice other scientific evidence that does not support the results of the ISAR-REACT 5 study [6–8].

This is particularly true for the results of a meta-analysis by Navarese et al. [9] summarizing the scientific evidence from all available randomized clinical trials and showing a significant mortality reduction for ticagrelor, but not for prasugrel in comparison with clopidogrel in patients with ACS. Thus, in our opinion, the preference for prasugrel over ticagrelor is not sufficiently supported by the evidence.

The ESC guidelines do not recommend routine pre-treatment with a P2Y₁₂ receptor inhibitor in NSTEMI-ACS patients in whom coronary anatomy is not known and an early invasive management is planned. To support this recommendation, the authors cited the ACCOAST trial [10], the SCCAR registry [11] and the ISAR-REACT 5 study [5]. However, analyzing these publications, we do not find sufficient evidence for such a recommendation. The ACCOAST trial demonstrated a lack of any ischaemic benefit for pre-treatment, but instead, a substantially higher bleeding risk with prasugrel pre-treatment in 4033 patients with NSTEMI acute coronary syndromes and a positive troponin level who were scheduled to undergo coronary angiography within 2 to 48 hours after randomization [10]. Nevertheless, according to prespecified subgroups analysis, pretreatment in patients who received the LD of prasugrel earlier than the median delay (15 hours) a 24% reduction in the primary efficacy end-point occurrence (CV death, MI, stroke, urgent revascularization, or the need for rescue therapy with GP IIb/IIIa inhibitors through day 7 after randomization) was observed, while no significant increase in major bleeding rate was found in this subset of patients. In fact, the subset of patients who received pretreatment with prasugrel early was the only group with clear benefit in the ACCOAST trial [10]. In the SCAAR registry, pre-treatment with ticagrelor, prasugrel, and clopidogrel in 64857 NSTEMI-ACS patients did not bring improvement in ischaemic outcomes, but was associated with a significantly increased risk of bleeding [11]. However, whether pre-treatment with P2Y₁₂ receptor antagonists in selected subsets of pa-

Corresponding author: Jacek Kubica, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, e-mail: jkubica@cm.umk.pl

Medical Research Journal 2022; Volume 7, Number 1, 1–2, DOI: 10.5603/MRJ.2022.0014, Copyright © 2022 Via Medica, ISSN 2451-2591, e-ISSN 2451-4101

This article is available in open access under Creative Commons Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.

tients (early vs late treatment, high and-very high risk vs low risk patients) is associated with improvement in clinical outcomes was not established in this study [11].

Finally, in the ISAR-REACT 5 study patients were pretreated with ticagrelor, but not with prasugrel, which does not allow for comparative assessment of the impact of pretreatment with these compounds at all. Thus, in our opinion, the recommendation to abandon pretreatment in NSTEMI-ACS patients is questionable.

According to the 2020 ESC guidelines, both ticagrelor and prasugrel exhibit a fast onset of action thereby allowing loading dose administration after diagnostic coronary angiography and directly before PCI [4]. However, the fast onset of action observed in stable patients was not confirmed in myocardial infarction patients, especially when concomitant treatment with opioids was applied [12–19]. Therefore, sufficient platelet inhibition at the time of PCI cannot be expected in patients in whom the loading dose of ticagrelor or prasugrel was given after diagnostic coronary angiography and directly before PCI.

In the ESC guidelines, in P2Y12-inhibitor naive patients undergoing PCI ticagrelor may be considered (class of recommendation IIb, level of evidence A) [4]. As much as this strategy seems attractive, sadly, it cannot be applied in practice as ticagrelor is not available yet in Poland [20–22].

Our position paper is a result of consensus carefully achieved after several months of discussions and debates within the author panel. On the one hand, it was our intention to incorporate the ESC guidelines as broadly as possible, on the other hand though, we remained critical in interpretation of the scientific evidence presented in these guidelines. In addition, we took into account the legal regulations specific for our country and aspects that are not described in the ESC guidelines [3].

References

- Kubica J, Adamski P, Paciorek P, et al. Anti-aggregation therapy in patients with acute coronary syndrome - recommendations for medical emergency teams. Experts' standpoint. *Kardiol Pol.* 2017; 75(4): 399–408, doi: [10.5603/KPa2017.0057](https://doi.org/10.5603/KPa2017.0057), indexed in Pubmed: [28421594](https://pubmed.ncbi.nlm.nih.gov/28421594/).
- Kubica J, Adamski P, Paciorek P, et al. Treatment of patients with acute coronary syndrome: Recommendations for medical emergency teams: Focus on antiplatelet therapies. Updated experts' standpoint. *Cardiol J.* 2018; 25(3): 291–300, doi: [10.5603/CJ.a2018.0042](https://doi.org/10.5603/CJ.a2018.0042), indexed in Pubmed: [29671864](https://pubmed.ncbi.nlm.nih.gov/29671864/).
- Kubica J, Adamski P, Ładny JR, et al. Pre-hospital treatment of patients with acute coronary syndrome: Recommendations for medical emergency teams. Expert position update 2022. *Medical Research Journal.* 2022; 7(1): 94–104, doi: [10.5603/MRJ.2022.0013](https://doi.org/10.5603/MRJ.2022.0013).
- Collet JP, Thiele H, Barbato E, et al. ESC Scientific Document Group, ESC Scientific Document Group, ESC Scientific Document Group, ESC Scientific Document Group. Questions and answers on workup diagnosis and risk stratification: a companion document of the 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021; 42(14): 1379–1386, doi: [10.1093/eurheartj/ehaa602](https://doi.org/10.1093/eurheartj/ehaa602), indexed in Pubmed: [32860030](https://pubmed.ncbi.nlm.nih.gov/32860030/).
- Lahu S, Ndrepepa G, Neumann FJ, et al. ISAR-REACT 5 Trial Investigators. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *N Engl J Med.* 2019; 381(16): 1524–1534, doi: [10.1056/NEJMoa1908973](https://doi.org/10.1056/NEJMoa1908973), indexed in Pubmed: [31475799](https://pubmed.ncbi.nlm.nih.gov/31475799/).
- Kubica J, Jaguszewski M. ISAR-REACT 5 - What have we learned? *Cardiol J.* 2019; 26(5): 427–428, doi: [10.5603/CJ.a2019.0090](https://doi.org/10.5603/CJ.a2019.0090), indexed in Pubmed: [31536136](https://pubmed.ncbi.nlm.nih.gov/31536136/).
- Crea F, Thiele H, Sibbing D, et al. Debate: Prasugrel rather than ticagrelor is the preferred treatment for NSTEMI-ACS patients who proceed to PCI and pretreatment should not be performed in patients planned for an early invasive strategy. *Eur Heart J.* 2021; 42(31): 2973–2985, doi: [10.1093/eurheartj/ehab277](https://doi.org/10.1093/eurheartj/ehab277), indexed in Pubmed: [34110420](https://pubmed.ncbi.nlm.nih.gov/34110420/).
- Kubica J, Jaguszewski M, Ostrowska M, et al. Creative scientific dispute — different points of view on the protocol and execution of the ISAR-REACT 5 trial. *Medical Research Journal.* 2020; 5(1): 41–45, doi: [10.5603/mrj.a2020.0008](https://doi.org/10.5603/mrj.a2020.0008).
- Navarese EP, Khan SU, James S, et al. Comparative Efficacy and Safety of Oral P2Y Inhibitors in Acute Coronary Syndrome: Network Meta-Analysis of 52 816 Patients From 12 Randomized Trials. *Circulation.* 2020; 142(2): 150–160, doi: [10.1161/CIRCULATIONAHA.120.046786](https://doi.org/10.1161/CIRCULATIONAHA.120.046786), indexed in Pubmed: [32468837](https://pubmed.ncbi.nlm.nih.gov/32468837/).
- Montalescot G, Bolognese L, Dudek D, et al. ACCOAST Investigators. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med.* 2013; 369(11): 999–1010, doi: [10.1056/NEJMoa1308075](https://doi.org/10.1056/NEJMoa1308075), indexed in Pubmed: [23991622](https://pubmed.ncbi.nlm.nih.gov/23991622/).
- Dworeck C, Redfors B, Angerås O, et al. Association of Pretreatment With P2Y12 Receptor Antagonists Preceding Percutaneous Coronary Intervention in Non-ST-Segment Elevation Acute Coronary Syndromes With Outcomes. *JAMA Netw Open.* 2020; 3(10): e2018735, doi: [10.1001/jamanetworkopen.2020.18735](https://doi.org/10.1001/jamanetworkopen.2020.18735), indexed in Pubmed: [33001202](https://pubmed.ncbi.nlm.nih.gov/33001202/).
- Kubica J, Kubica A, Jilma B, et al. Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors. *Int J Cardiol.* 2016; 215: 201–208, doi: [10.1016/j.ijcard.2016.04.077](https://doi.org/10.1016/j.ijcard.2016.04.077), indexed in Pubmed: [27128531](https://pubmed.ncbi.nlm.nih.gov/27128531/).
- Ostrowska M, Gorog D. Does morphine remain a standard of care in acute myocardial infarction? *Medical Research Journal.* 2020; 5(1): 46–49, doi: [10.5603/mrj.a2020.0009](https://doi.org/10.5603/mrj.a2020.0009).
- Kubica J, Adamski P, Ostrowska M, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. *Eur Heart J.* 2016; 37(3): 245–252, doi: [10.1093/eurheartj/ehv547](https://doi.org/10.1093/eurheartj/ehv547), indexed in Pubmed: [26491112](https://pubmed.ncbi.nlm.nih.gov/26491112/).
- Niezgoda P, Sikora J, Barańska M, et al. Crushed sublingual versus oral ticagrelor administration strategies in patients with unstable angina. A pharmacokinetic/pharmacodynamic study. *Thromb Haemost.* 2017; 117(4): 718–726, doi: [10.1160/TH16-08-0670](https://doi.org/10.1160/TH16-08-0670), indexed in Pubmed: [28203684](https://pubmed.ncbi.nlm.nih.gov/28203684/).
- Buszko K, Kubica K, Hobl EL, et al. Pharmacokinetic Modeling of Morphine's Effect on Plasma Concentrations of Ticagrelor and Its Metabolite in Healthy Volunteers. *Front Physiol.* 2021; 12: 663170, doi: [10.3389/fphys.2021.663170](https://doi.org/10.3389/fphys.2021.663170), indexed in Pubmed: [34248659](https://pubmed.ncbi.nlm.nih.gov/34248659/).
- Hobl EL, Reiter B, Schoergenhofer C, et al. Morphine decreases ticagrelor concentrations but not its antiplatelet effects: a randomized trial in healthy volunteers. *Eur J Clin Invest.* 2016; 46(1): 7–14, doi: [10.1111/eci.12550](https://doi.org/10.1111/eci.12550), indexed in Pubmed: [26449338](https://pubmed.ncbi.nlm.nih.gov/26449338/).
- Adamski P, Sikora J, Laskowska E, et al. Comparison of bioavailability and antiplatelet action of ticagrelor in patients with ST-elevation myocardial infarction and non-ST-elevation myocardial infarction: A prospective, observational, single-centre study. *PLoS One.* 2017; 12(10): e0186013, doi: [10.1371/journal.pone.0186013](https://doi.org/10.1371/journal.pone.0186013), indexed in Pubmed: [29023473](https://pubmed.ncbi.nlm.nih.gov/29023473/).
- Adamski P, Adamska U, Ostrowska M, et al. New directions for pharmacotherapy in the treatment of acute coronary syndrome. *Expert Opin Pharmacother.* 2016; 17(17): 2291–2306, doi: [10.1080/14656566.2016.1241234](https://doi.org/10.1080/14656566.2016.1241234), indexed in Pubmed: [27677394](https://pubmed.ncbi.nlm.nih.gov/27677394/).
- Tantry U, Chaudhary R, Kubica J, et al. Cangrelor for the treatment of patients with Arterial Thrombosis. *Expert Opin Pharmacother.* 2018; 19(12): 1389–1398, doi: [10.1080/14656566.2018.1506767](https://doi.org/10.1080/14656566.2018.1506767), indexed in Pubmed: [30102083](https://pubmed.ncbi.nlm.nih.gov/30102083/).
- Kubica J, Kozinski M, Navarese EP, et al. Cangrelor: an emerging therapeutic option for patients with coronary artery disease. *Curr Med Res Opin.* 2014; 30(5): 813–828, doi: [10.1185/03007995.2014.880050](https://doi.org/10.1185/03007995.2014.880050), indexed in Pubmed: [24393016](https://pubmed.ncbi.nlm.nih.gov/24393016/).
- Ostrowska M, Kubica J, Adamski P, et al. Stratified Approaches to Antiplatelet Therapies Based on Platelet Reactivity Testing. *Front Cardiovasc Med.* 2019; 6: 176, doi: [10.3389/fcvm.2019.00176](https://doi.org/10.3389/fcvm.2019.00176), indexed in Pubmed: [31850373](https://pubmed.ncbi.nlm.nih.gov/31850373/).