EuroIntervention
2025;21:e1238-e1240
published online e-edition November 2025
DOI: 10.4244/EIJ-E-25-00047

EDITORIAL

Closing the loop: from evidence to everyday care

Adnan Kastrati[1,2]*, MD; Fiorenzo Simonetti[1,3], MD

Corresponding author: TUM Klinikum Deutsches Herzzentrum, Technische Universität München, Lazarettstraße 36, 80636, Munich, Germany. E-mail: kastrati@dhm.mhn.de

In this issue of EuroIntervention, Jacobsen and her colleagues[1] report on the results of an interesting study that establishes a benchmark for validating evidence from randomised controlled trials (RCTs) in real-world practice.

Article, see page e1259

They make a highly original contribution to the unprecedented debate surrounding the publication of the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT 5) trial[2] by evaluating whether the results of this trial can be replicated in patients with acute myocardial infarction (AMI) in everyday practice. The present study is based on a nationwide registry in Denmark that included patients with AMI who were treated with percutaneous coronary intervention (PCI) between 1 January 2019 and 31 December 2022. This is a relatively short period of time for important advances in drug and device therapies to have occurred. During this period, the Danish Society of Cardiology's guidelines recommended prasugrel over ticagrelor for patients with acute coronary syndromes (ACS) undergoing PCI, in line with the analogous 2020 and 2023 guidelines of the European Society of Cardiology[3,4]. This marked a shift in dominance from ticagrelor to prasugrel as the preferred $P2Y_{12}$ inhibitor drug for treating patients with ACS who undergo PCI, enabling a comparison of 1-year outcomes between these two treatment groups.

To some degree, the design of the present study resembles that of the ongoing, cluster-based SWITCH SWEDEHEART study[5]. The difference is that the clustering sequence was performed randomly in the latter study, whereas it was triggered by a guideline recommendation in the former. Patients were assigned to a treatment group based on whether they had redeemed a prescription for prasugrel or ticagrelor within 7 days of discharge. Patients who died in hospital or within 7 days of discharge, those who received clopidogrel or no $P2Y_{12}$ inhibitor, and patients with a prior stroke or transient ischaemic attack (which represent contraindications to prasugrel) were excluded. The final cohort comprised 10,984 patients: 5,568 with ST-segment elevation myocardial infarction (STEMI), 4,113 with non-STEMI, and 1,303 with unspecified AMI. Of these patients, 4,179 were treated with prasugrel and 6,805 with ticagrelor. Clearly, the rigour of an RCT cannot be fully applied to drug assignment in a registry. Consequently, around 20% of patients ≥75 years of age were prescribed ticagrelor at a time when prasugrel was the recommended drug. To account for similar unavoidable imbalances, the authors conducted their main analyses after adjusting for a number of patient characteristics, including the year of treatment, and after creating propensity score-matched groups.

Before assessing whether the present study could replicate the results of the ISAR-REACT 5 trial, several limitations should be considered in addition to those inherent in its registry design. Firstly, the inclusion of only patients with drug prescription information within 7 days of discharge creates a bias towards the exclusion of higher-risk patients, such as those who died or were deemed unsuitable to receive either prasugrel or ticagrelor due to major complications within this period. However, the investigators of the study managed to capture the differential efficacy between prasugrel and ticagrelor, as most of the difference between the two drugs was observable after discharge[6]. Secondly, information on

when treatment was started is missing, which is particularly important for patients with non-STEMI. Thirdly, it would have been interesting to also compare patients enrolled in 2019, the majority of whom were treated with ticagrelor, with those enrolled in 2022, the majority of whom were treated with prasugrel, as separate cohorts, irrespective of the $P2Y_{12}$ inhibitor received.

The proportion of patients who discontinued initial prasugrel or ticagrelor therapy, mostly switching to clopidogrel, was 13.3%. This proportion was much higher among ticagrelor patients (18.8%) than among prasugrel patients (4.3%). This is not unexpected, as the same trend was observed in other ticagrelor studies, including the ISAR-REACT 5 trial[2] and is important to bear in mind when evaluating the relative efficacy of ticagrelor.

Table 1 shows the main results achieved by prasugrel versus ticagrelor in the Danish cohort of the present study and in the ISAR-REACT 5 trial[2]. There is striking consistency between the two studies throughout the analysed outcomes. In brief, the present study, which is in line with the trial that prompted a change to the Danish ACS guidelines, showed that prasugrel can reduce ischaemic events in patients with AMI without increasing the risk of bleeding compared to ticagrelor. It is worth noting that the larger treatment effect of prasugrel among patients with non-STEMI compared with those with STEMI was confirmed in the present study, as was found in the ISAR-REACT 5 trial[6,7].

Although it is not necessarily the task of the investigators of a clinical study such as the present one or the ISAR-REACT 5 trial to offer mechanisms for their findings, the stronger platelet inhibition[8] and positive effect on endothelial function and inflammation[9] with prasugrel as compared to ticagrelor, as well as higher patient adherence to prasugrel, are plausible explanations for the superiority of prasugrel. Danish cardiologists did not expose the patients to excess risk when they decided to switch from ticagrelor to prasugrel for AMI treated by PCI. Even the most sceptical voices regarding the findings of the ISAR-REACT 5 trial did not claim anything other than that the effects of prasugrel and ticagrelor are equivalent. However, the reluctance to acknowledge the superiority of prasugrel, as demonstrated in the ISAR-REACT 5 trial and the present study, is curious at best. The strong results of the PLATelet Inhibition and Patient Outcomes (PLATO) trial, which showed a reduction in mortality with ticagrelor versus clopidogrel in patients with ACS[10], are one of the reasons for scepticism. However, thus far, no studies have been able to replicate the PLATO trial's results[11].

The open-label design of the ISAR-REACT 5 trial has also been criticised. However, most of the trials on which the current guideline recommendations are based are open-label trials. It is almost impossible for investigator-initiated trials lacking industry support to be double-blind and placebo-controlled, particularly if the placebo is intended to mimic drugs under patent protection. Nevertheless, investigator-initiated trials are an indispensable necessity for independent drug-to-drug comparisons. On the other hand, being double-blind and placebo-controlled does not make a trial immune to doubts about the data's accuracy[12,13].

Replication RCTs are important for validating the results of an existing single trial. However, they also lack a real-world setting and carry an increased risk of exposing patients in the control group to a potentially inferior therapy. Jacobsen and her colleagues deserve recognition for conducting a study that avoids these limitations. Their patients directly benefited from switching to guideline-recommended treatment, while the broader medical community has gained confidence in the evidence generated by RCTs, even when they are conducted with an open-label design.

Authors' affiliations

1. Klinik für Herz- und Kreislauferkrankungen, TUM Klinikum Deutsches Herzzentrum, Technische Universität München, Munich, Germany; 2. Deutsches Zentrum für Herz- und Kreislauf-Forschung (DZHK) e.V. (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany; 3. Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy

Conflict of interest statement

F. Simonetti has received a research grant from the CardioPath PhD programme. A. Kastrati has no conflicts of interest related to the submitted work to declare.

References

1. Jacobsen MR, Graversen PL, Jabbari R, Grove EL, Glinge C, Holmvang L, Geisler T, Køber L, Torp-Pedersen C, Engstrøm T, Sørensen R. Impact of shifting from routine use of ticagrelor to prasugrel in myocardial infarction patients after PCI: a nationwide cohort study. *EuroIntervention.* 2025;21:e1259-68.

2. Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, Richardt G, Liebetrau C, Witzenbichler B, Antoniucci D, Akin I, Bott-Flügel L, Fischer M, Landmesser U, Katus HA, Sibbing D, Seyfarth M, Janisch M, Boncompagni D, Hilz R, Rottbauer W, Okrojek R, Möllmann H, Hochholzer W, Migliorini A, Cassese S, Mollo P, Xhepa E, Kufner S, Strehle A, Leggewie S, Allali A, Ndrepepa G, Schühlen H, Angiolillo DJ,

Table 1. A summary of the treatment effect estimates of prasugrel versus ticagrelor in the present study and in the ISAR-REACT 5 trial.

	Hazard ratio (95% confidence interval) Prasugrel vs ticagrelor	
Outcomes*	Danish cohort	ISAR-REACT 5
All-cause death, myocardial infarction, or stroke	0.67 (0.47-0.95)	0.74 (0.59-0.92)
All-cause death	0.75 (0.50-1.13)	0.81 (0.60-1.10)
Myocardial infarction	0.65 (0.44-0.96)	0.61 (0.44-0.85)
Stroke	0.75 (0.52-1.08)	0.85 (0.47-1.59)
Bleeding	0.79 (0.60-1.05)	0.89 (0.66-1.20)

*Myocardial infarction and bleeding are reported as defined in the respective studies. Adjusted hazard ratios are reported for the Danish cohort study.

Hamm CW, Hapfelmeier A, Tölg R, Trenk D, Schunkert H, Laugwitz KL, Kastrati A; ISAR-REACT 5 Trial Investigators. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *N Engl J Med*. 2019;381:1524-34.

3. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289-367.

4. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan GA, Dweck MR, Galbraith M, Gilard M, Hinterbuchner L, Jankowska EA, Jüni P, Kimura T, Kunadian V, Leosdottir M, Lorusso R, Pedretti RFE, Rigopoulos AG, Rubini Gimenez M, Thiele H, Vranckx P, Wassmann S, Wenger NK, Ibanez B; ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44:3720-826.

5. Omerovic E, Erlinge D, Koul S, Frobert O, Andersson J, Ponten J, Björklund F, Kastberg R, Petzold M, Ljungman C, Bolin K, Redfors B. Rationale and design of switch Swedeheart: A registry-based, stepped-wedge, cluster-randomized, open-label multicenter trial to compare prasugrel and ticagrelor for treatment of patients with acute coronary syndrome. *Am Heart J*. 2022;251:70-7.

6. Valina C, Neumann FJ, Menichelli M, Mayer K, Wöhrle J, Bernlochner I, Aytekin A, Richardt G, Witzenbichler B, Sibbing D, Cassese S, Angiolillo DJ, Kufner S, Liebetrau C, Hamm CW, Xhepa E, Hapfelmeier A, Sager HB, Wustrow I, Joner M, Trenk D, Laugwitz KL, Schunkert H, Schüpke S, Kastrati A. Ticagrelor or Prasugrel in Patients With Non-ST-Segment Elevation Acute Coronary Syndromes. *J Am Coll Cardiol*. 2020;76:2436-46.

7. Aytekin A, Ndrepepa G, Neumann FJ, Menichelli M, Mayer K, Wöhrle J, Bernlochner I, Lahu S, Richardt G, Witzenbichler B, Sibbing D, Cassese S, Angiolillo DJ, Valina C, Kufner S, Liebetrau C, Hamm CW, Xhepa E, Hapfelmeier A, Sager HB, Wustrow I, Joner M, Trenk D, Fusaro M, Laugwitz KL, Schunkert H, Schüpke S, Kastrati A. Ticagrelor or Prasugrel in Patients With ST-Segment-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. *Circulation*. 2020;142:2329-37.

8. Mayer K, Bongiovanni D, Karschin V, Sibbing D, Angiolillo DJ, Schunkert H, Laugwitz KL, Schüpke S, Kastrati A, Bernlochner I. Ticagrelor or Prasugrel for Platelet Inhibition in Acute Coronary Syndrome Patients: The ISAR-REACT 5 Trial. *J Am Coll Cardiol*. 2020;76:2569-71.

9. Schnorbus B, Daiber A, Jurk K, Warnke S, Koenig J, Lackner KJ, Münzel T, Gori T. Effects of clopidogrel vs. prasugrel vs. ticagrelor on endothelial function, inflammatory parameters, and platelet function in patients with acute coronary syndrome undergoing coronary artery stenting: a randomized, blinded, parallel study. *Eur Heart J*. 2020;41:3144-52.

10. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators; Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045-57.

11. Watanabe A, Aikawa T, Miyamoto Y, Ueyama HA, Fujisaki T, Shoji S, Hosseini K, Slipczuk L, Briasoulis A, Kampaktsis PN, Wiley J, Secemsky EA, Iwagami M, Tsugawa Y, Kuno T. Ticagrelor Paradox: Systematic Review and Network Meta-Analysis. *J Am Heart Assoc*. 2025;14:e041959.

12. Doshi P. Doubts over landmark heart drug trial: ticagrelor PLATO study. *BMJ*. 2024;387:q2550.

13. Doshi P. Ticagrelor doubts: inaccuracies uncovered in key studies for AstraZeneca's billion dollar drug. *BMJ*. 2025;389:r1201.