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ISAR-REACT 5: should this trial change clinical practice?

ISAR-REACT 5 — czy to badanie powinno zmienić praktykę kliniczną?

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Abstract

Prasugrel and ticagrelor are oral $P2Y_{12}$ receptor inhibitors indicated by the European Society of Cardiology as the preferred antiplatelet therapy in patients with acute coronary syndrome (ACS). Despite the long-term and widespread presence of these agents in clinical practice, to date they have never been directly compared in a large, randomised clinical trial. ISAR-REACT 5 was the first such study, and it reported the superiority of prasugrel over ticagrelor. However, due to the arguable methodology of both the planning and the execution of this study, its results should be interpreted with caution, and they should not be considered sufficient to justify any changes to the current treatment strategies for patients with ACS.

Key words: acute coronary syndrome, antiplatelet therapy, prasugrel, ticagrelor

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Introduction

Dual antiplatelet therapy, consisting of acetylsalicylic acid and a $P2Y_{12}$ receptor inhibitor, is the standard for the treatment of patients with acute coronary syndrome (ACS). According to the current guidelines of the European Society of Cardiology (ESC) regarding myocardial revascularization, the preferred drugs in patients with ACS are prasugrel and ticagrelor (class of recommendation I, level of evidence B), except for patients treated with thrombolysis and those receiving oral anticoagulants, in whom we should use clopidogrel [1]. The use of prasugrel is limited to patients who have not previously received a $P2Y_{12}$ receptor inhibitor and are qualified for percutaneous coronary intervention (PCI). However, in ACS without persistent ST-segment elevation this drug should not be used unless the anatomy of the coronary arteries is known. In contrast, ticagrelor can be given regardless of previous treatment with a $P2Y_{12}$ receptor inhibitor, and regardless of the treatment strategy adopted. Prasugrel is not recommended for the elderly (≥ 75 years) or for patients with a low body weight (< 60 kg). A history of ischaemic stroke or transient ischaemic attack are contraindications to this drug [2, 3].

Clinical efficacy of prasugrel and ticagrelor

The clinical trials that have triggered a change in ESC guidelines and have put ticagrelor and prasugrel above clopidogrel in the treatment of patients with ACS were, for ticagrelor — the PLATO study (Platelet Inhibition and Patient Outcomes), and for prasugrel — the TRITON-TIMI 38 trial (TRial to assess Improvement in Therapeutic Outcomes by optimising platelet inhibitioN with prasugrel — Thrombolysis In Myocardial Infarction 38 trial) [4, 5].

Both studies were international, multicentre, randomized and double-blind, and aimed to compare the efficacy of new antiplatelet agents to that of clopidogrel in the prevention of cardiovascular events among patients with ACS.

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In the PLATO study 18,624 ACS patients were included, and 13,608 ACS patients were enrolled in the TRITON-TIMI 38 study, for whom PCI was planned. In both studies, the primary endpoint was a composite of: death from cardiovascular causes, myocardial infarction, and stroke. The follow-up period in the PLATO study was 12 months with a median of 277 days, and in the TRITON-TIMI 38 study was up to 15 months with a median of 9.5 months. In the PLATO study, the primary endpoint occurred in 9.8% of ticagrelor-treated patients and in 11.7% of clopidogrel-treated patients [hazard ratio (HR, hazard ratio) 0.84, 95% confidence interval (CI, confidence interval) 0.77–0.92, p < 0.001]. Analysing endpoints, in the ticagrelor treated patients there was a significant reduction in cardiovascular deaths (4.0% vs. 5.1%, HR 0.79, 95% CI 0.69–0.91, p = 0.001) as well as fewer myocardial infarctions (5.8% vs. 6.9%, HR 0.84, 95% CI 0.75–0.95, p = 0.005). Surprisingly, it was observed that not only the number of cardiovascular deaths but also all-cause deaths were reduced in the ticagrelor group (4.5% vs. 5.9%, HR 0.78, 95% CI 0.69–0.89, p < 0.001) and deaths other than cardiovascular (0.5% vs. 0.8%, HR 0.71, 95% CI 0.49–1.04, p = 0.08). In TRITON-TIMI 38 trial, the primary endpoint occurred in 9.9% of patients treated with prasugrel and in 12.1% of patients receiving clopidogrel (HR 0.81, 95% CI 0.73–0.90, p < 0.001). The reduction in the incidence of the primary endpoint among patients treated with prasugrel was mainly due to a reduction in the incidence of myocardial infarction (7.3% vs. 9.5%, HR 0.76, 95% CI 0.67–0.85, p < 0.001). There were no differences between the groups in terms of the incidence of cardiovascular deaths (2.1% vs. 2.4%, HR 0.89, 95% CI 0.70–1.12, p = 0.31), stroke (1.0% vs. 1.0%, HR 1.02, 95% CI 0.71–1.45, p = 0.93), or overall deaths (3.0% vs. 3.2 %, HR 0.95, 95% CI 0.78–1.16, p = 0.64).

Safety of prasugrel and ticagrelor

The primary safety endpoint in the PLATO study was major bleeding defined by study criteria: it occurred in 11.6% of patients in the ticagrelor group and in 11.2% of patients in the clopidogrel group (HR 1.04, 95% CI 0.95–1.13, p = 0.43). There were also no significant differences between the study groups in the frequency of major bleeding assessed according to the TIMI criteria (7.9% vs. 7.7%, HR 1.03, 95% CI 0.93–1.05, p = 0.57) or combined life-threatening and fatal bleeds (5.8% vs. 5.8%, HR 1.03, 95% CI 0.9–1.16, p = 0.70). Analysis of secondary safety endpoints showed a significantly higher incidence of major bleeding not associated with coronary artery by-pass grafting (CABG) in the ticagrelor group (4.5% vs. 3.8%, HR 1.19, 95% CI 1.02–1.38, p = 0.03). The primary safety endpoints in the TRITON-TIMI 38 study were major non-CABG-related bleeding events defined according to the TIMI criteria: these occurred in 2.4% of patients treated with prasugrel and in 1.8% of patients treated with clopidogrel (HR 1.32, 95% CI 1.03–1.68, p = 0.03). In the prasugrel group as compared with the clopidogrel arm, life-threatening bleeding (1.4% vs. 0.9%, HR 1.52, 95% CI 1.08–2.13, p = 0.01) and fatal bleeding (0.4% vs. 0.1%, HR 4.19, 95% CI 1.58–11.11, p = 0.002) were also significantly more commonly observed. Major and minor bleeding assessed according to the TIMI criteria also occurred significantly more frequently in the prasugrel group (5.0% vs. 3.8%, HR 1.31, 95% CI 1.11–1.56, p = 0.002), as did CABG-related bleeding (13.4% vs. 3.2%, HR 4.73, 95% CI 1.90–11.82, p < 0.001).

Clinical comparison of prasugrel and ticagrelor

Despite the long-standing and ever-growing presence of prasugrel and ticagrelor in clinical practice, these drugs have never been directly compared in a large, randomized clinical trial. On the other hand, data from subanalyses of clinical trials, large registries or meta-analyses are not conclusive as to which of these two drugs is more effective in preventing adverse cardiovascular events, as well as in comparing the safety of use [6–14].

ISAR-REACT 5 study

The first clinical trial to directly compare the efficacy and safety of ticagrelor and prasugrel in patients with ACS was the ISAR-REACT 5 study (The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) — a randomized, multicentre, open-label, phase IV study [15]. The study reported superiority of prasugrel over ticagrelor in the incidence of a composite endpoint consisting of death, myocardial infarction or stroke within a year of randomization in patients with ACS. The reduction in the incidence of the composite endpoint in patients assigned to the prasugrel treatment group was not associated with an increased risk of bleeding compared with ticagrelor [16]. Based on available data, the cardiological community generally expected somewhat different results from the ISAR-REACT 5 study. Therefore, it seems necessary to investigate and to critically examine the protocol of this study, the research methods used, the study population, and the conduct of this clinical trial.

The goal of this study was to verify the hypothetical superiority of ticagrelor over prasugrel in patients with ACS. In fact, it compared different strategies for antiplatelet therapy only partially overlapping with the ESC recommendations. Patients (n = 4,018) with ST-segment elevation myocardial infarction (STEMI) were randomized to the study in the hospital phase of treatment. One of the exclusion criteria was previous administration of prasugrel or ticagrelor, in this case it prevented the initiation of anti-aggregation therapy as soon as possible. In addition, patients with confirmed

ACS who were assigned to conservative treatment after coronary angiography received a $P2Y_{12}$ receptor inhibitor designated in the randomization process, although the use of prasugrel in this group of patients is off-label. Therefore, it should be emphasized that the results of this clinical trial do not exactly relate to actual clinical practice.

In addition, the study protocol, and how it was organised, led to potential bias, the degree of which however is difficult to assess for several reasons. Both the open nature of the study and the fact that it was carried out in only two countries (21 centres in Germany and 2 in Italy) could have had some, though probably negligible, impact on the results. However, the reported percentage of patients who followed the recommendations for study medication is astonishing, and was 99.1% in the prasugrel group and 99.6% in the ticagrelor group. For comparison, among the entire population of the PLATO study, 82.8% of patients declared compliance with medical recommendations [4]. The above data seems to clearly indicate an underestimation of the phenomenon of non-adherence to the recommended therapy in accordance with the ISAR-REACT 5 study protocol, all the more so because the follow-up visits were mainly without face-to-face contact — in 83% of participants it was a telephone conversation, and in 7% follow-up was based on written correspondence. Only 10% of study participants had follow-up visits in a hospital or outpatient clinic. The 0.9% and 0.4% non-adherence rates seem simply unrealistic, especially since ticagrelor or prasugrel was prescribed by the attending physician after the end of the hospital phase and the patient had to purchase the drug without any reimbursement. In addition, careful analysis of the patient baseline characteristics of both study groups demonstrates a slightly higher risk population in the ticagrelor arm as compared with the prasugrel arm. However, these differences were not statistically significant.

The intention-to-treat analysis (*i.e.* including all patients depending on the group to which they were randomly assigned, regardless of the treatment received) is a commonly accepted method used in similar clinical trials. However, this study model could have seriously distorted the results of the ISAR-REACT 5 study because as many as 410 out of 2,012 (20.4%) and 410 out of 2,006 (20.4%) patients were discharged from hospital without the $P2Y_{12}$ receptor inhibitor assigned in the randomization process in the ticagrelor and prasugrel groups respectively. In addition, a further 243 patients from the ticagrelor group, and 199 from the prasugrel group, discontinued the prescribed antiplatelet drug after discharge from the hospital. A further 19 and 18 patients in each group (37 in total, 0.92%) were lost to follow-up. For comparison, in the TRITON-TIMI 38 study this percentage was 0.12%, and in the PLATO study it was 0.01% [4, 5]. Consequently, the intention-to-treat analysis used in the ISAR-REACT 5 study led to the inclusion in the final analysis of as many as 1,299 patients who were not treated with the assigned drug [treated with ticagrelor: 653 of 2,012 participants (32.5%); treated with prasugrel: 609 out of 2,006 participants (30.4%)].

The primary composite endpoint (death, myocardial infarction, or stroke) within a year from randomization occurred in 184 of the 2,012 (9.1%) patients assigned to the ticagrelor group, and in 137 of the 2,006 (6.8%) patients in the group receiving prasugrel (HR 1.36, 95% CI 1.09–1.70, p = 0.006). Considering that the analysis of 4,018 patients included as many as 1,262 people (31.4%) who should have been on the assigned drug, but were in fact not treated according to the study protocol, and that a further 37 were lost from observation, an absolute difference in the frequency of the occurrence of a main endpoint of 47 events is hardly significant. All the more so because, in the analysis of the occurrence of the primary endpoint in the period from the hospital discharge to the time of discontinuation of therapy or completion of clinical observation in patients the hospital discharge on the drug assigned during the randomization process, *i.e.* in patients presumed to be on the study drug (on-treatment analysis), which included 1,602 participants in the ticagrelor group and 1,596 participants in the prasugrel group, there were no differences between the study groups (ticagrelor--treated: 92 events, treated with prasugrel: 71 events; HR 1.34, 95% CI 0.98–1.82). It is worth emphasizing that the difference in the incidence of the primary endpoint was mainly due to differences in the occurrence of myocardial infarction (treated with ticagrelor: 96 patients (4.8%); treated with prasugrel: 60 patients (3.0%), HR 1.63, 95% CI 1.18–2.25), including the relatively frequent type 4a or 4b myocardial infarction (19 and 20 cases in the ticagrelor group, respectively, and 11 cases in the prasugrel group). This again raises the question of the true degree of patient compliance in the study.

In modified intention-to-treat analysis, the safety-related endpoint [severe bleeding according to the BARC (Bleeding Academic Research Consortium) criteria, *i.e.* type 3–5] occurred in 95 patients (5.4%) from the ticagrelor group and in 80 patients (4.8%) in the prasugrel group (HR 1.12, 95% CI 0.83–1.51, p = 0.46). The absolute difference between the study groups of 15 haemorrhagic events is extremely difficult to interpret, given that 233 out of 2,006 patients (12%) from the prasugrel group, and only 23 out of 2,012 patients (1%) from the ticagrelor group, were excluded from this analysis.

Conclusions

The results of the ISAR-REACT 5 study raise a number of questions and must be interpreted with caution [17]. Particularly incomprehensible are the researchers' decisions to discontinue the study drug in the hospital phase, which

in effect led to a comparison of groups in which almost one third of patients was not treated with the assigned drug. Similarly, the assumption that more than 99% of patients purchased and took the prescribed drug without actual control of this fact seems at least to be risky. Such doubts multiply when comparing the results of this study with previous clinical trials in which the study groups were many times larger. The incidence of the primary endpoint in ticagrelor treated patients in the ISAR-REACT 5 study and the PLATO study was similar at 9.3% and 9.8%, respectively. However, the comparison of the results of the ISAR-REACT 5 study and the TRITON-TIMI 38 study shows surprising and difficult-to-explain differences: the incidence of the primary endpoint in the prasugrel treated patients being 6.9% and 9.9%, respectively.

Given the significant limitations of the ISAR-REACT 5 study, the results obtained should be treated with extreme caution and cannot be considered sufficient to alter the current treatment strategy. In addition, an in-depth reflection on the methodology of how clinical trials are conducted is called for.

Conflict of interest

JK — gave a lecture for AstraZeneca; the other authors declare no conflict of interest.

Streszczenie

Prasugrel i tikagrelor są doustnymi inhibitorami receptora $P2Y_{12}$ wskazywanymi w wytycznych Europejskiego Towarzystwa Kardiologicznego jako preferowane leczenie przeciwpłytkowe u pacjentów z ostrymi zespołami wieńcowymi (ACS). Mimo wieloletniej i coraz powszechniejszej obecności w praktyce klinicznej obu tych leków, dotychczas nigdy nie porównywano ich bezpośrednio w dużym, randomizowanym badaniu klinicznym. Pierwszym takim badaniem była próba kliniczna ISAR-REACT 5, w której wykazano wyższość prasugrelu nad tikagrelorem. Tym niemniej, ze względu na wątpliwości odnośnie do metodologii planowania i przeprowadzenia tej próby klinicznej, jej wyniki należy interpretować z ostrożnością i nie powinno się ich uznawać za wystarczające do wprowadzenia zmian w dotychczasowej strategii leczenia pacjentów z ACS.

Słowa kluczowe: leczenie przeciwpłytkowe, ostre zespoły wieńcowe, prasugrel, tikagrelor

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