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Early treatment with inhibitors of P2Y12 receptor in patients with ST-segment elevation myocardial infarction — 2023 ESC recommendations and scientific evidence. Is clinical evidence sufficient to suggest a move towards precision medicine? The ELECTRA-SIRIO 2 investigators' viewpoint

Jacek Kubica[1], Piotr Adamski[1], Jolita Badariene[2], Marc Bonaca[3], Piotr Buszman[4], Rahima Gabulova[5], Robert Gajda[6], Tobias Geisler[7], Robert Gil[8], Diana A. Gorog[9–11], Paul A. Gurbel[12], Tomasz Hajdukiewicz[13], Bartosz Hudzik[14, 15], Stefan James[16], Young-Hoon Jeong[17, 18], Adam Kern[19], Wacław Kochman[20], Aldona Kubica[21], Wiktor Kuliczkowski[22], Przemysław Magielski[23], Piotr Niezgoda[1], Małgorzata Ostrowska[1], Paolo Raggi[24], Uzeyir Rahimov[25], Grzegorz Skonieczny[26], Jolanta M. Siller-Matula[27], Giuseppe Specchia[28], Łukasz Szarpak[29], Paweł Szymański[30], Udaya Tantry[12], Julia Umińska[1], Eliano Pio Navarese[31]

[1]Department of Cardiology and Internal Medicine, L. Rydygier *Collegium Medicum* in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland
[2]Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[3]CPC Clinical Research, Aurora, United States
[4]Cardiology Department, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland; Center for Cardiology and Cardiac Surgery of American Heart of Poland, Bielsko-Biała, Poland
[5]Teaching-Therapeutical Hospital, Azerbaijan Medical University, Baku, Azerbaijan
[6]Gajda-Med District Hospital in Pultusk, Poland
[7]Medical Clinic III, University Hospital Tübingen, Tübingen, Germany
[8]Department of Invasive Cardiology, Centre of Postgraduate Medical Education, Central Clinical Hospital of the Ministry of Interior and Administration, Warsaw, Poland
[9]Postgraduate Medical School, University of Hertfordshire, Hertfordshire, United Kingdom
[10]Faculty of Medicine, National Heart and Lung Institute, London, United Kingdom
[11]Cardiology Department, Royal Brompton & Harefield NHS Trust, Part of Guys and St Thomas' Hospitals, London, United Kingdom
[12]Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital of Baltimore, Baltimore, Maryland, United States
[13]Department of Cardiology, Provincial Hospital, Elblag, Poland
[14]Department of Metabolic Disease Prevention, Faculty of Public Health in Bytom, Medical University of Silesia, Bytom, Poland
[15]Third Department of Cardiology, Silesian Center for Heart Disease, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Zabrze, Poland

Address for correspondence: Piotr Niezgoda, Department of Cardiology and Internal Medicine, L. Rydygier *Collegium Medicum* in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland, tel: +48 52 585 4023, e-mail: piotr.niezgoda1986@gmail.com

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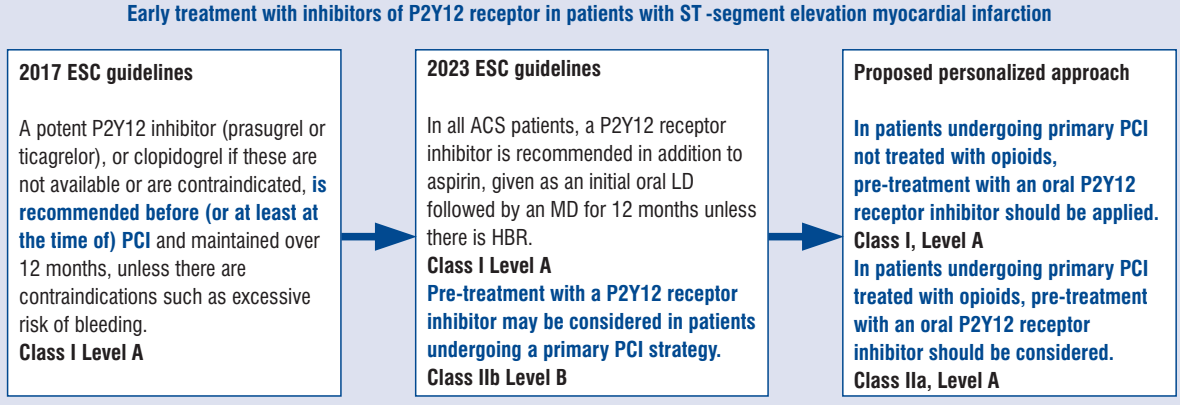
[16]Department of Medical Sciences, Cardiology, Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden
[17]CAU Thrombosis and Biomarker Center, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Republic of Korea
[18]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Republic of Korea
[19]Department of Cardiology and Internal Medicine, Medical Faculty, University of Warmia and Mazury in Olsztyn, Poland
[20]The National Institute of Cardiology, Department of Cardiology, Bielanski Hospital, Warsaw, Poland
[21]Department of Cardiac Rehabilitation and Health Promotion, *Collegium Medicum*, Nicolaus Copernicus University, Bydgoszcz, Poland
[22]Institute of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland
[23]Interventional Cardiology and Cardiovascular Medicine Research, Department of Cardiology and Internal Medicine, Nicolaus Copernicus University, Bydgoszcz, Poland
[24]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
[25]Department of Cardiology, Baku Medical Plaza, Baku, Azerbaijan
[26]Department of Cardiology and Intensive Cardiological Care, Rydygier Provincial Hospital, Torun, Poland
[27]Department of Cardiology, Medical University of Vienna, Vienna, Austria
[28]Department of Cardiology, Policlinico di Monza, Monza, Italy
[29]Department of Clinical Research and Development, LUXMED Group, Warsaw, Poland
[30]Department of Cardiology, Interventional Cardiology and Electrophysiology with Cardiac Intensive Care Unit, Tertiary Care Hospital in Grudziadz, Poland
[31]Clinical and Interventional Cardiology, Sassari University Hospital, Italy

Abstract

The 2023 ESC guidelines changed the previously recommended strategy of early treatment in patients with STEMI. Pre-treatment with a P2Y12 receptor inhibitor may be considered in patients undergoing a primary PCI strategy (Class IIb, Level of evidence B). However, the available scientific evidence justifies a personalized approach differentiating the indications for pre-treatment with oral P2Y12 receptor inhibitors depending on the concomitant administration of opioids. In our opinion, in patients undergoing primary PCI not treated with opioids, pre-treatment with an oral P2Y12 receptor inhibitor should be applied, while in patients undergoing primary PCI treated with opioids, pre-treatment with an oral P2Y12 receptor inhibitor should be considered. (Cardiol J 2025; 32, 2: 189–194)

Keywords: ACS, STEMI, P2Y12, pretreatment, ESC guidelines

Central illustration. The evolution of early antiplatelet therapy in STEMI



Introduction

The recently published 2023 European Society of Cardiology (ESC) guidelines for the management of acute coronary syndromes have introduced a number of new recommendations. The class and/or the level of evidence have also been modified in some cases [1]. The justification for some of these changes seems insufficient or at least incomprehensible based upon current evidence and practice. Our doubts include the recommendations regarding pre-treatment with P2Y12 receptor inhibitors in patients with acute coronary syndrome (ACS).

The 2017 ESC guidelines for the management of patients presenting with ST-segment elevation myocardial infarction

The previous 2017 ESC guidelines for the management of patients presenting with ST-segment elevation myocardial infarction (STEMI) recommended administration of a potent P2Y12 receptor inhibitor (prasugrel or ticagrelor), or clopidogrel if the former were not available or contraindicated, before (or at latest at the time of) PCI and maintenance of this therapy over 12 months, unless contraindications such as excessive risk of bleeding were present (Class I, Level of evidence A) [2]. This recommendation was supported by the results of two landmark randomized clinical trials, the TRITON-TIMI 38 (STEMI n = 3534) and the PLATO (STEMI n = 7008) studies, both showing a favorable efficacy-to-safety ratio of the tested strategy with prasugrel and ticagrelor, respectively, compared to clopidogrel [3, 4]. The Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial [5] — the only trial testing the safety and efficacy of prehospital versus in-hospital ticagrelor initiation in STEMI patients – showed no difference regarding the pre-specified primary endpoint defined as improved ST-segment elevation resolution or TIMI flow before intervention between study arms. The bleeding rates were also similar in both arms. Moreover, the incidence of definite stent thrombosis — a potentially devastating complication — was lower in the prehospital group than in the in-hospital group. A major limitation of this study was the short time difference of 31 minutes between prehospital and in-hospital loading doses. Nevertheless, the authors of the 2017 ESC guidelines highlighted that pre-treatment with P2Y12 receptor inhibitor in STEMI patients is a common practice in Europe supported by consistent pharmacokinetic data and by results of clinical studies with clopidogrel [2, 6, 7, 8]. Upstream treatment with a loading dose of clopidogrel at the point of diagnosis of STEMI has been shown to reduce the combined risk of death or myocardial infarction (MI), as well as death alone, in patients treated with primary PCI in a group of 13,847 consecutive patients in the national Swedish Coronary Angiography and Angioplasty Registry (SCAAR) [6]. This was in line with data from a multicenter registry showing clopidogrel pre-treatment before arrival at the PCI center to be associated with reduced mortality in a population of 5955 STEMI patients undergoing primary PCI in Austria [7]. These observational studies were supported by the results of the CIPAMI randomized trial comparing a loading dose of 600 mg clopidogrel given in the prehospital phase versus clopidogrel administered only after a diagnostic angiogram in patients with STEMI scheduled for primary PCI [8]. In this relatively small study (n = 337), the time interval between initiation of clopidogrel therapy and diagnostic angiography was 47 min. There was a trend towards reduction of the combined endpoint of death, re-infarction, and urgent target vessel revascularization in the prehospital-treated patients (3.0 vs. 7.0%, p = 0.09), and this difference was significant if patients were classified as treated (4/161 vs. 13/174; 2.5 vs. 7.5%, $p < 0.05$). There was no difference with regard to major bleeding complications [8]. Moreover, the meta-analysis including 3 randomized clinical trials (RCT) and 16 non-RCT studies, with a total of 79,300 STEMI patients, showed that pre-treatment with dual antiplatelet therapy, including a P2Y12 receptor inhibitor (66.1% pre-treated, 66.0% treated with clopidogrel), was associated with a reduction in definite stent thrombosis (odds ratio [OR] 0.61 [0.38–0.98]), all-cause death (OR 0.77 [0.60–0.97]), and cardiogenic shock (OR 0.60 [0.48–0.75]) and better pre-PCI coronary patency (OR 0.78 [0.67–0.92]) without a negative impact on risk of major bleeding events (OR 0.83 [0.75–0.92]) [9]. This meta-analysis was published in October 2023; therefore, it could not have been taken into account in the 2023 ESC guidelines, in contrast to the source data, which were available.

The 2023 ESC guidelines for the management of acute coronary syndromes

The 2023 ESC guidelines changed the recommended strategy regarding early treatment in patients with STEMI, despite the lack of new

scientific evidence to support this decision apart from one observational study [1, 10]. Use of a P2Y12 receptor inhibitor is still recommended in addition to aspirin, given as an initial oral loading dose in all patients with acute coronary syndrome (Class I, Level of evidence A); however, pre-treatment with a P2Y12 receptor inhibitor may be considered in patients undergoing a primary PCI strategy (Class IIb, Level of evidence B). To support the latter recommendation, publications reporting the results of the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) study (ISAR-REACT 5) and the ATLANTIC studies are cited. It needs to be stressed, however, that the ISAR-REACT 5 study was neither designed to nor evaluated the pre-treatment in patients treated with ticagrelor or in subjects receiving prasugrel, because only those assigned to the ticagrelor arm received pre-treatment as a standard of care, and not in every case [10]. The authors of the 2023 ESC guidelines reiterated the arguments regarding the lack of expected superiority of early administration of P2Y12 inhibitors in STEMI patients in the ATLANTIC trial, also disavowing the reduced rates of definitive stent thrombosis. Moreover, it was added that these results were supported by real-world data obtained from the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry in STEMI patients [5, 9].

By reading the ESC guidelines from 2017 and 2023, regardless of differently formulated recommendations, one may get the impression that the results of the ATLANTIC study were interpreted superficially [1, 2]. It should be emphasized that this study is the only one that attempted to assess the efficacy and safety of pre-treatment with a P2Y12 inhibitor in patients with STEMI; therefore, its results should be analyzed with particular care [5]. There was no significant difference between the prehospital group and the in-hospital group in terms of the proportion of patients who did not achieve the prespecified endpoint of a 70% or greater resolution of ST-segment elevation before PCI (OR 0.93; 95% confidence interval [CI], 0.69 to 1.25; p = 0.63). However, the results were not consistent across prespecified subgroups because prehospital administration of ticagrelor in patients in whom concomitant treatment with morphine was not applied was associated with significant improvement with regard to the primary endpoint of ST-segment resolution (OR 0.63; 95% CI, 0.42 to 0.94; p = 0.005). These results were to be expected considering the drug-drug interaction confirmed in the IMPRESSION study. In this study morphine was shown to decrease the total exposure to ticagrelor within 6 hours after the loading dose administration by 55%, reflected by a similar reduction of the total exposure to an active metabolite of ticagrelor [11, 12]. Lower overall concentrations and delayed maximal concentrations of ticagrelor resulted in impaired and delayed inhibition of P2Y12 platelet receptors, increasing the risk of thrombotic events [13, 14]. Understanding these interactions leads to the conclusion that the results of the ATLANTIC trial strongly suggest a benefit of pre-treatment in patients with STEMI who did not receive concomitant morphine [15, 16]. Moreover, definite stent thrombosis was reduced in the prehospital group both at 24 hours (0% in the prehospital group vs. 0.8% in the in-hospital group, p = 0.008) and at 30 days (0.2% vs. 1.2%, p = 0.02) regardless of morphine administration [5]. Of note, definite stent thrombosis is one of the most serious complications increasing long- and very long-term mortality. According to the authors of the 2023 guidelines, the lack of a beneficial effect of pre-treatment in STEMI patients is supported by real-world data obtained from the SWEDEHEART registry. However, one of the main limitations of this study is the lack of data on morphine intake and dosage; therefore, the SWEDEHEART does not contradict the benefit of pre-treatment with oral P2Y12 receptor inhibitors in patients in whom morphine was not applied [6]. In contrast, adequate P2Y12 receptor inhibition in STEMI patients with incremental ticagrelor dosage has been shown to decrease the rate of MACE after PCI without increasing major and minor bleeding [17]. The summary of changes in the guidelines for early antiplatelet therapy in STEMI is presented in the Central illustration.

Conclusion

In summary, in our opinion, a move towards precision medicine differentiating the indications for pre-treatment with oral P2Y12 receptor inhibitors depending on the concomitant administration of opioids in patients with STEMI is justified. We suggest the following recommendations: In patients undergoing primary PCI not treated with opioids, pre-treatment with an oral P2Y12 receptor inhibitor should be applied (Class I, Level of evidence A); In patients undergoing primary PCI treated with opioids, pre-treatment with an oral P2Y12 receptor

inhibitor should be considered (Class IIa, Level of evidence A). Patients treated with opioids regardless of pre-treatment with an oral P2Y12 receptor inhibitor are potentially optimal candidates for treatment with cangrelor. This, however, needs to be proven in a randomized clinical trial [17–21]. Avoiding drug-drug interactions by replacing opioids with other analgesics may be an alternative therapeutic option, which is currently being tested [22–25].

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