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Modern therapy of acute coronary syndromes based on prasugrel — available to Polish patients

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Abstract

Patients with acute coronary syndromes undergoing primary percutaneous coronary intervention should receive dual-antiplatelet therapy, a combination of acetylsalicylic acid and a $P2Y_{12}$ inhibitor. The preferred $P2Y_{12}$ inhibitors are prasugrel or ticagrelor. These drugs have a more rapid onset of action, greater potency, and are superior to clopidogrel in terms of clinical outcomes. Prasugrel is contraindicated in patients with previous stroke/transient ischaemic attack, and its use is generally not recommended in patients aged > 75 years or in patients with lower body weight (< 60 kg) as it has not been associated with net clinical benefit in these subsets. If prasugrel is used in these patients after benefits and risks have been weighted, a reduced maintenance dose (5 mg) is recommended.

Ticagrelor may cause transient dyspnoea at the onset of therapy, which rarely leads to permanent discontinuation. Neither prasugrel nor ticagrelor should be used in patients with a previous haemorrhagic stroke, in patients on oral anticoagulants, or in patients with moderate-to-severe liver disease. When neither of these agents is available (or if they are contraindicated), clopidogrel should be given instead. In most cases, Polish patients have been deprived of modern treatment strategies using potent $P2Y_{12}$ inhibitors for economic reasons, but generic prasugrel is currently available.

Key words: acute coronary syndrome, antiplatelet agents, prasugrel

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Introduction

The annual incidence of acute coronary syndromes (ACS) in Poland is about 160,000, including unstable angina (UA) in about 41%, non-ST elevation myocardial infarction (NSTEMI) in 28%, and ST elevation myocardial infarction (STEMI) in 31% [1]. Percutaneous coronary intervention (PCI) is performed in 59% of patients with the diagnosis of myocardial infarction (MI) and although with introduction of modern therapies in-hospital mortality has been reduced to less than 10%, 1-year mortality among patients discharged after MI remains high. Depending on the therapies used, hospitalization settings, and patients' age, it ranges from 6.5% to 24% [2]. The standard approach to drug therapy of ACS includes dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and a platelet $P2Y_{12}$ receptor antagonist. Available evidence indicates that DAPT reduces the risk of in-stent thrombosis over a very large time span, from acute to very late events, and reduces the incidence of spontaneous MI [3]. The risk of bleeding in patients receiving DAPT is proportional to its duration both within the first year of treatment and with therapies for more than one year, and thus treatment individualization based on the ischemic risk and bleeding risk balance is warranted [4].

Available $P2Y_{12}$ inhibitors

Three oral $P2Y_{12}$ inhibitors are currently used in combination with ASA, including clopidogrel, prasugrel, and ticagrelor. Although clopidogrel is currently the most

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commonly used $P2Y_{12}$ inhibitor in ACS patients in Poland, according to the current guidelines for the management of ACS patients undergoing PCI, and patients with STEMI it is an alternative for prasugrel and ticagrelor only when the latter two are unavailable or contraindicated. Clopidogrel is characterized by a wide variation of pharmacodynamics response depending on several factors, including genetic polymorphisms. In randomized clinical trials in ACS patients undergoing PCI, clopidogrel was shown to be less effective compared to both prasugrel [TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction)] and ticagrelor [PLATO (Platelet Inhibition and Patient Outcomes)] [5, 6].

The type and duration of DAPT in patients with coronary syndromes depends on the clinical scenario (acute or chronic coronary syndrome), management strategy (invasive versus conservative), and bleeding risk (high or low). These factors determine the choice of antiplatelet agents and the duration of DAPT. If anticoagulant therapy is also indicated, it further modifies the approach to antiplatelet therapy.

Compared to clopidogrel, prasugrel allows more rapid, potent, and constant inhibition of platelet $P2Y_{12}$ receptors. In the TRITON-TIMI 38 study in patients with STEMI or ACS with coronary anatomy suitable for PCI, the combined end point (cardiovascular death, non-fatal MI or non-fatal stroke) was reduced by 18% ($p = 0.002$) in prasugrel-treated patients compared to those receiving clopidogrel. These clinical benefits were not evident, however, in patients ≥ 75 years of age and with low body weight (< 60 kg). At the same time, bleeding was significantly more common in the prasugrel group compared to the clopidogrel group. In the TRITON-TIMI 38 study, prasugrel was not tested in ACS patients undergoing conservative treatment. Based on the TRITON-TIMI 38 study results, prasugrel may be used in patients after coronary angiography in whom PCI is indicated. Pretreatment is acceptable only in STEMI patients undergoing primary PCI.

Ticagrelor is a direct oral reversible $P2Y_{12}$ inhibitor with the plasma half-life of about 12 hours, which implicates twice daily dosing. In the PLATO study, ticagrelor was shown to be superior to clopidogrel in ACS patients regardless of the revascularization strategy (*i.e.*, planned or unplanned invasive management) who were pretreated with clopidogrel on admission.

$P2Y_{12}$ inhibitor treatment in patients with ACS

Patients with STEMI

Data on when to initiate $P2Y_{12}$ inhibitor treatment in STEMI patients are limited but it is believed that earlier initiation may be justified to achieve early treatment effectiveness, while when the diagnosis of STEMI is not clear, delaying administration of a $P2Y_{12}$ inhibitor should be considered until coronary anatomy is determined [7]. In the periprocedural period (before or at the latest during PCI) in patients undergoing primary PCI, the preferred $P2Y_{12}$ inhibitors are prasugrel (loading dose 60 mg, maintenance dose 10 mg once daily orally) and ticagrelor (loading dose 180 mg, maintenance dose 90 mg twice daily orally). These drugs are characterized by more rapid onset of action, more potent platelet inhibition, and superior clinical outcomes compared to clopidogrel [7]. Administering a potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), and clopidogrel only when prasugrel and ticagrelor are unavailable or contraindicated, is a class I indication with the highest (A) level of evidence. Combined treatment with prasugrel or ticagrelor and ASA should be continued for 12 months unless contraindications exist, such as an excessive bleeding risk. In patients undergoing primary PCI or not receiving reperfusion therapy, prasugrel is administered as an oral 60 mg loading dose followed by the maintenance dose of 10 mg daily. In patients with body weight ≤ 60 kg, the maintenance dose of 5 mg daily is recommended. Prasugrel is contraindicated in patients after a previous stroke. In patients ≥ 75 years of age, prasugrel is generally not recommended but when such treatment is deemed necessary, the maintenance dose of 5 mg daily should be used. Ticagrelor is administered as an oral 180 mg loading dose followed by the maintenance dose of 90 mg twice daily. Clopidogrel is administered as an oral 600 mg loading dose followed by the maintenance dose of 75 mg daily.

Patients with NSTEMI

In patients with NSTEMI, DAPT including ASA and a potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor) is recommended. Clopidogrel should be used only if prasugrel and ticagrelor are unavailable or contraindicated, and in patients requiring concomitant oral anticoagulant therapy (class of recommendation I, level of evidence B). Recommendations regarding the initiation of $P2Y_{12}$ inhibitor treatment are consistent with the timing of administration of these drugs in pivotal clinical trials, *i.e.*, as early as possible and safe in case of ticagrelor and clopidogrel, and after determining indications for PCI based on known coronary anatomy in case of prasugrel. Prasugrel is administered as a 60 mg loading dose followed by 10 mg daily in combination with ASA. In patients with body weight ≤ 60 kg, the maintenance dose of 5 mg daily is recommended. In patients ≥ 75 years of age, prasugrel is generally not recommended but when deemed necessary, the maintenance dose of 5 mg daily should be used. An $P2Y_{12}$ inhibitor is recommended in combination with ASA for 12 months unless contraindications exist, such as excessive bleeding risk [4, 7–9].

Percutaneous coronary intervention in chronic coronary syndromes

In patients undergoing elective PCI, ASA and clopidogrel are indicated, and prasugrel or ticagrelor may be considered only in selected patients in specific situations associated with a high risk elective stenting (*e.g.*, complex PCI procedures, such as left main coronary artery stenting, and treatment of chronic total occlusion), and in patients with a history of in-stent thrombosis during clopidogrel treatment (class of recommendations IIb, level of evidence C) [9].

Comparison of prasugrel and ticagrelor

Few data from randomized clinical trials are available to compare ticagrelor with prasugrel in patients with ACS, but the randomized the PRAGUE-18 (Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction) study showed similar safety and efficacy profiles of ticagrelor and prasugrel in the setting of primary PCI [10].

In 2019, a widely discussed the ISAR-REACT 5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) study was published, a well-designed phase IV international multicenter randomized clinical trial that was not sponsored by the pharma industry [11]. It showed a superiority of prasugrel over ticagrelor in reducing the combined endpoint of death, myocardial infarction, and stroke over one year after randomization in patients with ACS, and these results were not associated with an excess bleeding risk in the prasugrel group [11]. The results of the study have been much debated and led to criticisms regarding the study protocol and its conduct which, however, seem unsound and unjustified [12, 13].

The hypothesis tested in the ISAR-REACT 5 was a superiority of ticagrelor over prasugrel in patients with ACS. The cardiologist community generally expected the results to be consistent with this hypothesis. The contrary results showing a superiority of prasugrel may be considered even more reliable.

The critics of the ISAR-REACT 5 study have noted its open design, underestimation of non-adherence to the prescribed therapy, and telephone call follow-up visits. In fact, however, these features constitute strengths of the study and indicate that it was conducted in the settings more close to routine clinical practice, and not in a carefully selected group of patients.

Criticisms regarding the intention-to-treat (ITT) approach and inclusion of patients who did not receive the allocated treatment are surprising both because it is a commonly accepted and used approach to the analysis of clinical trial data and due to the fact that the proportion of patients included in this analysis was comparable in the prasugrel and ticagrelor groups. It is thus difficult to conclude that the difference in the rate of the primary endpoint (death, myocardial infarction or stroke) at one year after randomization between the ticagrelor group (9.8%) and the prasugrel group (6.8%) was not significant [12, 13].

It is also difficult to accept criticisms towards the ISAR-REACT 5 study resulting from comparing its findings with the TRITON-TIMI 38 study results [5, 11]. It is surprising that the difference in the rate of the primary endpoint, 6.9% in the ISAR-REACT 5 study versus 9.9% in the TRITON-TIMI 38 study, has been considered unexpected and difficult to explain. This statement could be commented with the words of Orville Wright: "If we all worked on the assumption that what is accepted as true is really true, there would be little hope of advance".

In the ISAR-REACT 5 study, the primary endpoint was analyzed in the ITT population that included all randomized patients regardless of their actual treatment. The patients were followed up since the randomization (time 0) to their death, consent withdrawal, or last patient contact. The ticagrelor group included evaluable 2012 patients, and the prasugrel group included 2006 patients.

The safety analysis was performed in the modified intention-to-treat (mITT) population. With this modification, treatment safety was evaluated in all patients who received at least one dose of randomly allocated medication and were followed up for up to 7 days after treatment discontinuation. This resulted in 1989 evaluable patients in the ticagrelor group and 1773 patients in the prasugrel group. This means that the difference between ITT and mITT populations was 23 patients in the ticagrelor group compared to 233 patients in the prasugrel group. Such a large number of patients excluded from the analysis in the prasugrel group and a large difference compared to the ticagrelor group were mostly related to the study protocol that called for mandatory ticagrelor pretreatment in all patients in the ticagrelor group but made no such requirement for non-ST segment elevation ACS in the prasugrel group. As a result, the loading dose was administered to a lower number of patients in the prasugrel group compared to the ticagrelor group. Essentially, this meant that the safety analysis did not include patients who did not receive any study drug dose. These were patients who were deemed not eligible for prasugrel treatment following coronary angiography. The diagnosis of ACS was not confirmed in 184 out of these 233 patients. It is difficult to accept the criticism that the reasons for excluding these patients from the analysis were not clear as that were explicitly stated in the ISAR-REACT 5 study publication [5, 11].

Very good outcomes of prasugrel treatment in STEMI patients undergoing primary PCI were noted in a registry study than included 89,000 patients in England who were treated with prasugrel, clopidogrel, or ticagrelor in 2007–2014. When 30-day and 1-year mortality was analyzed using propensity score matching and multivariate logistic regression, a statistically significantly lower 30-day

and 1-year mortality was found among prasugrel-treated patients compared to those treated with ticagrelor and clopidogrel. Mortality in patients treated with ticagrelor or clopidogrel was similar.

Switching between oral $P2Y_{12}$ inhibitors

In the "2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS" [4], clear guidance was offered for the first time regarding the possibility and mode of switching between oral $P2Y_{12}$ inhibitors. In ACS patients who were previously treated with clopidogrel, a switch from clopidogrel to a ticagrelor 180 mg loading dose is recommended early after admission irrespective of the timing of clopidogrel administration and use of its loading dose, unless ticagrelor is contraindicated (class of recommendations I, level of evidence B). In case of adverse effects/treatment intolerance, an additional switch between oral $P2Y_{12}$ inhibitors may be considered in accordance with the presented algorithm (class of recommendations II, level of evidence C) (Figure 1) [4].

Of note, a switch in the acute setting should always involve administration of a loading dose. When clopidogrel is switched to prasugrel or ticagrelor, the loading dose

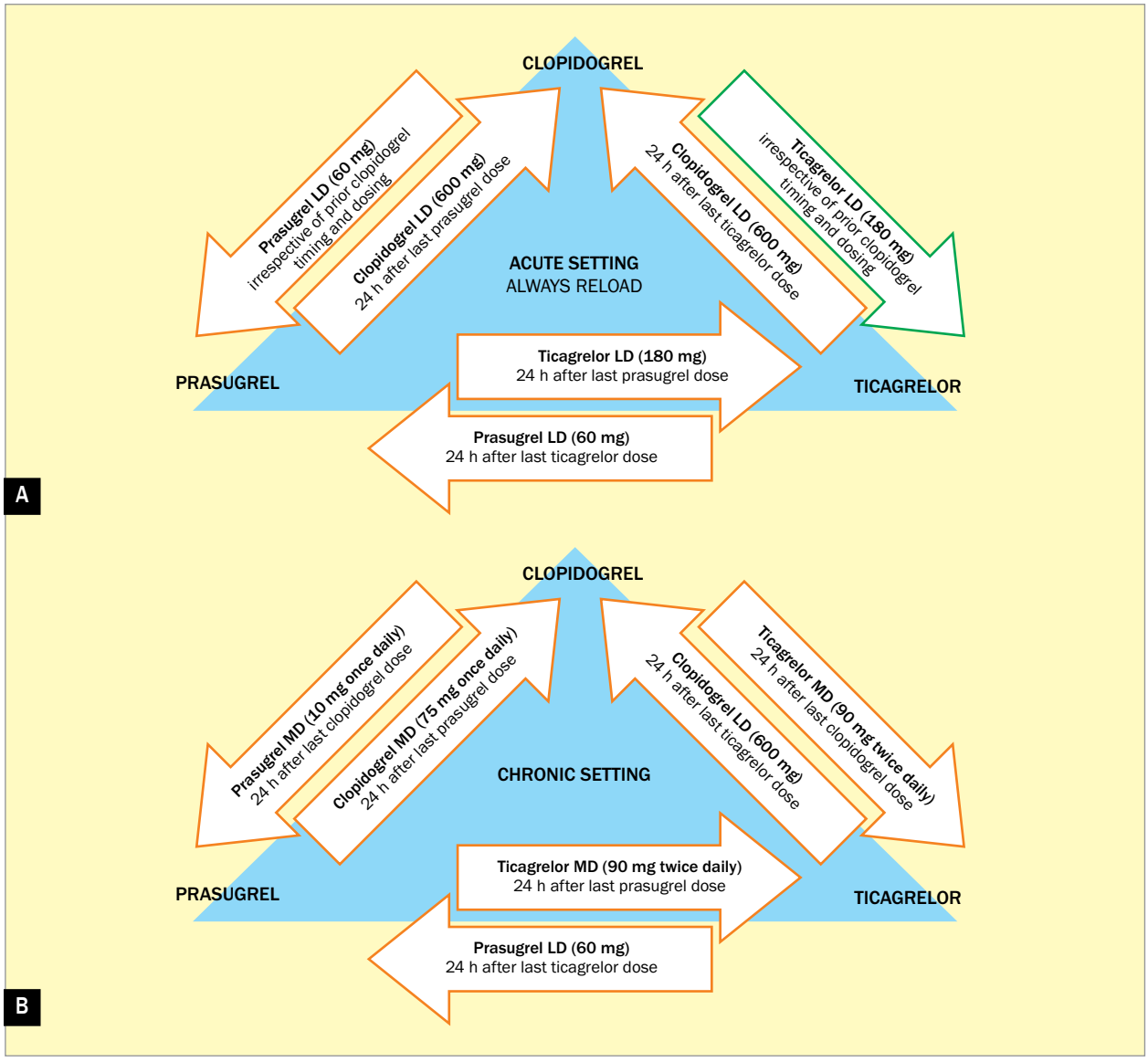

Figure 1A, B. Algorithm for switching between oral $P2Y_{12}$ inhibitors in the acute and chronic setting. Colour-coding refers to the European Society of Cardiology (ESC) Classes of Recommendations (green — Class I; orange — Class IIb). The green arrow from clopidogrel to ticagrelor highlights the only switching algorithm for which outcome data are available in patients with acute coronary syndromes. No outcome data (orange arrows) are available for all other switching algorithms. Acute setting is considered as a switching occurring during hospitalization (source [4]); LD — loading dose; MD — maintenance dose

should be administered regardless of the timing and dose of previous clopidogrel treatment. In the chronic setting, such a switch is also possible but a loading dose should be administered only if ticagrelor is switched to prasugrel or clopidogrel. However, a 24-hour interval from the last dose of previously used $P2Y_{12}$ inhibitor is always mandatory in the chronic setting.

In which patients prasugrel should be considered?

Prasugrel is the $P2Y_{12}$ inhibitor of choice in patients with ACS and should be used in appropriately selected patients with this diagnosis. This includes patients without a history of stroke or transient ischaemic attack (TIA), and without active pathological bleeding. It is also necessary to observe dose reduction in patients ≥ 75 years of age and/or with body mass below 60 kg. Prasugrel should be used in ACS patients undergoing primary or deferred PCI. It is warranted to prefer this drug in patients with STEMI. In patients with NSTEMI, the choice of $P2Y_{12}$ inhibitor should be made after coronary angiography is performed. The routine practice of ACS management in Poland suggests that the current guidelines, already published several years ago, that clearly recommend preferring prasugrel or ticagrelor over clopidogrel are commonly not adhered to. Poland is a clopidogrel country, which mainly results from economic factor-driven low availability of potent $P2Y_{12}$ inhibitor that are preferred in the guidelines. Unfortunately, it is often the case that modern $P2Y_{12}$ inhibitor treatment initiated during the hospitalization for ACS is withdrawn after weeks or months due to financial constraints of Polish patients, or ticagrelor is dosed once daily instead of twice daily for the same reason. Thus, appearance of a modern $P2Y_{12}$ inhibitor on the market in the form of a competitively priced generic prasugrel creates an opportunity for the treatment that is consistent with the current guidelines and should change the currently prevailing ACS management strategy in Polish patients. It may also be hoped that in this way, excessive 1-year mortality seen in patients discharged after MI may be reduced.

Conflict(s) of interest

Lecture fees from the companies: Adamed, AstraZeneca, Bayer, Gedeon Richter, Sanofi.

References

1. Poloński L, Gierlotka M, Zdrojewski T. Narodowa baza danych zawałów serca AMI-PL i Ogólnopolski rejestr ostrych zespołów wieńcowych PL-ACS. Medycyna Praktyczna, Kraków 2015.
2. Gierlotka M, Zdrojewski T, Wojtyniak B, et al. Incidence, treatment, in-hospital mortality and one-year outcomes of acute myocardial infarction in Poland in 2009–2012 — nationwide AMI-PL database. Kardiol Pol. 2015; 73(3): 142–158, doi: 10.5603/KP.a2014.0213, indexed in Pubmed: 25371307.
3. Mozaffarian D, Benjamin EJ, Go AS, et al. Writing Group Members, American Heart Association Statistics Committee, Stroke Statistics Subcommittee. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation. 2016; 133(4): e38–e360, doi: 10.1161/CIR.0000000000000350, indexed in Pubmed: 26673558.
4. Uaktualnione stanowisko ESC dotyczące stosowania podwójnej terapii przeciwpłytkowej w chorobie wieńcowej w 2017 roku, przygotowane we współpracy z EACTS. Grupa Robocza Europejskiego Towarzystwa Kardiologicznego (ESC) i Europejskiego Stowarzyszenia Chirurgii Serca i Klatki Piersiowej (EACTS) do spraw stosowania podwójnej terapii przeciwpłytkowej w chorobie wieńcowej. Kardiol Pol. 2017; 75: 1217–1299, doi: 10.5603/KP.2017.0224.
5. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007; 357(20): 2001–2015, doi: 10.1056/nejmoa0706482.
6. Wallentin L, Becker R, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009; 361(11): 1045–1057, doi: 10.1056/nejmoa0904327, indexed in Pubmed: 19717846.
7. Ibanez B, James S, Agewall S, et al. Wytyczne ESC dotyczące postępowania w ostrym zawale serca z uniesieniem odcinka ST w 2017 roku. Grupa Robocza Europejskiego Towarzystwa Kardiologicznego (ESC) do spraw postępowania w ostrym zawale serca z uniesieniem odcinka ST. Kardiol Pol. 2018; 76: 229–313, doi: 10.5603/KP.2018.0041.
8. Roffi M, Patrono C, Collet JP, et al. Wytyczne ESC dotyczące postępowania w ostrych zespołach wieńcowych bez przetrwałego uniesienia odcinka ST w 2015 roku. Grupa Robocza Europejskiego Towarzystwa Kardiologicznego (ESC) do spraw postępowania w ostrych zespołach wieńcowych bez przetrwałego uniesienia odcinka ST. Kardiol Pol. 2015; 73: 1207–1294, doi: 10.5603/KP.2015.0243.
9. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. Wytyczne ESC/EACTS dotyczące rewaskularyzacji mięśnia sercowego. Grupa Robocza ds. rewaskularyzacji mięśnia sercowego Europejskiego Towarzystwa Kardiologicznego (ESC) i Europejskiego Stowarzyszenia Chirurgii Serca i Klatki Piersiowej (EACTS). Kardiol Pol. 2018; 76: 1585–1664, doi: 10.5603/KP.2018.0228.
10. Motovska Z, Hlinomaz O, Kala P, et al. PRAGUE-18 Investigators, PRAGUE-18 Study Group. Prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: multicenter randomized PRAGUE-18 study. Circulation. 2016; 134(21): 1603–1612, doi: 10.1161/CIRCULATIONAHA.116.024823, indexed in Pubmed: 27576777.
11. Schüpke S, Neumann FJ, Menichelli M, 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, indexed in Pubmed: 31475799.
12. Adamski P, Kubica J. ISAR-REACT 5 — czy to badanie powinno zmienić praktykę kliniczną? Folia Cardiol. 2019; 14(5): 483–487, doi: 10.5603/FC.a2019.0099.
13. Kubica J, Jaguszewski M. ISAR-REACT 5 — what have we learned? Cardiol J. 2019; 26(5): 427–428, doi: 10.5603/CJ.a2019.0090, indexed in Pubmed: 31536136.
14. Olier I, Sirker A, Hildick-Smith DJR, et al. British Cardiovascular Intervention Society and the National Institute for Cardiovascular Outcomes Research. Association of different antiplatelet therapies with mortality after primary percutaneous coronary intervention. Heart. 2018; 104(20): 1683–1690, doi: 10.1136/heartjnl-2017-312366, indexed in Pubmed: 29437885.