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Maintenance therapy with a P2Y12 receptor inhibitor after cangrelor in patients with acute coronary syndrome. The ELECTRA-SIRIO 2 investigators' viewpoint

Running title: **Which P2Y12 inhibitor after cangrelor?**

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Abstract

According to the ESC guidelines, cangrelor may be considered in P2Y₁₂-inhibitor-naïve acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). The aim of this review is to summarize available evidence on the optimal maintenance therapy with P2Y₁₂ receptor inhibitor after cangrelor. Transitioning from cangrelor to a thienopyridine, but not ticagrelor, can be associated with a drug-drug interaction (DDI); therefore, a ticagrelor loading dose (LD) can be given any time before, during, or at the end of a cangrelor infusion, while a LD of clopidogrel or prasugrel should be administered at the time the infusion of cangrelor ends or within 30 minutes before the end of infusion in the case of a LD of prasugrel. Administration of any oral antiplatelet agent at the end of a cangrelor infusion will also result in a transient period of increased platelet reactivity. The inter-individual variability of this period is difficult to predict because it depends on many factors related to the patient and the treatment. In addition, experimental studies indicate that cangrelor may exert a cardioprotective effect beyond the blockade of platelet aggregation. Considering the available data, the potential use of cangrelor in ACS patients goes well beyond the current indications. Furthermore, we believe that it might be prudent to avoid use of thienopyridines during and soon after a cangrelor infusion until conclusive data on the effect of the DDI on the clinical outcome are available. On the other hand, ticagrelor seems to

be an optimal oral agent for continuation of P2Y12 inhibition in patients receiving cangrelor infusion.

Keywords: antiplatelet therapy, cangrelor, ticagrelor, P2Y12 receptor inhibition

Introduction

The optimal treatment of patients with acute coronary syndrome (ACS) should be focused on myocardial salvage by prompt restoration of myocardial perfusion, cardioprotection preventing reperfusion injury, and prevention of infarct-related artery re-occlusion due to a thrombotic event [1, 2]. The potent oral P2Y12 receptor inhibitors, prasugrel and ticagrelor, provide significant reduction of thrombotic events in ACS patients when compared with clopidogrel, and are therefore recommended as the first-line therapy in this subset of patients [1–7]. However, even prasugrel and ticagrelor may fail to achieve adequate platelet inhibition in ACS patients undergoing immediate invasive treatment. The onset of action of oral P2Y12 receptor inhibitors is substantially delayed in patients diagnosed with ST-segment elevation myocardial infarction (STEMI) [8, 9], especially in those who are critically ill [10–12], including patients undergoing targeted temperature management [13–17], or if morphine is used [18–22]. All such cases result in inadequate platelet inhibition during primary percutaneous coronary intervention (PCI), when the antiplatelet effect is most desired. In contrast to commonly used oral P2Y12 receptor inhibitors with delayed onset and offset of action, the favorable properties of intravenous P2Y12 receptor inhibitor cangrelor make it a desirable agent in the setting of high-risk ACS. Cangrelor is a potent, quickly reversible, direct-acting P2Y12 receptor antagonist with a linear and dose-dependent pharmacokinetic profile with predictable plasma levels, reaching optimal platelet inhibition within minutes

after the start of infusion. It is rapidly metabolized through dephosphorylation by an endonucleotidase located on the surface of vascular endothelial cells, with an elimination half-life of 2.9 to 5.5 minutes [23–26]. Platelet function recovers within 60–90 minutes after termination of cangrelor infusion [27–29]. These unique properties of rapid onset and offset of antiplatelet effect make cangrelor an attractive therapeutic option complementary to available oral antiaggregatory agents. The aim of this review is to discuss available evidence on the optimal maintenance therapy with P2Y₁₂ receptor inhibitor after cangrelor in patients with ACS.

The current place of cangrelor in the treatment of ACS patients

According to the ESC guidelines cangrelor may be considered in P2Y₁₂ inhibitor-naïve patients undergoing PCI in STEMI and non-ST-elevation ACS (class IIb recommendation) or in those who are considered unable to absorb oral agents [1, 2]. Cangrelor should be administered in a bolus of 30 mcg/kg i.v. followed by 4 mcg/kg/min infusion for at least 2 hours or the duration of the procedure (whichever is longer) [2].

The European Medicines Agency approved the use of cangrelor in patients undergoing PCI who did not receive another P2Y₁₂ receptor inhibitor before the procedure and in subjects in whom oral P2Y₁₂ inhibitor therapy is not feasible or desirable [31].

In the latest ACC/AHA/SCAI Guidelines for Coronary Artery Revascularization, cangrelor is recommended for patients undergoing PCI, who are naïve to oral P2Y₁₂ receptor inhibitors, to reduce periprocedural ischemic events (class 2B recommendation with level of evidence B-R) [32].

The Food and Drug Administration approved cangrelor in the United States as an adjunct to PCI to reduce the risk of stent thrombosis, periprocedural myocardial infarction, and repeated

revascularization in patients not pre-treated with an oral P2Y12 inhibitor and without indication to receive glycoprotein IIb/IIIa inhibitors [33].

The timing of administration of oral P2Y12 inhibitors in patients receiving an infusion of cangrelor at the time of PCI should be drug specific (Central Illustration). According to the ESC guidelines in the transition from cangrelor to a thienopyridine, the thienopyridine should be administered immediately after discontinuation of cangrelor with a loading dose (LD) (clopidogrel 600 mg or prasugrel 60 mg); to avoid a potential drug-drug interaction (DDI), prasugrel may also be administered 30 min before the cangrelor infusion is stopped. Ticagrelor (LD 180 mg) should be administered at the time of PCI to minimize the potential gap in platelet inhibition during the transition phase [2].

The potential of cangrelor in the treatment of ACS patients

The results of the ATLANTIC trial provided good evidence for the clinical benefits associated with early inhibition of P2Y12 platelet receptors [35]. The study conducted in 1862 patients with STEMI failed to show superiority of early, pre-hospital administration of ticagrelor LD versus later administration in the catheterization laboratory, with regard to the co-primary end points defined as the proportion of patients who did not have 70% or greater resolution of ST-segment elevation before PCI and the proportion of patients who did not meet the criteria for thrombolysis in myocardial infarction (TIMI) flow grade 3 in the infarct-related artery at angiography before PCI. The lack of benefit of the tested strategy of earlier ticagrelor administration was suggested to have resulted from a relatively small time difference of 31 minutes between the prehospital vs. in-hospital administration. Moreover, as many as 50% of the study participants received morphine, which may have further influenced the outcome of the study. In fact, a subgroup analysis revealed superiority of the tested strategy, as far as the primary endpoint was concerned, only in patients who had not received morphine [35].

Additionally, administration of morphine has been reported in the past to be associated with delayed onset of action of ticagrelor [36] and increased use of glycoprotein IIb/IIIa inhibitors [37].

P2Y₁₂ receptor inhibition with cangrelor has the potential to produce even better results because it has an earlier, more potent effect, overcoming the impact of delayed and decreased absorption seen with oral P2Y₁₂ inhibitors in patients with STEMI, in cardiogenic shock, in those receiving morphine or undergoing mild therapeutic hypothermia [8, 9, 11, 13, 14, 17, 18, 38, 39]. Sufficient platelet inhibition may also be uncertain in patients with nausea or vomiting, or in those who are unable to swallow or promptly absorb orally administered P2Y₁₂ receptor inhibitors, i.e., patients who are sedated and/or intubated. In contrast, cangrelor produces rapid, effective, and predictable platelet inhibition in these subgroups of patients [25, 26, 29].

In addition, experimental studies indicate that cangrelor may exert a cardioprotective effect beyond the blockade of platelet aggregation [40, 41]. This effect appears to be related to the same signal transduction pathway involved in pre- and post-conditioning. Administration of cangrelor shortly before reperfusion in rabbits reduced infarct size by approximately 50% [40]. Cangrelor-related myocardial salvage was dose dependent and correlated with the degree of inhibition of platelet aggregation. Cardioprotection was absent when cangrelor was used in crystalloid-perfused isolated hearts, indicating the involvement of an undefined whole-blood component in this process. This myocardium saving effect against reperfusion injury may be a class effect and hence common for all P2Y₁₂ inhibitors. However, with cangrelor the protective effect develops within a short time — typically required in the target population of patients with myocardial infarction and occluded infarct-related artery [41, 42]. To date, these experimental findings have never been tested in a clinical trial.

Interactions of cangrelor with oral inhibitors of P2Y12 receptor

Cangrelor rapidly disappears from the plasma after termination of infusion due to its very short half-life. Furthermore, because of its reversible binding, the drug dissociates from the P2Y12 receptors, making them available for binding with clopidogrel active metabolite [26, 29]. To continue P2Y12 inhibition after a PCI, it is necessary to transition to an oral agent in the immediate post-procedure period. However, transitioning from cangrelor to a thienopyridine (clopidogrel and prasugrel), but not ticagrelor, can be associated with a DDI [43–51].

Steinhubl et al. [46] showed that cangrelor and clopidogrel administered alone in healthy volunteers produce the expected level of platelet inhibition. The anticipated effect of clopidogrel treatment did not occur when cangrelor was initiated simultaneously. Such an effect was not found when clopidogrel was started upon completion of the cangrelor infusion. However, a transient recovery of platelet reactivity was observed as the inhibitory effect of cangrelor disappeared, followed by further inhibition as the clopidogrel was metabolized to its active form [46]. The *in vitro* experiments reported by Dovlatova et al. provided a mechanistic explanation for these findings and showed the possibility of a parallel scenario arising when prasugrel is used in the place of clopidogrel [47]. They confirmed the interaction between cangrelor and both thienopyridines, limiting the antiplatelet effect of clopidogrel and prasugrel to a degree dependent on the concentration of cangrelor. Presumably, occupation of the platelet P2Y12 receptors by cangrelor prevents the covalent binding of the clopidogrel or prasugrel metabolite. Therefore, due to the relatively short half-life of the active metabolites of clopidogrel and prasugrel, administration of thienopyridines at high concentrations of cangrelor precludes irreversible blocking of P2Y12 receptors, and the full effect of oral therapy may not be achieved until the subsequent administration of the second dose of the drug [47–50]. On the other hand, administration of any oral antiplatelet agent at the end of

cangrelor infusion will also result in a transient period of increased platelet reactivity. The inter-individual variability of this period is very difficult to predict because it depends on many factors related to the patient and treatment.

In contrast to thienopyridines, a lack of interaction between cangrelor and ticagrelor reported in several studies [44, 53, 54] is to be expected because the mechanism of action of these reversible P2Y₁₂ receptor inhibitors is similar. Therefore, the LD of ticagrelor should be administered at the initiation of cangrelor infusion or even before. As a result, when the cangrelor infusion is stopped and the drug is rapidly cleared from the circulation, ticagrelor can bind to the P2Y₁₂ receptors. During the transition period, the platelet reactivity should reflect current plasma concentrations of both these agents [53].

These findings may be clinically relevant, but much more data are required to validate our limited knowledge of the transition from intravenous to oral inhibitor of P2Y₁₂ receptor [45–47, 51–55].

Summary

Considering the available data, the potential use of cangrelor in ACS patients goes far beyond the current indications. Furthermore, we believe that it might be prudent to avoid use of thienopyridines during and soon after a cangrelor infusion until conclusive data on the effect of the DDI on clinical outcome are available. On the other hand, ticagrelor seems to be an optimal oral agent for continuation of P2Y₁₂ inhibition in patients receiving a cangrelor infusion.

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References

1. Collet JP, Thiele H, Barbato E, et al. 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(14): 1289–1367, doi: [10.1093/eurheartj/ehaa575](https://doi.org/10.1093/eurheartj/ehaa575), indexed in Pubmed: [32860058](https://pubmed.ncbi.nlm.nih.gov/32860058/).
2. Byrne RA, Rossello X, Coughlan JJ, et al. ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J.* 2023; 44(38): 3720–3826, doi: [10.1093/eurheartj/ehad191](https://doi.org/10.1093/eurheartj/ehad191), indexed in Pubmed: [37622654](https://pubmed.ncbi.nlm.nih.gov/37622654/).
 3. Wiviott SD, Braunwald E, McCabe CH, et al. TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007; 357(20): 2001–2015, doi: [10.1056/NEJMoa0706482](https://doi.org/10.1056/NEJMoa0706482), indexed in Pubmed: [17982182](https://pubmed.ncbi.nlm.nih.gov/17982182/).
 4. Wallentin L, Becker RC, Budaj A, et al. PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009; 361(11): 1045–1057, doi: [10.1056/NEJMoa0904327](https://doi.org/10.1056/NEJMoa0904327), indexed in Pubmed: [19717846](https://pubmed.ncbi.nlm.nih.gov/19717846/).
 5. 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/).
 6. 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. *Cardiol J.* 2022; 29(4): 540–552, doi: [10.5603/CJ.a2022.0026](https://doi.org/10.5603/CJ.a2022.0026), indexed in Pubmed: [35514089](https://pubmed.ncbi.nlm.nih.gov/35514089/).
 7. Hudzik B, Błachut A, Lesiak M, et al. Summary of the European Society of Cardiology guidelines on dual antiplatelet therapy in patients after percutaneous coronary interventions. *Kardiol Pol.* 2022; 80(10): 974–989, doi: [10.33963/KP.a2022.0198](https://doi.org/10.33963/KP.a2022.0198), indexed in Pubmed: [36036339](https://pubmed.ncbi.nlm.nih.gov/36036339/).

8. 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/).
9. Agrawal K, Bhatt DL. Antiplatelet therapy: Does prasugrel or ticagrelor suffice in patients with STEMI? *Nat Rev Cardiol*. 2013; 10(3): 121–122, doi: [10.1038/nrcardio.2012.199](https://doi.org/10.1038/nrcardio.2012.199), indexed in Pubmed: [23319096](https://pubmed.ncbi.nlm.nih.gov/23319096/).
10. Schoergenhofer C, Hobl EL, Staudinger T, et al. Prasugrel in critically ill patients. *Thromb Haemost*. 2017; 117(8): 1582–1587, doi: [10.1160/TH17-03-0154](https://doi.org/10.1160/TH17-03-0154), indexed in Pubmed: [28692105](https://pubmed.ncbi.nlm.nih.gov/28692105/).
11. Adamski P, Buszko K, Sikora J, et al. Determinants of high platelet reactivity in patients with acute coronary syndromes treated with ticagrelor. *Sci Rep*. 2019; 9(1): 3924, doi: [10.1038/s41598-019-40628-0](https://doi.org/10.1038/s41598-019-40628-0), indexed in Pubmed: [30850677](https://pubmed.ncbi.nlm.nih.gov/30850677/).
12. Aradi D, Collet JP, Mair J, et al. Study Group on Biomarkers in Cardiology of the Acute Cardiovascular Care Association of the European Society of Cardiology, Working Group on Thrombosis of the European Society of Cardiology. Platelet function testing in acute cardiac care - is there a role for prediction or prevention of stent thrombosis and bleeding? *Thromb Haemost*. 2015; 113(2): 221–230, doi: [10.1160/TH14-05-0449](https://doi.org/10.1160/TH14-05-0449), indexed in Pubmed: [25413597](https://pubmed.ncbi.nlm.nih.gov/25413597/).
13. Kubica J, Pstrągowski K, Adamski P, et al. Mild therapeutic hypothermia for patients with acute coronary syndrome and cardiac arrest treated with percutaneous coronary intervention (UNICORN). The design and rationale for the prospective, observational, multicenter study. *Medical Research Journal*. 2016; 1(1): 23–27, doi: [10.5603/mrj.2016.0004](https://doi.org/10.5603/mrj.2016.0004).

14. Umińska JM, Ratajczak J, Buszko K, et al. Impact of mild therapeutic hypothermia on bioavailability of ticagrelor in patients with acute myocardial infarction after out-of-hospital cardiac arrest. *Cardiol J.* 2020; 27(6): 780–788, doi: [10.5603/CJ.a2019.0024](https://doi.org/10.5603/CJ.a2019.0024), indexed in Pubmed: [30799546](https://pubmed.ncbi.nlm.nih.gov/30799546/).
15. Bednar F, Kroupa J, Ondrakova M, et al. Antiplatelet efficacy of P2Y12 inhibitors (prasugrel, ticagrelor, clopidogrel) in patients treated with mild therapeutic hypothermia after cardiac arrest due to acute myocardial infarction. *J Thromb Thrombolysis.* 2016; 41(4): 549–555, doi: [10.1007/s11239-015-1274-7](https://doi.org/10.1007/s11239-015-1274-7), indexed in Pubmed: [26340851](https://pubmed.ncbi.nlm.nih.gov/26340851/).
16. Flierl U, Röntgen P, Zauner F, et al. Platelet inhibition with prasugrel in patients with acute myocardial infarction undergoing therapeutic hypothermia after cardiopulmonary resuscitation. *Thromb Haemost.* 2016; 115(5): 960–968, doi: [10.1160/TH15-07-0599](https://doi.org/10.1160/TH15-07-0599), indexed in Pubmed: [26790884](https://pubmed.ncbi.nlm.nih.gov/26790884/).
17. Umińska JM, Ratajczak J, Pstrągowski K, et al. The impact of mild therapeutic hypothermia on platelet reactivity in comatose survivors of cardiac arrest with acute myocardial infarction treated with ticagrelor. *Cardiol J.* 2024; 31(3): 472–478, doi: [10.5603/CJ.a2022.0029](https://doi.org/10.5603/CJ.a2022.0029), indexed in Pubmed: [35514087](https://pubmed.ncbi.nlm.nih.gov/35514087/).
18. 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/).
19. 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/).

20. Bartko J, Schoergenhofer C, Schwameis M, et al. Morphine Interaction with Aspirin: a Double-Blind, Crossover Trial in Healthy Volunteers. *J Pharmacol Exp Ther.* 2018; 365(2): 430–436, doi: [10.1124/jpet.117.247213](https://doi.org/10.1124/jpet.117.247213), indexed in Pubmed: [29540563](https://pubmed.ncbi.nlm.nih.gov/29540563/).
21. Kubica J, Adamski P, Ostrowska M, et al. Influence of Morphine on Pharmacokinetics and Pharmacodynamics of Ticagrelor in Patients with Acute Myocardial Infarction (IMPRESSION): study protocol for a randomized controlled trial. *Trials.* 2015; 16: 198, doi: [10.1186/s13063-015-0724-z](https://doi.org/10.1186/s13063-015-0724-z), indexed in Pubmed: [25925591](https://pubmed.ncbi.nlm.nih.gov/25925591/).
22. Siller-Matula JM, Specht S, Kubica J, et al. Abciximab as a bridging strategy to overcome morphine-prasugrel interaction in STEMI patients. *Br J Clin Pharmacol.* 2016; 82(5): 1343–1350, doi: [10.1111/bcp.13053](https://doi.org/10.1111/bcp.13053), indexed in Pubmed: [27366874](https://pubmed.ncbi.nlm.nih.gov/27366874/).
23. Ferreiro JL, Ueno M, Angiolillo DJ. Cangrelor: a review on its mechanism of action and clinical development. *Expert Rev Cardiovasc Ther.* 2009; 7(10): 1195–1201, doi: [10.1586/erc.09.101](https://doi.org/10.1586/erc.09.101), indexed in Pubmed: [19814662](https://pubmed.ncbi.nlm.nih.gov/19814662/).
24. Akers WS, Oh JJ, Oestreich JH, et al. Pharmacokinetics and pharmacodynamics of a bolus and infusion of cangrelor: a direct, parenteral P2Y₁₂ receptor antagonist. *J Clin Pharmacol.* 2010; 50(1): 27–35, doi: [10.1177/0091270009344986](https://doi.org/10.1177/0091270009344986), indexed in Pubmed: [19779037](https://pubmed.ncbi.nlm.nih.gov/19779037/).
25. 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/).
26. 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/).

27. Bhatt DL, Lincoff AM, Gibson CM, et al. CHAMPION PLATFORM Investigators. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med.* 2009; 361(24): 2330–2341, doi: [10.1056/NEJMoa0908629](https://doi.org/10.1056/NEJMoa0908629), indexed in Pubmed: [19915222](https://pubmed.ncbi.nlm.nih.gov/19915222/).
28. Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med.* 2009; 361(24): 2318–2329, doi: [10.1056/NEJMoa0908628](https://doi.org/10.1056/NEJMoa0908628), indexed in Pubmed: [19915221](https://pubmed.ncbi.nlm.nih.gov/19915221/).
29. 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/).
30. Niezgoda P, Ostrowska M, Adamski P, et al. Pretreatment with P2Y Receptor Inhibitors in Acute Coronary Syndromes-Is the Current Standpoint of ESC Experts Sufficiently Supported? *J Clin Med.* 2023; 12(6), doi: [10.3390/jcm12062374](https://doi.org/10.3390/jcm12062374), indexed in Pubmed: [36983373](https://pubmed.ncbi.nlm.nih.gov/36983373/).
31. Kangrexal EPAR summary for the public . <https://www.ema.europa.eu/en/medicines/human/EPAR/kengrexal> (15.05.2023).
32. Lawton JS, Tamis-Holland JE, Bangalore S, et al. Writing Committee Members. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022; 79(2): e21–e2e129, doi: [10.1016/j.jacc.2021.09.006](https://doi.org/10.1016/j.jacc.2021.09.006), indexed in Pubmed: [34895950](https://pubmed.ncbi.nlm.nih.gov/34895950/).
33. Cangrelor United States full prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204958lbl.pdf (15.05.2023).

34. Valgimigli M, Bueno H, Byrne RA, et al. ESC Scientific Document Group, ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018; 39(3): 213–260, doi: [10.1093/eurheartj/ehx419](https://doi.org/10.1093/eurheartj/ehx419), indexed in Pubmed: [28886622](https://pubmed.ncbi.nlm.nih.gov/28886622/).
35. Montalescot G, van 't Hof AW, Lapostolle F, et al. ATLANTIC Investigators. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med*. 2014; 371(11): 1016–1027, doi: [10.1056/NEJMoa1407024](https://doi.org/10.1056/NEJMoa1407024), indexed in Pubmed: [25175921](https://pubmed.ncbi.nlm.nih.gov/25175921/).
36. Silvain J, Storey RF, Cayla G, et al. P2Y12 receptor inhibition and effect of morphine in patients undergoing primary PCI for ST-segment elevation myocardial infarction. The PRIVATE-ATLANTIC study. *Thromb Haemost*. 2016; 116(2): 369–378, doi: [10.1160/TH15-12-0944](https://doi.org/10.1160/TH15-12-0944), indexed in Pubmed: [27196998](https://pubmed.ncbi.nlm.nih.gov/27196998/).
37. Lapostolle F, Van't Hof AW, Hamm CW, et al. ATLANTIC Investigators. Morphine and Ticagrelor Interaction in Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction: ATLANTIC-Morphine. *Am J Cardiovasc Drugs*. 2019; 19(2): 173–183, doi: [10.1007/s40256-018-0305-0](https://doi.org/10.1007/s40256-018-0305-0), indexed in Pubmed: [30353444](https://pubmed.ncbi.nlm.nih.gov/30353444/).
38. 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/).
39. Adamski P, Adamska U, Ostrowska M, et al. Evaluating current and emerging antithrombotic therapy currently available for the treatment of acute coronary

- syndrome in geriatric populations. *Expert Opin Pharmacother*. 2018; 19(13): 1415–1425, doi: [10.1080/14656566.2018.1510487](https://doi.org/10.1080/14656566.2018.1510487), indexed in Pubmed: [30132731](https://pubmed.ncbi.nlm.nih.gov/30132731/).
40. Yang XM, Liu Y, Cui L, et al. Platelet P2Y₁₂ blockers confer direct postconditioning-like protection in reperfused rabbit hearts. *J Cardiovasc Pharmacol Ther*. 2013; 18(3): 251–262, doi: [10.1177/1074248412467692](https://doi.org/10.1177/1074248412467692), indexed in Pubmed: [23233653](https://pubmed.ncbi.nlm.nih.gov/23233653/).
41. Yang XM, Liu Y, Cui L, et al. Two classes of anti-platelet drugs reduce anatomical infarct size in monkey hearts. *Cardiovasc Drugs Ther*. 2013; 27(2): 109–115, doi: [10.1007/s10557-012-6436-7](https://doi.org/10.1007/s10557-012-6436-7), indexed in Pubmed: [23318690](https://pubmed.ncbi.nlm.nih.gov/23318690/).
42. Adamski P, Koziński M, Ostrowska M, et al. Overview of pleiotropic effects of platelet P2Y₁₂ receptor inhibitors. *Thromb Haemost*. 2014; 112(2): 224–242, doi: [10.1160/TH13-11-0915](https://doi.org/10.1160/TH13-11-0915), indexed in Pubmed: [24763899](https://pubmed.ncbi.nlm.nih.gov/24763899/).
43. Angiolillo DJ, Rollini F, Storey RF, et al. International Expert Consensus on Switching Platelet P2Y Receptor-Inhibiting Therapies. *Circulation*. 2017; 136(20): 1955–1975, doi: [10.1161/CIRCULATIONAHA.117.031164](https://doi.org/10.1161/CIRCULATIONAHA.117.031164), indexed in Pubmed: [29084738](https://pubmed.ncbi.nlm.nih.gov/29084738/).
44. Schneider DJ, Agarwal Z, Seecheran N, et al. Pharmacodynamic effects during the transition between cangrelor and ticagrelor. *JACC Cardiovasc Interv*. 2014; 7(4): 435–442, doi: [10.1016/j.jcin.2013.08.017](https://doi.org/10.1016/j.jcin.2013.08.017), indexed in Pubmed: [24656538](https://pubmed.ncbi.nlm.nih.gov/24656538/).
45. Schneider DJ, Seecheran N, Raza SS, et al. Pharmacodynamic effects during the transition between cangrelor and prasugrel. *Coron Artery Dis*. 2015; 26(1): 42–48, doi: [10.1097/MCA.0000000000000158](https://doi.org/10.1097/MCA.0000000000000158), indexed in Pubmed: [25089928](https://pubmed.ncbi.nlm.nih.gov/25089928/).
46. Steinhubl SR, Oh JJ, Oestreich JH, et al. Transitioning patients from cangrelor to clopidogrel: pharmacodynamic evidence of a competitive effect. *Thromb Res*. 2008; 121(4): 527–534, doi: [10.1016/j.thromres.2007.05.020](https://doi.org/10.1016/j.thromres.2007.05.020), indexed in Pubmed: [17631948](https://pubmed.ncbi.nlm.nih.gov/17631948/).

47. Dovlatova NL, Jakubowski JA, Sugidachi A, et al. The reversible P2Y antagonist cangrelor influences the ability of the active metabolites of clopidogrel and prasugrel to produce irreversible inhibition of platelet function. *J Thromb Haemost.* 2008; 6(7): 1153–1159, doi: [10.1111/j.1538-7836.2008.03020.x](https://doi.org/10.1111/j.1538-7836.2008.03020.x), indexed in Pubmed: [18485086](https://pubmed.ncbi.nlm.nih.gov/18485086/).
48. Karaźniewicz-Łada M, Danielak D, Burchardt P, et al. Clinical pharmacokinetics of clopidogrel and its metabolites in patients with cardiovascular diseases. *Clin Pharmacokinet.* 2014; 53(2): 155–164, doi: [10.1007/s40262-013-0105-2](https://doi.org/10.1007/s40262-013-0105-2), indexed in Pubmed: [24127209](https://pubmed.ncbi.nlm.nih.gov/24127209/).
49. Wang H, Qi J, Li Yi, et al. Pharmacodynamics and pharmacokinetics of ticagrelor vs. clopidogrel in patients with acute coronary syndromes and chronic kidney disease. *Br J Clin Pharmacol.* 2018; 84(1): 88–96, doi: [10.1111/bcp.13436](https://doi.org/10.1111/bcp.13436), indexed in Pubmed: [28921624](https://pubmed.ncbi.nlm.nih.gov/28921624/).
50. Dobesh PP. Pharmacokinetics and pharmacodynamics of prasugrel, a thienopyridine P2Y₁₂ inhibitor. *Pharmacotherapy.* 2009; 29(9): 1089–1102, doi: [10.1592/phco.29.9.1089](https://doi.org/10.1592/phco.29.9.1089), indexed in Pubmed: [19698014](https://pubmed.ncbi.nlm.nih.gov/19698014/).
51. Judge HM, Buckland RJ, Jakubowski JA, et al. Cangrelor inhibits the binding of the active metabolites of clopidogrel and prasugrel to P2Y₁₂ receptors in vitro. *Platelets.* 2016; 27(3): 191–195, doi: [10.3109/09537104.2015.1069809](https://doi.org/10.3109/09537104.2015.1069809), indexed in Pubmed: [26270719](https://pubmed.ncbi.nlm.nih.gov/26270719/).
52. Rymer JA, Bhatt DL, Angiolillo DJ, et al. Cangrelor Use Patterns and Transition to Oral P2Y Inhibitors Among Patients With Myocardial Infarction: Initial Results From the CAMEO Registry. *J Am Heart Assoc.* 2022; 11(11): e024513, doi: [10.1161/JAHA.121.024513](https://doi.org/10.1161/JAHA.121.024513), indexed in Pubmed: [35621210](https://pubmed.ncbi.nlm.nih.gov/35621210/).
53. Ravnefjord A, Weilitz J, Emanuelsson BM, et al. Evaluation of ticagrelor pharmacodynamic interactions with reversibly binding or non-reversibly binding

P2Y₁₂ antagonists in an ex-vivo canine model. *Thromb Res.* 2012; 130(4): 622–628, doi: [10.1016/j.thromres.2012.07.021](https://doi.org/10.1016/j.thromres.2012.07.021), indexed in Pubmed: [22909827](https://pubmed.ncbi.nlm.nih.gov/22909827/).

54. Adamski P, Skonieczny G, Hajdukiewicz T, et al. Reversal of Platelet Inhibition in Patients Receiving Ticagrelor. *Rev Cardiovasc Med.* 2022; 23(9): 300, doi: [10.31083/j.rcm2309300](https://doi.org/10.31083/j.rcm2309300), indexed in Pubmed: [39077695](https://pubmed.ncbi.nlm.nih.gov/39077695/).

55. Schneider DJ. Transition strategies from cangrelor to oral platelet P2Y₁₂ receptor antagonists. *Coron Artery Dis.* 2016; 27(1): 65–69, doi: [10.1097/MCA.0000000000000311](https://doi.org/10.1097/MCA.0000000000000311), indexed in Pubmed: [26444255](https://pubmed.ncbi.nlm.nih.gov/26444255/).