Supplementary material

Hudzik B, Błachut A, Lesiak M, et al. Summary of ESC guidelines on dual antiplatelet therapy in patients after percutaneous coronary interventions. Kardiol Pol. 2022.

A BRIEF OVERVIEW OF ANTIPLATELET DRUGS

The basic antiplatelet treatment regimen includes the use of acetylsalicylic acid (ASA) in a dose of 75–100 mg and an oral P_2Y_{12} inhibitor for 6 or 12 months after coronary revascularization, depending on clinical indications (CCS/ACS).

Currently orally used P_2Y_{12} inhibitors include thienopyridines (clopidogrel and prasugrel, as well as the very rarely used ticlopidine) and ticagrelor. The use of ticlopidine has been largely limited by side effects and presently is not recommended in patients with coronary artery disease [1, 2].

- There are no cardiological recommendations.
- Numerous serious side effects.
- Non-cardiac indications in selected clinical situations.

The only parenterally administered P_2Y_{12} inhibitor — cangrelor was registered in 2015. Utilization of cangrelor appears to be particularly advantageous in the case of percutaneous coronary intervention (PCI) procedures in patients, who may experience oral drug malabsorption or in patients in whom persistent platelet inhibition may be especially inadvisable, i.e. with post-PCI bleeding complications or requiring urgent coronary artery bypass graft surgery. Subsequent guidelines on the treatment of patients with myocardial infarction with ST-segment elevation, myocardial revascularization, and acute myocardial syndrome without persistent ST-segment elevation suggested that cangrelor therapy could be considered in patients undergoing percutaneous coronary revascularization if another P_2Y_{12}

inhibitor has not been previously used (class of recommendation IIb, level of evidence A) [3–5]. The indications for the use of cangrelor were not included in the 2019 guidelines on the treatment of chronic coronary syndromes [6].

- The only approved intravenous $P2Y_{12}$ inhibitor.
- The rapid onset and offset of action.
- Currently not available in Poland.

Thienopyridines

Clopidogrel, similar to prasugrel, is a thienopyridine prodrug that irreversibly blocks the P_2Y_{12} receptor through active metabolites, inhibiting ADP-induced platelet aggregation. Both drugs must be metabolized by the hepatic cytochrome P450 (CYP) enzyme system for activation, which delaying the full effect and necessitating administration of loading doses to obtain faster ADP receptor blockade.

- CLOPIDOGREL

In the case of acute coronary syndrome and/or percutaneous coronary angioplasty, a loading dose (300–600 mg) of clopidogrel is required, followed by a continuation of treatment at a maintenance dose of 75 mg once a day. Food intake does not affect drug metabolism, and in most cases, clopidogrel is rapidly absorbed from the gastrointestinal tract. The onset of action of the loading dose, thereby inhibiting ADP-induced platelet aggregation, starts within 2 to 6 hours. About 5 days after stopping therapy, platelet function returns to normal. It is recommended that surgery, including coronary artery bypass graft surgery operation, be postponed, if possible, until then. Cytochrome CYP2C19 blockers, such as the commonly used proton pump inhibitors (PPIs) — omeprazole or esomeprazole, decrease the effectiveness of clopidogrel by reducing metabolic activation of the drug, which may be associated with a higher number of adverse cardiovascular events [7]. An alternative, in these cases, may be the use of PPIs, which are weaker inhibitors of CYP2C19, such as pantoprazole [8]. Despite several limitations, clopidogrel, besides aspirin, remains the most frequently prescribed antiplatelet drug [9]. It is most certainly dictated by economic considerations (both prasugrel and ticagrelor are not reimbursed in Poland), the limited availability of the drug in ambulances and primary health care clinics, that have the first medical contact with a patient with acute coronary syndrome and begin appropriate treatment. The practice developed over the years and the list

of exclusions hindering the use of newer antiplatelet medication (drug contraindications, uncertain medical history in emergency cases) are also important.

CLOPIDOGREL IN CHRONIC CORONARY SYNDROMES AND OTHER INDICATIONS

Clopidogrel remains the first choice of antiplatelet drugs for patients with chronic coronary syndrome undergoing percutaneous coronary intervention. After stent implantation, patients should receive acetylsalicylic acid at a dose of 75–100 mg once daily (IA) [6] (for premedication before a procedure, a loading dose of 300 mg is required) and clopidogrel at a 600 mg loading dose followed by 75 mg once daily for 6 months (IA) [6]. The loading dose may be omitted when 75 mg maintenance treatment is used daily for more than 5 days prior to stent implantation. The use of prasugrel or ticagrelor in place of clopidogrel may be considered in patients with a high risk of stent thrombosis, or if a single antiplatelet agent is required due to ASA intolerance (IIbC) [6]. However, the use of clopidogrel instead of acetylsalicylic acid in case of its intolerance in the long-term prevention of thrombotic events has a higher class of recommendations (IB) [6]. Clopidogrel can also be used as the drug of the first choice at the standard dose of 75 mg once daily in patients with peripheral arterial disease, stroke, or transient ischemic attack (IIbA) [6]. The increasing use of transradial access allows consideration the use of clopidogrel even before coronarography in stable patients, who are highly likely to undergo coronary angioplasty, but the optimal time to start P_2Y_{12} inhibitor therapy has not been precisely defined.

CLOPIDOGREL IN ACUTE CORONARY SYNDROMES

In acute coronary syndromes, clopidogrel has become the drug of the second choice in the absence of prasugrel or ticagrelor (IB) [3]. However, it may be considered as a first-line treatment option, when there are indications for switching to a less potent P2Y12 inhibitor (IIbB) [3]. If fibrinolytic therapy is required, clopidogrel with acetylsalicylic acid should be used as an adjuvant therapy to reduce cardiovascular events and all-cause mortality [5]. A meta-analysis of three randomized trials showed that switching from clopidogrel to ticagrelor within 24 hours of fibrinolysis was associated with a similar risk of ischemic events and bleeding complications as with continued clopidogrel therapy [10].

Of note, the currently recommended treatment regimens in patients after coronary interventions and/or myocardial infarction requiring anticoagulant therapy prefer to use clopidogrel [11] in a

loading dose of 300–600 mg (unless the patient has been using the drug chronically) followed by a standard dose of 75 mg once daily (IC) [6].

- Irreversible $P2Y_{12}$ inhibitor.
- First-line drug for patients with chronic coronary syndrome undergoing PCI.
- The drug of the second choice for ACS.
- Favored in selected clinical situations (coexistence of indications for anticoagulant therapy, fibrinolysis treatment).
- Clopidogrel resistance may be a significant clinical problem.

- PRASUGREL

Prasugrel has a faster, more potent, and more predictable effect compared to clopidogrel. As standard, a loading dose of 60 mg is recommended when initiating therapy, followed by a continuation of treatment at a maintenance dose of 10 mg once daily. Prasugrel is less susceptible to the impact of CYP2C19 loss-of-function variants, but due to greater antiplatelet effect, is associated with more frequent bleeding complications, which makes it difficult to decide on the implementation of prasugrel therapy in emergency situations with an uncertain medical history. In patients with body weight <60 kg, a reduction of the maintenance dose to 5 mg daily is necessary. Due to the increased risk of bleeding complications, prasugrel usage in the population over 75 years of age is generally not recommended, and if such therapy is considered beneficial, a reduction of the daily dosage to 5 mg is applied. Prasugrel is contraindicated in patients with a history of stroke (ischemic and hemorrhagic) or transient ischemic attack.

The onset of inhibition of ADP-induced platelet aggregation is apparent as early as 30 minutes after administration of the loading dose. Unlike clopidogrel, prasugrel has a single-step activation process in the liver. This translates into more rapid onset and greater predictability. The duration of action is 5 to 10 days, the necessary withdrawal period before surgery is 7 days.

- Faster, more potent and homogeneous antiaggregation action compared to clopidogrel
- Irreversible blockage of platelets
- The first-line drug for ACS in patients treated invasively
- Contraindicated in patients with a history of stroke / TIA
- The need for dose reduction in selected clinical situations

Ticagrelor

Ticagrelor is the only direct oral P_2Y_{12} inhibitor that binding platelets in a reversible manner and achieves a faster therapeutic effect with a shorter duration of action, therefore it must be used twice a day, in a dose of 2 × 90 mg. After a loading dose (180 mg), the effect of the drug onset after about 30 minutes and lasts for 3–4 days. Experts recommend postponing elective surgery for at least 5 days after stopping the medication. Ticagrelor is contraindicated in patients with a history of hemorrhagic stroke, moderate to severe hepatic impairment, there are insufficient data from clinical trials in dialysis patients, therefore, drug usage in this group of patients is not recommended. Due to drug metabolism via cytochrome CYP3A, it should not be combined with drugs that strongly affect this receptor, either with strong inhibitors (ketoconazole, clarithromycin) or agonists (dexamethasone, phenytoin, carbamazepine, phenobarbital). The use of ticagrelor may be associated with the occurrence of transient dyspnea, which usually resolves spontaneously and is well tolerated by the patient, and thus does not require an immediate change of therapy to another antiplatelet drug. In the initial period of treatment, there may also occur asymptomatic pauses and slightly increased level of uric acid in the blood.

- The most potent direct oral $P2Y_{12}$ inhibitor
- Reversible blocking of platelets
- The first-line drug in ACS
- Contraindicated in patients with a history of hemorrhagic stroke
- The most common side effects are transient dyspnea and asymptomatic pauses

Table S1. CRUSADE Bleeding Risk Score

CRUSADE Score		
Predictor	Range	Score points
Baseline hematocrit, %	<31	+9
	31–33.9	+7
	34–36.9	+3
	37–39.9	+2
	≥40	0
Creatinine clearance, ml/min[a]	≤15	+39
	>15–30	+35
	>30–60	+28
	>60–90	+17
	>90–120	+7
	>120	0
Heart rate, bpm	≤70	0
	71–80	+1
	81–90	+3
	91–100	+6
	101–110	+8
	111–120	+10
	≥121	+11
Sex	Male	0
	Female	+8
Signs of congestive heart failure at presentation	No	0
	Yes	+7
History of diabetes mellitus	No	0
	Yes	+6
History of vascular disease	No	0
	Yes	+6
Systolic blood pressure, mm Hg	≤90	+10
	91–100	+8
	101–120	+5

	121–180	+1
	181–200	+3
	≥201	+5
Total score points +100 CRUSADE bleeding risk groups: very low risk ≤20 points, low 21–30 points, moderate 31–40 points, high 41-50 points, very high >50 points		

[a]Estimated using the Cockcroft-Gault formula

Table S2. DAPT Score

DAPT Score		
Predictor		Score
Age	≥75	–2
	65 to <75	–1
	<65	0
Cigarette smoking		+1
Diabetes mellitus		+1
MI at presentation		+1
Prior PCI or prior MI		+1
Paclitaxel-eluting stent		+1
Stent diameter <3 mm		+1
CHF or LVEF <30%		+2
Vein graft stent		+2
Available results from –2 to 10 points		
Score ≥2 → Long DAPT Score <2 → Standard DAPT (12 months)		

Abbreviations: CHF, congestive heart failure; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention

REFERENCES

1. Bhatt DL, Bertrand ME, Berger PB, et al. Meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting. J Am Coll Cardiol. 2002; 39(1): 9–14, doi: 10.1016/s0735-1097(01)01713-2, indexed in Pubmed: 11755280.
2. Moussa I, Oetgen M, Roubin G, et al. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. Circulation. 1999; 99(18): 2364–2366, doi: 10.1161/01.cir.99.18.2364, indexed in Pubmed: 10318654.
3. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87–165, doi: 10.1093/eurheartj/ehy394, indexed in Pubmed: 30165437.
4. Collet J, Thiele H, Barbato E, et al. 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, indexed in Pubmed: 32860058.
5. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39(2): 119–177, doi: 10.1093/eurheartj/ehx393, indexed in Pubmed: 28886621.
6. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020; 41(3): 407–477, doi: 10.1093/eurheartj/ehz425, indexed in Pubmed: 31504439.
7. Serbin MA, Guzauskas GF, Veenstra DL. Clopidogrel-proton pump inhibitor drug-drug interaction and risk of adverse clinical outcomes among pci-treated ACS patients: a meta-analysis. J Manag Care Spec Pharm. 2016; 22(8): 939–947, doi: 10.18553/jmcp.2016.22.8.939, indexed in Pubmed: 27459657.
8. Cuisset T, Frere C, Quilici J, et al. Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose the PACA (Proton Pump Inhibitors And Clopidogrel Association) prospective randomized study. J Am Coll Cardiol. 2009; 54(13): 1149–1153, doi: 10.1016/j.jacc.2009.05.050, indexed in Pubmed: 19761935.
9. Goodman SG, Nicolau JC, Requena G, et al. Longer-term oral antiplatelet use in stable post-myocardial infarction patients: Insights from the long Term rIsk, clinical

manaGement and healthcare Resource utilization of stable coronary artery dISease (TIGRIS) observational study. Int J Cardiol. 2017; 236: 54–60, doi: 10.1016/j.ijcard.2017.02.062, indexed in Pubmed: 28268087.

10. Kheiri B, Osman M, Abdalla A, et al. Ticagrelor versus clopidogrel after fibrinolytic therapy in patients with ST-elevation myocardial infarction: a systematic review and meta-analysis of randomized clinical trials. J Thromb Thrombolysis. 2018; 46(3): 299–303, doi: 10.1007/s11239-018-1706-2, indexed in Pubmed: 29934940.
11. Lip GYH, Collet JP, Haude M, et al. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). Europace. 2019; 21(2): 192–193, doi: 10.1093/europace/euy174, indexed in Pubmed: 30052888.