



Switching between P2Y₁₂ antagonists – From bench to bedside

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ABSTRACT

Platelet P2Y₁₂ receptors play a key role in platelet activation and thrombus formation. Accordingly, P2Y₁₂ receptor antagonists are the cornerstone of secondary prevention of atherothrombotic events in patients undergoing percutaneous coronary intervention (PCI). The availability of different oral P2Y₁₂ antagonists (clopidogrel, prasugrel, ticagrelor) along with the introduction of the first intravenous P2Y₁₂ antagonist cangrelor offer an opportunity to individualize antiplatelet therapy according to the changing clinical setting. The recent International Expert Consensus provided the first recommendations on switching between the P2Y₁₂ antagonists. While the consensus greatly helps to guide switching between P2Y₁₂ antagonists, a number of controversial clinical scenarios remain where the evidence regarding the optimal switch strategy is scarce. In such clinical scenarios, understanding of the (i) pharmacological properties of P2Y₁₂ antagonists, (ii) recent evidence from pharmacodynamics studies, clinical trials and registries, and (iii) factors affecting the efficacy and safety of the P2Y₁₂ antagonists, all summarized below, are crucial to choose the optimal switch strategy.

1. Introduction

Platelet P2Y₁₂ receptors are essential for platelet activation and thrombus formation [1]. From this reason, P2Y₁₂ receptor antagonists are the cornerstone of secondary prevention of atherothrombotic events for patients with acute coronary syndrome (ACS) and for those undergoing percutaneous coronary intervention (PCI) [2]. Among the P2Y₁₂ antagonists, clopidogrel was the standard treatment for the last two decades. Novel and more potent P2Y₁₂ antagonists prasugrel and ticagrelor were demonstrated to improve long-term prognosis in patients with ACS [3,4]. Consequently, prasugrel and ticagrelor are recommended as the first-line treatment in patients with ACS, regardless of the initial treatment strategy [2]. Clopidogrel, in turn, should be used only if ticagrelor and prasugrel are not available, or are contraindicated [2]. Because pre-treatment with clopidogrel in the pre-hospital phase remains a standard-of-care in many countries [5], switching to ticagrelor or prasugrel is a frequent clinical scenario after hospital admission. On the other hand, patients initially administered ticagrelor or prasugrel may be willing to switch to clopidogrel due to the development of contraindications or financial constraints. Finally, introduction

of the first intravenous P2Y₁₂ antagonist, cangrelor, which was demonstrated to reduce the rate of thrombotic events compared to clopidogrel in P2Y₁₂-naïve patients undergoing PCI, added to the multitude of clinical scenarios where the switch between P2Y₁₂ antagonists is required [6].

The recent International Expert Consensus provided the first recommendations on switching between P2Y₁₂ receptor antagonists [7]. Here we summarize the (i) pharmacological properties of P2Y₁₂ antagonists, (ii) recent evidence from pharmacodynamics studies, clinical trials and registries, and (iii) factors affecting the efficacy and safety of the P2Y₁₂ antagonists, all of which are crucial to choose the optimal switch strategy in clinical practice. Moreover, we propose an additional algorithm to deal with the clinical scenarios where the evidence regarding the optimal switch strategy is still scarce.

2. Pharmacology of the P2Y₁₂ receptors antagonists

The P2Y₁₂ receptor is a purinergic G protein-coupled receptor for adenosine diphosphate (ADP), which plays a pivotal role in platelet activation and thrombus formation [8]. The P2Y₁₂ receptor is found

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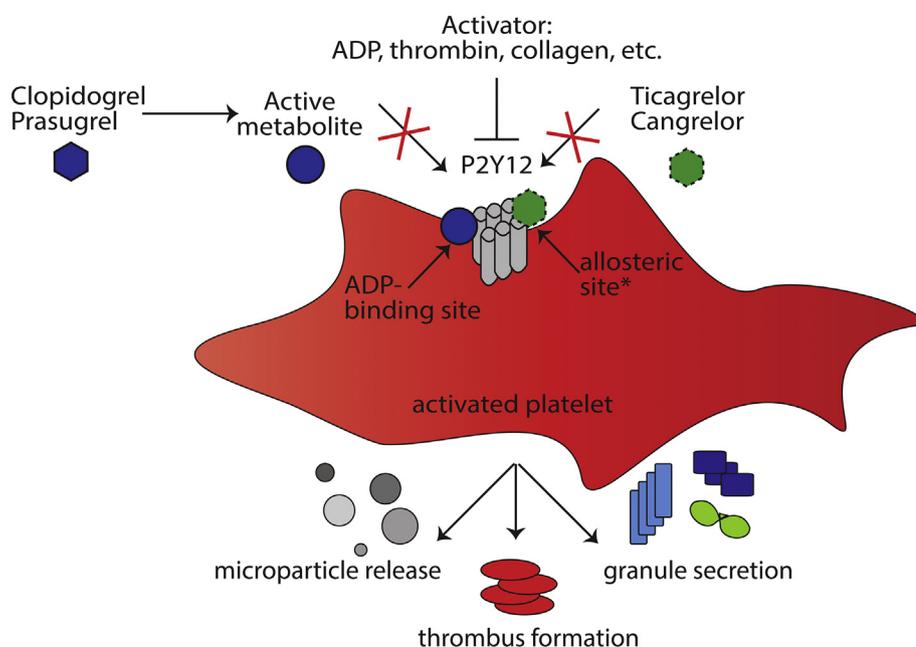


Fig. 1. Effects of the P2Y₁₂ antagonists on the P2Y₁₂ receptor. Following intestinal absorption, clopidogrel and prasugrel are transformed to active metabolites which irreversibly block the adenosine diphosphate (ADP)-binding site of the P2Y₁₂ receptor (indicated by a blue circle with a solid line). Ticagrelor and cangrelor directly, but reversibly bind to the P2Y₁₂ receptor (indicated by a green circle with a dashed line). Whereas ticagrelor binds to the allosteric site of the P2Y₁₂ receptor, the binding site of cangrelor is not yet defined. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Pharmacodynamics and pharmacokinetics of the P2Y₁₂ antagonists.

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Pharmacokinetics				
Administration route [12]	Oral	Oral	Oral	Intravenous
Frequency [2]	Once daily	Once daily	Twice daily	Bolus + infusion
Dosage (LD; MD) [2]	300/600 mg; 75 mg	60 mg; 10 mg	180 mg; 2 × 90 mg	30 µg/kg; 4 µg/kg/min ^a
Prodrug [12,13]	Yes	Yes	No	No
Active metabolite [13]	Yes	Yes	Yes	No
Onset of action [12,13]	2–8 h	30 min–4 h	30 min–4 h	2 min
Offset of action [12,13]	5–7 days	7–10 days	3–5 days	30–60 min
Pharmacodynamics				
Binding site [17,18]	ADP site	ADP site	Non-ADP site	Undefined
Receptor blockade [17,18]	Irreversible	Irreversible	Reversible	Reversible
CYP interaction [14,53]				
Inhibition of platelet aggregation (%) [2]	50–70	90	90	90

ADP – adenosine diphosphate; CYP – cytochrome P450; LD – loading dose; MD – maintenance dose.

^a In case of transition from oral P2Y₁₂ antagonist to cangrelor: 0.75 µg/kg/min infusion without a bolus.

predominantly on platelets, although its presence on leukocytes, endothelial cells, vascular smooth muscle cells, dendritic cells and neurons has also been demonstrated [9,10]. Binding of the oral or intravenous P2Y₁₂ antagonists to the P2Y₁₂ receptor increases the cytosolic concentration of cyclic adenosine monophosphate, which makes platelets less sensitive to activation in response to any platelet agonist, such as thrombin and collagen [11]. Although all P2Y₁₂ antagonists target the same receptor, differences in the pharmacology of the P2Y₁₂ antagonists regarding their metabolic pathways and mechanism of receptor blockade are important factors to define switching strategies. Principally, the P2Y₁₂ antagonists are divided into three main categories, which determine their metabolism and mode of action: (i) oral and intravenous, (ii) prodrugs and direct-acting drugs, and (iii) irreversibly and reversibly binding drugs. The effects of the P2Y₁₂ antagonists on the P2Y₁₂ receptor are shown in Fig. 1, and the summary of the pharmacokinetic and pharmacodynamic properties the P2Y₁₂ antagonists is presented in Table 1.

The thienopyridines clopidogrel and prasugrel are both orally administered prodrugs, where the active metabolites irreversibly bind to the ADP-binding site of the P2Y₁₂ receptor [12]. Because clopidogrel is inactivated by blood esterases, only 15% of the drug is further metabolized in a two-step process by hepatic cytochromes P450 (CYP450) isoenzymes [12]. The two-step metabolism has implications for the

delayed onset of action of clopidogrel (2–8 h), whereas the irreversible P2Y₁₂ inhibition accounts for the offset of action equal to the platelet lifespan (5–7 days) [13]. In turn, genetic polymorphism of the metabolizing enzymes as well as co-administration of clopidogrel with other substrates of the CYP450 (proton pump inhibitors, statins, calcium-channel blockers, coumarin derivatives) may affect the generation of the clopidogrel active metabolite and contribute to large inter-individual variability in platelet response to clopidogrel [14,15]. As a result, about one-third of the clopidogrel recipients have inefficient response to clopidogrel, a phenomenon called high on-treatment platelet reactivity (HTPR), which is associated with increased risk of ischemic complications [16].

Although prasugrel also needs conversion to an active metabolite, which is equipotent to that of clopidogrel, only one CYP450 step is involved in this process, and therefore prasugrel metabolism is less dependent on genetic variability and drug-drug interactions [17]. Peak concentration of prasugrel active metabolite is achieved within 30 min following oral administration. Although the active metabolite of prasugrel is equipotent to that of clopidogrel, the plasma concentration of the active metabolite of prasugrel is higher, which translates into faster, more consistent and stronger antiplatelet effect compared to clopidogrel, however at the cost of higher rate of major bleeding [4]. The higher degree of P2Y₁₂ receptors inhibition with prasugrel translates

into the longer recovery time of platelet function after treatment discontinuation (7–10 days).

Ticagrelor is an oral P2Y₁₂ antagonist which belongs to the cyclopentyltriazolopyrimidine class. In contrast to thienopyridines, ticagrelor does not require metabolic activation and inhibits the binding of ADP to P2Y₁₂ receptor in a non-competitive and reversible manner [18]. Owing to its rapid absorption and direct activity, ticagrelor inhibits platelet aggregation within 30 min. Owing to its reversible binding and fairly short half-life (6–12 h), requiring administration twice daily, the recovery of platelet function is faster after discontinuation of ticagrelor (3–5 days) than after discontinuation of clopidogrel or prasugrel. In contrast to prasugrel, the faster and stronger platelet inhibition with ticagrelor is not associated with an increase in total major bleeding, although increases non-coronary artery bypass graft (CABG) and non-procedure-related major bleeding [5]. Importantly, ticagrelor is likely the only oral P2Y₁₂ antagonist which increases the concentration of adenosine, which may contribute to ticagrelor pleiotropic effects [19]. The increased concentration of adenosine in presence of ticagrelor is caused both by inhibition of adenosine re-uptake by blocking human equilibrative nucleoside transporter 1 on hepatocytes and erythrocytes, and by increased release of adenosine triphosphate, which is subsequently transformed into adenosine [19].

Cangrelor is an analogue of adenosine triphosphate, the natural antagonist of the ADP receptor, and the first intravenous, direct-acting, reversible P2Y₁₂ receptor antagonist [20]. Upon binding to the P2Y₁₂ receptor, cangrelor changes the conformation of the receptor and results in a rapid (~2 min) and potent platelet inhibition. Since cangrelor is rapidly inactivated by dephosphorylation to the nucleoside, metabolism of cangrelor is independent from renal or hepatic function, offering advantage compared with oral P2Y₁₂ receptor antagonists [21]. The ultra-short half-life of 3–6 min allows complete recovery of platelet function within 30–60 min, reducing the need for an antidote (not available for ADP receptor antagonists) and providing flexibility in the case of acute bleeding, procedural complications, or need of prompt surgical revascularization [21]. The intravenous administration and rapid onset/offset of action make cangrelor an appealing treatment option also for patients unable to take oral medications. Like ticagrelor, cangrelor inhibits adenosine uptake by blocking human equilibrative nucleoside transporter 1, thereby increasing its plasma concentration [22].

3. Switch strategies

The current recommendations on switching between the P2Y₁₂ are summarized in Fig. 2.

3.1. From clopidogrel to novel oral P2Y₁₂ antagonists: escalation of therapy

3.1.1. Findings from pharmacodynamics studies

To date, many pharmacodynamic studies have been conducted aiming to evaluate the platelet reactivity (platelet aggregation in response to stimulation with agonist *in vitro*) following the switch from clopidogrel to newer P2Y₁₂ antagonists. These studies have consistently shown more potent antiplatelet effect of the newer P2Y₁₂ antagonists compared to clopidogrel, both among patients with ACS and those with SCAD. Data on the switch between the P2Y₁₂ antagonists from the pharmacodynamics studies are summarized in Table 2.

3.1.1.1. Clopidogrel to prasugrel. The SWAP study (SWitching Anti Platelet) evaluated the response to dual antiplatelet therapy (DAPT) in patients after ACS treated with aspirin and maintenance dose (MD) of clopidogrel (75 mg once daily) [23]. After 10–14 days of DAPT with MD of clopidogrel, patients were randomized to one of the three following groups: placebo followed by clopidogrel MD, placebo followed by prasugrel MD (10 mg once daily), or prasugrel loading dose (LD;

60 mg) followed by prasugrel MD. Platelet function was tested using light transmittance aggregometry (LTA) with ADP as agonist, VerifyNow P2Y₁₂, and vasodilator-stimulated phosphoprotein phosphorylation (VASP) assay. Maximum platelet aggregation (MPA) was lower at 2 h and 24 h following randomization to prasugrel LD + MD group, compared with the other two regimens. At day 7 and day 14, MPA was lower in prasugrel MD group and prasugrel LD + MD group, compared with clopidogrel MD, but there were no significant differences in MPA between prasugrel MD group and prasugrel LD + MD group. Because administration of prasugrel LD on top of clopidogrel MD decreased MPA already 2 h following administration, the authors suggested to use LD of prasugrel while switching clopidogrel to prasugrel, especially in the ACS setting, where fast and potent platelet inhibition is required [23].

Platelet reactivity after switching from clopidogrel to prasugrel among patients with ACS undergoing PCI was evaluated also in the TRIPLET study (Transferring From Clopidogrel Loading Dose to Prasugrel Loading Dose in Acute Coronary Syndrome Patients) [24]. In the TRIPLET study, patients were randomized to receive one of the three treatment strategies: placebo followed by prasugrel LD (60 mg), clopidogrel LD (600 mg) followed by prasugrel LD (60 mg), or clopidogrel LD followed by prasugrel LD (30 mg). Platelet function was assessed using VerifyNow P2Y₁₂. There were no significant differences in platelet reactivity at any time point up to 72 h following randomization across the 3 groups, which indicates no additive benefits, but also no risks of pre-treatment with clopidogrel prior to switching to prasugrel [24].

3.1.1.2. Clopidogrel to ticagrelor. The RESPOND study (Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies) evaluated a response to ticagrelor in clopidogrel responders and non-responders, along with the pharmacodynamic effect of switching between the therapies [25]. In the first phase of the study, patients with SCAD on aspirin were administered clopidogrel 300 mg, and divided into responders or non-responders based on the results of LTA. In the second phase, both cohorts were randomized to either clopidogrel LD (600 mg) followed by clopidogrel MD (75 mg once daily) or ticagrelor LD (180 mg) followed by MD (90 mg twice daily) for 14 ± 2 days. Subsequently, all patients from the non-responder group switched treatment (from clopidogrel to ticagrelor and vice versa), while in the responder group half of patients continued the same treatment, and the other half switched treatment same as in the responders group for 14 ± 2 days. Platelet function was assessed using LTA, VerifyNow P2Y₁₂, VASP assay and glycoprotein IIb/IIIa and P-selectin expression. In the non-responder group, in patients who switched from clopidogrel to ticagrelor platelet reactivity decreased from the mean 59 ± 9% to 35 ± 11%, whereas in patients who switched from ticagrelor to clopidogrel platelet reactivity increased from 36 ± 14% to 56 ± 9%. Similarly, in the responder group, the switch to ticagrelor resulted in more potent inhibition of platelet aggregation, compared with clopidogrel. Of note, 98%–100% of patients treated with ticagrelor had platelet reactivity below the cut-points associated with increased ischemic risk, irrespective of the cohort, in contrast to only 44%–76% of patients treated with clopidogrel. These results suggest that the antiplatelet effect of ticagrelor outperforms the antiplatelet effect of clopidogrel both in clopidogrel responders and non-responders, and that ticagrelor can overcome HTPR during treatment with clopidogrel [25].

The SHIFT-OVER study (Administration of a Loading Dose Has No Additive Effect on Platelet Aggregation During the Switch From Ongoing Clopidogrel Treatment in Patients With Acute Coronary Syndrome) assessed the effect of the switch from clopidogrel to ticagrelor LD on platelet reactivity among patients with ACS on DAPT (aspirin plus clopidogrel) [26]. Patients were randomized to the LD of ticagrelor (180 mg) or the MD of ticagrelor (90 mg). Platelet function

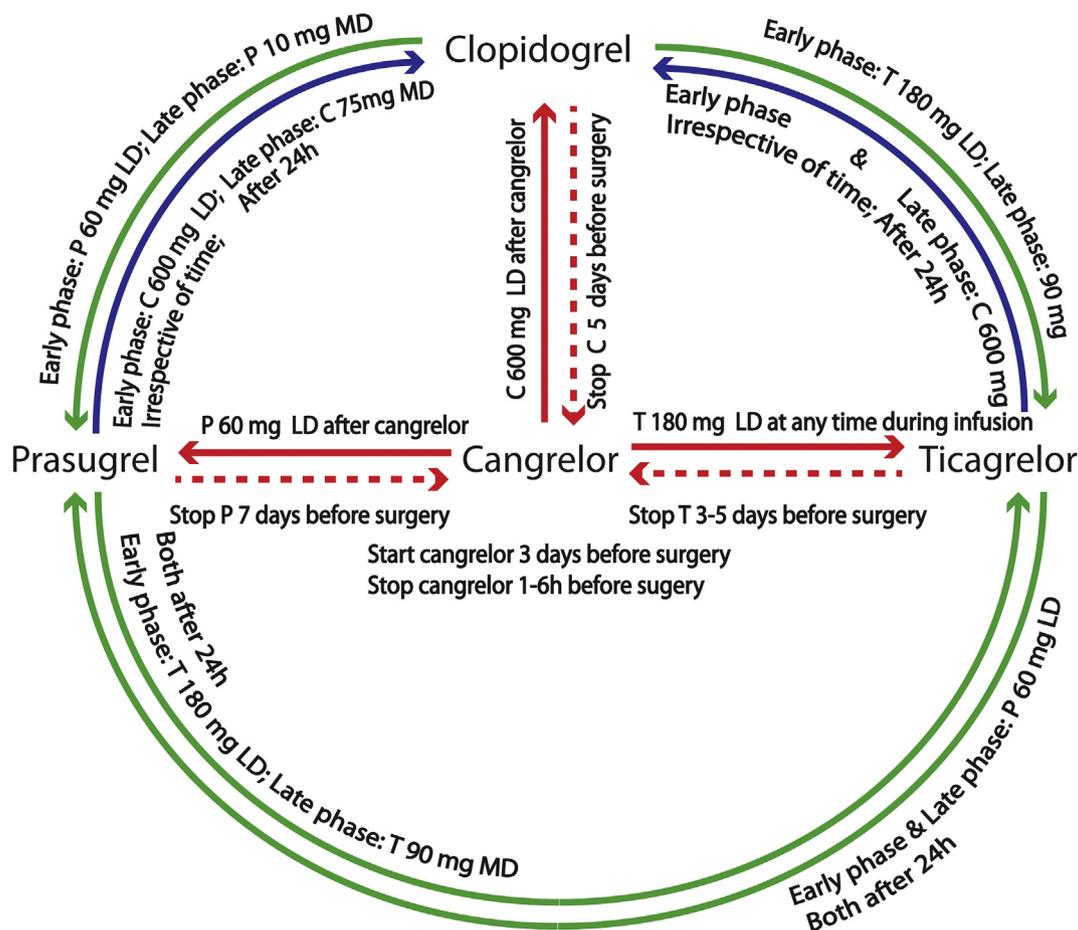


Fig. 2. Summary of the current recommendations on how to switch between the P2Y₁₂ antagonist [7]. The early phase is defined as the first 30 days following ACS; the late phase – as > 30 days following ACS. Escalation or maintenance of the potent antiplatelet therapy is indicated with green arrows, de-escalation of the therapy is indicated with blue arrows, and switch from oral P2Y₁₂ antagonists to cangrelor – with red arrows. The dashed red lines indicate the transient switch to cangrelor, for example in case of urgent surgery. Whereas in the early phase, the administration of loading dose (LD) of a new P2Y₁₂ antagonist is recommended (unless the switch is due to bleeding), in the late phase only the switch from ticagrelor to thienopyridines requires administration of a loading dose of clopidogrel or prasugrel. Further, whereas ticagrelor may be administered at any time during cangrelor infusion, thienopyridines should be administered immediately afterwards. Only prasugrel LD and ticagrelor LD in the early phase may be administered regardless of the timing of the last dose of clopidogrel, whereas all other types of switch may be conducted 24 h after the last dose of the previous oral P2Y₁₂ antagonist. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

was measured using LTA and impedance aggregometry. Already 2 h after the switch platelet reactivity was significantly reduced in both groups, with no differences between the groups. Similar results were observed up to 72 h, indicating that the switch from clopidogrel to ticagrelor without the LD of ticagrelor seems to provide a similar platelet inhibition compared to the LD of ticagrelor and hence might be safe. However, because platelet aggregation in response to agonists in vitro does not reflect the situation in vivo, where platelet agonists (ADP, collagen, thrombin) act in concert to form a thrombus, these results need to be interpreted with caution [26].

3.1.2. Findings from clinical studies

3.1.2.1. Clopidogrel to prasugrel. At present, no clinical trial was specifically designed to identify the optimal switch strategy to escalate the antiplatelet therapy from clopidogrel to more potent P2Y₁₂ antagonists. In the landmark *TRITON-TIMI 38* study (Trial to Assess Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) patients previously exposed to a P2Y₁₂ antagonist were excluded [4]. Hence, the only evidence regarding switching from clopidogrel to prasugrel is derived from the *TRILOGY-ACS* trial (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage ACS), which

compared long-term use of prasugrel and clopidogrel in patients with non-ST elevation ACS selected for optimal medical therapy without revascularization [27], and from the *ACCOAST* trial (Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients With Non-ST Elevation Myocardial Infarction), which compared different treatment regimens of prasugrel in patients with non-ST elevation myocardial infarction [28]. In the *TRILOGY-ACS* trial, the pre-treatment with clopidogrel did not increase the rate of major bleeding in patients who were subsequently administered prasugrel [27]. However, the results should be interpreted with caution, since the trial did not reach its primary efficacy end point. In the *ACCOAST* trial, in turn, although the administration of prasugrel before PCI increased the rate of major bleeding without ischemic benefits, pre-treatment with clopidogrel did not have aggravate this increase [28]. Overall, pre-treatment with clopidogrel seems to have no effect on the efficacy and safety of prasugrel.

3.1.2.2. Clopidogrel to ticagrelor. In the *PLATO* trial (Platelet Inhibition and Patient Outcomes), which demonstrated the superiority of ticagrelor over clopidogrel in patients with ACS undergoing PCI, approximately 50% of patients randomized to ticagrelor were pre-

Table 2
Summary of the data on the switch between the P2Y₁₂ antagonists from pharmacodynamics studies.

Study	Population (n)	Platelet function test	Laboratory outcomes	Clinical outcomes
From clopidogrel to prasugrel PRINCIPAL TIMI 44 [50]	Elective PCI (201)	LTA, VASP, VerifyNow P2Y ₁₂	IPA 45.4% on 150 mg C → 60.8% after 15 days on 10 mg P PRI 39.7% on 150 mg C → 25.1% after 15 days on 10 mg P VNP2Y ₁₂ consistent findings	At 29 days: bleeding events in 4 patients switched from C to P
SWAP [31]	ACS in previous 30–330 days (139)	LTA, VerifyNow P2Y ₁₂ , VASP	MPA 60.2% on 75 mg C → 41.1% after 7 days on 10 mg MD P MPA 55.5% on 75 mg C → 41% after 60 mg LD P + 10 mg MD P for 7 days MPA 53.8% on 75 mg C → 55% after 7 days on 75 mg MD C VNP2Y ₁₂ and VASP: consistent findings	At 15 days: bleeding (by TIMI criteria) in 12.5% of patients in the 75 mg MD C cohort, in 8.5% of patients in the 10 mg MD P cohort, in 13.6% of patients in the 60 mg LD + 10 mg MD P cohort
TRIPLE T [32]	ACS undergoing planned PCI (282)	VNP2Y ₁₂	PRU 57.9 at 6 h after placebo + 60 mg P PRU 35.6 at 6 h after 600 mg C + 60 mg P PRU 53.9 at 6 h after 600 mg C + 30 mg P	At 72 h: 3 treatment related adverse events in the placebo + 60 mg P cohort, 4 in the 600 mg C + 60 mg P cohort, 7 in the 600 mg C + 30 mg P cohort. There were two deaths in the placebo + 60 mg P cohort
From clopidogrel to ticagrelor RESPOND [33]	Stable CAD (98)	LTA, VerifyNow P2Y ₁₂ , VASP	Nonresponder cohort: MPA 59 ± 9% on C → 35 ± 11% at 4 h after 180 mg T Responder cohort: MPA 47 ± 15% on C → 32 ± 8% at 4 h after 180 mg T VNP2Y ₁₂ and VASP: consistent findings AU 34.4 ± 1.3 on C → 17.6 ± 7.2 at 2 h after 90 mg T AU 41.7 ± 2.0 on C → 18.1 ± 6 at 2 h after 180 mg T MPA 24 ± 17% on C → 9 ± 4% at 2 h after 90 mg T MPA 25 ± 14% on C → 9 ± 3% at 2 h after 180 mg T	At 30 days: 4 patients (two from both groups) had five serious adverse events, all events occurred on T, 1 major and 3 minor bleeding events on T, no bleeding events on C, dyspnoea occurred in 13 patients on T and in 4 patients on C
SHIFT-OVER [34]	ACS (50)	MEA, LTA		At 30 days: no deaths after switching, no strokes after switching
From novel P2Y ₁₂ receptor inhibitors to clopidogrel RESPOND [33]	Stable CAD (98)	LTA, VNP2Y ₁₂ , VASP	Nonresponder cohort: MPA 36 ± 14% on T → 56 ± 9% at 4 h after 600 mg C Responder cohort: MPA 25 ± 11% on T → 45 ± 8% at 4 h after 600 mg C VNP2Y ₁₂ and VASP: consistent findings IPA 61.9% on 10 mg P → 46.8% after 15 days on 150 mg C PRI 21.7% on 10 mg P → 48% after 15 days on 150 mg C VNP2Y ₁₂ consistent findings	At 30 days: 4 patients (two from both groups) had five serious adverse events, all events occurred on T, 1 major and 3 minor bleeding events on T, no bleeding events on C, dyspnoea occurred in 13 patients on T and in 4 patients on C
PRINCIPAL TIMI 44 [50]	Planned PCI (201)	LTA, VASP, VNP2Y ₁₂	IPA 61.9% on 10 mg P → 46.8% after 15 days on 150 mg C PRI 21.7% on 10 mg P → 48% after 15 days on 150 mg C VNP2Y ₁₂ consistent findings	At 29 days: no bleeding events in subjects switched from P to C
CAPITAL OPTI-CROSS [38]	ACS (60)	VNP2Y ₁₂	PRU ~40 on T → 114 ± 73.1 at 48 h after 600 mg C PRU ~40 on T → 165.1 ± 70.5 at 48 h after 75 mg C PRU ~40 on T → 165.8 ± 71 at 72 h after 600 mg C PRU ~40 on T* → 184.1 ± 68 at 72 h after 75 mg C HPR rate after 600 mg C: 27% HPR rate after 75 mg C: 57%	At 30 days: ~ MACE, ~ major bleeding events (according to TIMI criteria), ~ stent thrombosis

ACS: acute coronary syndrome; AU: aggregation unit; C: clopidogrel; CAD: coronary artery disease; HPR: high on-treatment platelet reactivity; IPA: inhibition of platelet aggregation; LD: loading dose; LTA: light transmission aggregometry; MACE: major adverse cardiovascular events; MD: maintenance dose; MEA: multiple electrode platelet aggregation; MPA: maximal platelet aggregation; P: prasugrel; PCI: percutaneous coronary intervention; PRI: platelet reactivity index; PRU: P2Y₁₂ reactivity units; T: ticagrelor; TIMI: Thrombolysis in Myocardial Infarction; VASP: asodilator-stimulated phosphoprotein; VNP2Y₁₂: VerifyNow P2Y₁₂.

treated with clopidogrel, and the efficacy and safety of ticagrelor were not affected by the prior use of clopidogrel [3]. Accordingly, in the PEGASUS trial (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin), which evaluated the safety and efficacy of a long-term treatment of ticagrelor in patients 1–3 years after AMI, approximately 30% of patients were previously treated with clopidogrel [29]. Although long-term treatment with ticagrelor increased the rate of major bleeding, this rate unaffected by pre-treatment with clopidogrel. Overall, the net clinical benefits of ticagrelor seem to be maintained in patients pre-treated with clopidogrel.

3.1.3. Findings from registries

Prospective registries designed for collecting data on switching strategies include ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With The Guideline), CathPCI (Catheterization and Percutaneous Coronary Intervention) registry [30], MULTIPRAC (European MULTInational non-interventional study of patients with ST-segment elevation myocardial infarction treated with Primary Angioplasty and Concomitant use of upstream antiplatelet therapy with prasugrel or clopidogrel) registry [31], GRAPE (GRreek AntiPlatElet) registry [32], and TRANSLATE-ACS (Treatment With Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome) registry [33,34]. Data on the switch between the P2Y₁₂ antagonists from the registries are summarized in Table 3.

3.1.3.1. Clopidogrel to prasugrel. In the ACTION Registry-GWTG and CathPCI registry, the frequency and factors associated with switching from clopidogrel to prasugrel were evaluated in 40,531 patients with AMI treated with PCI who initially received clopidogrel [30]. In these registries, the frequency of switching between P2Y₁₂ antagonists varied widely across hospitals (median: 4%, minimum: 0%, maximum: 43%). Interestingly, only 5% of patients initially treated with clopidogrel were discharged on prasugrel, whereas according to the current guidelines prasugrel and ticagrelor are recommended as the first-line treatment in patients with ACS, regardless of the initial treatment strategy [2]. Factors associated with switching from clopidogrel to prasugrel included recurrent PCI procedures during hospitalization and high-risk angiographic characteristics (intracoronary thrombus, long lesions, bifurcating lesions, multivessel PCI), clinical risk factors (diabetes mellitus or previous PCI), and private health insurance [30].

In the MULTIPRAC registry, over 2000 patients with ST-elevation myocardial infarction (STEMI) were allocated to two groups, according to the P2Y₁₂ receptor antagonist initially administered (clopidogrel or prasugrel) [31]. Out of patients initially treated with clopidogrel, 49% switched to prasugrel. There were no differences in MACE between patients who switched from clopidogrel to prasugrel and those initially treated with prasugrel (2.3 vs. 1.6%). Importantly, the non-CABG-

related bleeding were nominally, but insignificantly more frequent in patients who switched from clopidogrel to prasugrel, compared with those treated with prasugrel from the beginning (6.1% vs. 4.1%).

3.1.3.2. Clopidogrel to prasugrel or ticagrelor. In the GRAPE registry [32], the prevalence, predictive factors and short-term outcomes of in-hospital switch between P2Y₁₂ inhibitors were assessed among 1794 patients with ACS undergoing PCI. Following PCI, the P2Y₁₂ antagonist was switched in 36% of patients and transition from clopidogrel to a more potent P2Y₁₂ antagonist the most common (90%). A loading dose of the new agent was administered more frequently in case of ticagrelor than in case of prasugrel (55% vs 44%, $p < 0.001$). Of note, this practice is not in accordance with the International Expert Consensus, which recommends administration of a loading dose of any new P2Y₁₂ antagonist in the early phase after PCI [7]. In patients initially treated with clopidogrel, the switch to a newer P2Y₁₂ antagonist was dependent on regional trends, admission to a non-PCI capable hospital, in-hospital bivalirudin use and age. At one month, the in-hospital switch from clopidogrel to a more potent P2Y₁₂ antagonist was associated with less major adverse cardiovascular (MACE: death, myocardial infarction, stent thrombosis, urgent revascularization, stroke; 1.2% vs 3.8%, $p = 0.03$) and more bleeding events (31% vs 12%, $p = 0.01$) compared to patients who continued treatment with clopidogrel. However, the rate of MACE and bleeding events was comparable in patients who switched from clopidogrel to a more potent P2Y₁₂ antagonist, and those initially treated with a potent P2Y₁₂ antagonist. The latter observation confirms that in real-life setting the more potent P2Y₁₂ antagonist efficiently prevent ischaemic events at the cost of more bleeding events, but these event rates are not affected by the pre-treatment with clopidogrel.

In the TRANSLATE-ACS registry, the frequency of switching from clopidogrel to newer P2Y₁₂ receptor antagonists and the risk of MACE (death, myocardial infarction, stroke, unplanned revascularization) and bleeding were assessed 6 months and 1 year post-discharge among 17,000 patients with AMI treated with PCI [33,34]. Switching to prasugrel or ticagrelor was associated with younger age, high school education, use of P2Y₁₂ receptor antagonists before the hospitalization and lower ACTION (Acute Coronary Treatment and Intervention Outcomes Network) mortality score. The most common reason to switch from clopidogrel to a more potent P2Y₁₂ antagonist reported by patients was physician's decision, followed by bleeding and/or bruising and other side effects. At 6 months, clopidogrel was switched to a more potent P2Y₁₂ antagonist only in 11.4% (10.4% to prasugrel, 1% to ticagrelor). Switching was most often done directly after PCI (61%) and at the time of the hospital discharge (27%), and was not associated with increased risk of MACE or bleeding at 6 months and 1 year post-discharge, compared with continuation of clopidogrel. These results confirm the efficacy and safety of switching clopidogrel to more potent P2Y₁₂ antagonists. Importantly, the switch from clopidogrel to a more potent P2Y₁₂ antagonist followed a MACE in 19% of patients and

Table 3

Summary of the data on the switch between the P2Y₁₂ antagonists from the registries.

Study	Population (n)	Switch from clopidogrel to newer P2Y ₁₂ antagonists (%)	Switch from newer P2Y ₁₂ antagonists to clopidogrel (%)	Switch between newer P2Y ₁₂ antagonists	Clinical outcomes
GRAPE [25]	ACS (1794)	C → P: 40.1 C → T: 50.3	P → C: 1.0 T → C: 4.3	T ↔ P: 4.3	At 1 month: ↓ MACE ↑ bleeding after switch C → P/T
ACTION-GWTG; CathPCI [26]	STEMI + NSTEMI (47,040)	C → P: 5.2 C → T: NA	P → C: 11.5 T → C: NA	NA	NA
MULTIPRAC [27]	STEMI (2053)	C → P: 48.7 C → T: 11.6	P → C: 8.3 T → C: NA	P → T: 2.8 T → P: NA	In-hospital outcomes: ~ MACE, ~ bleeding after switch C → P/T
TRANSLATE-ACS [28]	STEMI + NSTEMI (11,999)	C → P: 10.4 C → T: 1.0	P → C: 11.5 T → C: 2.1	P → T: 0.3 T → P: 3.4	At 6 months: ~ MACE, ~ bleeding for any switch

ACS: acute coronary syndrome; C: clopidogrel; MACE: major adverse cardiovascular events; NA: not available; NSTEMI: non-ST-segment elevation myocardial infarction; P: prasugrel; STEMI: ST-segment elevation myocardial infarction; T: ticagrelor.

definite stent thrombosis in 6% of patients within the previous 7 days, confirming the non-responsiveness to clopidogrel in about one-third of the recipients.

To sum up, the frequency of switching from clopidogrel to newer oral P2Y₁₂ receptor antagonists reported in registries ranges from 5% to 50% [30,31,33,34]. The decision to switch clopidogrel to newer P2Y₁₂ antagonists depends on several factors, including patient clinical presentation (STEMI, high-risk angiographic lesions, stent thrombosis or restenosis), absence of contraindications (history of stroke, age > 75 years or body weight < 60 kg in case of prasugrel; risk of bradycardia or dyspnoea in case of ticagrelor) and socioeconomic factors (health insurance coverage, employment status). The switch from clopidogrel to ticagrelor or prasugrel seems to improve the prognosis regarding MACE, including decreased rate of stent thrombosis, at the cost of higher bleeding rate with prasugrel, thereby confirming the initial findings from the PLATO study [3] and TRITON-TIMI 38 study [4].

3.2. From novel oral P2Y₁₂ antagonists to clopidogrel

3.2.1. Findings from pharmacodynamics studies

The pharmacodynamics effects of switching from newer oral P2Y₁₂ receptor antagonist to clopidogrel were evaluated in several studies, which have consistently showed that switching prasugrel or ticagrelor to clopidogrel decreases platelet inhibition and increases the percentage of patients with HTPR.

3.2.1.1. Prasugrel to clopidogrel. In PRINCIPLE-TIMI 44 study (The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation- Thrombolysis in Myocardial Infarction 44) the effect of switching from prasugrel to clopidogrel and vice versa on inhibition of platelet aggregation (IPA) was assessed in 201 patients undergoing elective PCI [35]. Patients received prasugrel LD (60 mg) followed by prasugrel MD (10 mg once daily), or clopidogrel LD (600 mg) followed by clopidogrel MD (150 mg once daily) for 14 ± 2 days. Subsequently, patients on prasugrel switched to MD of clopidogrel and vice versa for 14 ± 2 days. IPA was assessed by LTA, VerifyNow P2Y₁₂ assay and VASP. Both at 6 h and at 14 days IPA in response to ADP was higher in patients on prasugrel, compared to patients on clopidogrel (75 ± 13% vs 32 ± 21%, and 61 ± 17% vs 46 ± 23%, respectively). The rate of bleeding was similar in both groups. In conclusion, among patients undergoing elective PCI, prasugrel resulted in more rapid and more consistent antiplatelet effect than clopidogrel, and pre-treatment with clopidogrel prior to prasugrel administration did not increase the risk of bleeding.

3.2.1.2. Ticagrelor to clopidogrel. In CAPITAL OPTI-CROSS study (OPTimizing CROSSover from Ticagrelor to Clopidogrel in Patients with Acute coronary syndrome) two different switch strategies from ticagrelor to clopidogrel were investigated in patients with ACS and with indications to change the antiplatelet treatment (including triple therapy, high risk of bleeding, drug cost) [36]. Patients were randomized to receive a LD of clopidogrel (600 mg), followed by MD dose (75 mg once daily), or to switch to clopidogrel without the LD. Platelet function was analyzed using VerifyNow with a value of ≥208 as the cut-point for HTPR. In both groups platelet reactivity increased 48 h after the switch to clopidogrel, with lower values in the clopidogrel LD group, compared to no LD group (114 ± 73 PRU vs 165 ± 71; *p* = .008). At 72 h there was no significant difference in platelet reactivity between two groups (166 ± 71 in the LD group vs 184 ± 68 in the no LD group; *p* = .19). However, HTPR was reported more frequently in patients without LD of clopidogrel, compared to those who received the LD of clopidogrel (56.7% vs 26.7%). There were no differences in the incidence of MACE and TIMI bleeding at 30 days between the two cohorts. Similar results were showed in the aforementioned RESPOND study, where platelet reactivity increased after the switch from ticagrelor to clopidogrel [25]. Based on the results

from pharmacodynamics suggest, to prevent the “rebound effect” while switching from ticagrelor to clopidogrel, it has been recommended to administer the LD of clopidogrel both in the early and in the late phase following ACS [7].

3.2.2. Findings from clinical trials

Switching from newer oral P2Y₁₂ receptor antagonists to clopidogrel seems less frequent than switching in the opposite direction. Overall, the prevalence of in-hospital switching from prasugrel or ticagrelor to clopidogrel reported in registries ranges from 5% to 14%. Socioeconomic factors (no insurance coverage of prasugrel and ticagrelor) and concerns about bleeding complications remain important reasons for switching the therapy to clopidogrel, along with elderly age, low body mass, history of stroke or transient ischemic attack (TIA), use of oral anticoagulant or history of treatment with CABG [27,30–34]. Recently, the results of two randomized trials on switch therapy from newer oral P2Y₁₂ receptor antagonist to clopidogrel have been published [37,38].

3.2.2.1. Prasugrel to clopidogrel. In the TROPICAL-ACS study (Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes) patients with ACS successfully treated with PCI were randomized to one of two groups: control group treated with prasugrel (10 mg or 5 mg once daily) based on the results or platelet function testing (PFT) for 12 months, and de-escalation group treated with prasugrel (10 mg or 5 mg once daily) for 7 days, followed by clopidogrel (75 mg once daily), initially for 7 days. After 14 days platelet function was measured using impedance aggregometry [37]. Based on the PFT results in the de-escalation group, patients with HTPR were switched back to prasugrel for 11.5 months (39% of patients), whereas patients with adequate platelet inhibition continued treatment with clopidogrel. Primary endpoint (death from cardiovascular causes, myocardial infarction, stroke and bleeding ≥2 according to BARC classification) occurred in 7% of patients in the de-escalation group, compared with 9% in the control group (*p* for non-inferiority = 0.0004), indicating that de-escalated therapy is non-inferior to conventional 12-month prasugrel therapy in terms of MACE and bleeding.

3.2.2.2. Prasugrel or ticagrelor to clopidogrel. In the TOPIC study (Timing of Platelet Inhibition After Acute Coronary Syndrome), patients with ACS undergoing PCI and treated with DAPT consisting of aspirin and newer P2Y₁₂ receptor antagonist without an adverse event for a month were assigned to one of two groups: switching P2Y₁₂ antagonist (ticagrelor or prasugrel to clopidogrel) or unchanged DAPT (continuation of the initial treatment with ticagrelor or prasugrel) [38]. The primary endpoint (a composite of cardiovascular death, urgent revascularization, stroke and bleeding ≥2 according to BARC classification) occurred more frequently in the unchanged DAPT group (26% vs 13%, *p* < 0.01). When analyzing separate components of the composite end-point, no significant differences were found in ischemic events between the groups. On the other hand, bleeding events occurred more often in the unchanged DAPT group, compared with the switched DAPT group (14.9% vs 4.0%, *p* < 0.01). The results suggest that switching ticagrelor or prasugrel to clopidogrel potentially reduces the risk of bleeding, without increasing risk of ischemic events. However, these results should be interpreted with caution, because the study was underpowered to evaluate either ischemic and bleeding events separately.

3.2.3. Findings from registries

3.2.3.1. Prasugrel or ticagrelor to clopidogrel. In the aforementioned MULTIPRAC registry, ACTION Registry-GWTG, GRAPE registry and CathPCI Registry only the prevalence of switch from clopidogrel to newer P2Y₁₂ antagonist among patients with myocardial infarction treated with PCI was evaluated, and this prevalence ranged from 1% to

11.5% [30–32]. Switching from prasugrel to clopidogrel was associated with older age, lower body weight, in-hospital bleeding, previous stroke or TIA, in-hospital CABG and use of oral anticoagulant at discharge, as well as lack of private insurance.

In the *TRANSLATE-ACS* registry it was showed that switching the ticagrelor or prasugrel therapy was the most common change in treatment after discharge among patients with AMI treated with PCI (28.3% and 15.4%, respectively) [33,34]. The vast majority of switches were to clopidogrel (87.5%, 97.3%, respectively). Switching occurred at a median of 80 days after discharge in prasugrel treated group and at a median of 62 day after discharge in ticagrelor treated group. The most common reason reported by patients who switched from newer P2Y₁₂ receptor antagonist to clopidogrel was high cost of treatment. The patients who switched were more likely to be women and to have a higher ACTION bleeding risk score. The incidence of moderate/severe bleeding within 1 week before the switch was very low and occurred only in 1 patient treated with prasugrel. No differences in MACE and bleeding rate were observed at 6 months and 1 year in patients who switched to clopidogrel, compared to those continuing treatment with newer P2Y₁₂ antagonists.

3.2.4. Between novel oral P2Y₁₂ antagonists

The prevalence of switching from ticagrelor to prasugrel or vice versa reported in the registries ranges from 2% to 4% only [30,31,33,34,39]. Ticagrelor is switched to prasugrel due to two main reasons: (i) adverse effects, including dyspnea and ventricular pauses [40,41], and (ii) administration twice daily, both of which affect the compliance. On the other hand, potential prasugrel is switched to ticagrelor due to development of contraindications for prasugrel during DAPT, such as cerebrovascular events (stroke, TIA) or weight loss (< 60 kg). The choice of one of these drugs may also depend on the type of insurance, depending on the country [30,31,33].

3.2.4.1. Ticagrelor to prasugrel. Pharmacodynamic effects of switching from ticagrelor to prasugrel among patients with SCAD were evaluated in the *SWAP-2* study [41]. In the run-in phase (3 to 5 days), patients on low-dose aspirin therapy received ticagrelor LD (180 mg) followed by a ticagrelor MD (90 mg twice daily). Then, patients were randomized to one of three groups: (i) continuation of ticagrelor therapy, (ii) switch to prasugrel LD (60 mg) followed by prasugrel MD (10 mg) or (iii) switch to prasugrel MD (10 mg) without LD. Platelet reactivity was assessed using Verify Now. The primary endpoint was non-inferior platelet reactivity at 7 days after the switch from ticagrelor to prasugrel, compared to continuation of ticagrelor. Platelet reactivity was higher in both prasugrel groups, compared with the ticagrelor group, so that the study failed to meet the primary end-point. In the combined prasugrel groups, platelet reactivity increased at 24 h after randomization, compared to the pre-randomization values, and decreased at 7 days post randomization. However, patients who received LD of prasugrel achieved smaller increase of platelet reactivity at 24 and 48 h, compared with those who received only a MD. The rate of HTPR was higher in both prasugrel cohorts than in ticagrelor cohort at 24 and 48 h, but there were no differences in HTPR at 7 days between cohorts. The results suggest the presence of potential pharmacodynamic interaction between ticagrelor to prasugrel, partially mitigated when LD of prasugrel is used. From this reason, switching from ticagrelor to thienopyridines (clopidogrel, prasugrel) requires administration of a loading dose of a new P2Y₁₂ antagonist both in the early and late phase of DAPT [7].

3.2.4.2. Prasugrel to ticagrelor. The *SWAP-3* study provided data on the pharmacodynamic effects of switching from prasugrel to ticagrelor among patients after ACS treated with PCI [42]. Patients enrolled in the study were randomized to one of the following cohorts: (i) continuation of prasugrel therapy (10 mg MD), (ii) switch to ticagrelor LD (180 mg) followed by MD (90 mg twice a day) or (iii) switch to ticagrelor

maintenance dose (90 mg twice daily) without ticagrelor LD. Platelet reactivity was assessed using VerifyNow P2Y₁₂. Switch from prasugrel to ticagrelor was non-inferior compared with continuation of prasugrel therapy at 7 days. A marked decrease in platelet reactivity was observed in both ticagrelor groups from 2 h to 48 h after randomization, compared with the prasugrel cohort, both with and without the use of ticagrelor LD. However, 7 days after randomization the platelet reactivity in the combined ticagrelor groups increased to a level comparable to prasugrel group. Hence, switching from prasugrel to ticagrelor leads to transiently higher platelet inhibition, irrespective of the use of a LD of ticagrelor. Therefore, in the late phase of DAPT it has been recommended to switch from thienopyridines (clopidogrel, prasugrel) to ticagrelor without administration of a ticagrelor LD [7].

3.2.5. From cangrelor to oral inhibitors

The effect of cangrelor on the ability of clopidogrel to inhibit platelet aggregation was evaluated in healthy volunteers, divided into two groups based on the time of clopidogrel administration [43]. One of the group received clopidogrel LD (600 mg) simultaneously with the cangrelor infusion, while the second group received clopidogrel LD immediately after termination of cangrelor infusion. Platelet function was assessed using flow cytometry and LTA. In volunteers who received clopidogrel *simultaneously* with cangrelor, inadequate antiplatelet effect of clopidogrel was observed, potentially explained by a short half-life (\approx 30–90 min) of clopidogrel active metabolite [44,45], which is rapidly eliminated from the circulation if it does not bind to the P2Y₁₂ receptor. Likely, once the P2Y₁₂ receptors are occupied by cangrelor, clopidogrel active metabolite is unable to bind them and is eliminated (pharmacodynamic interaction). In volunteers who received clopidogrel *after* cangrelor, the antiplatelet effect of clopidogrel was not impaired. Likely, the rapid offset of action of cangrelor gives the possibility of the active metabolites of clopidogrel to bind to the receptor before the metabolite is eliminated. Similar results were obtained in patients with SCAD who received clopidogrel *simultaneously* with cangrelor [46], and in vitro when the active metabolites of clopidogrel or prasugrel were added to the blood pre-incubated with cangrelor [47]. From this reason, if switching from cangrelor to thienopyridines is undertaken, clopidogrel and prasugrel should be administered immediately after cangrelor discontinuation [7], and not during the infusion.

The effect of transition from cangrelor to ticagrelor and vice versa were evaluated in patients with SCAD on aspirin [48]. The antiplatelet effects of ticagrelor and cangrelor were maintained regardless of the order of drugs administration, although modest increase in platelet reactivity was observed during the first hour after cangrelor was stopped. Nevertheless, due to lack of overt interactions between cangrelor to ticagrelor, ticagrelor may be administered already at the start of cangrelor infusion or at any time during the infusion [7]. Importantly, ticagrelor should be the oral P2Y₁₂ inhibitor of choice, when cangrelor was initially used, which is due to lack of pharmacodynamic interaction between cangrelor and ticagrelor.

3.2.6. From oral inhibitors to cangrelor

Switching from oral P2Y₁₂ inhibitors to cangrelor is defined as bridging, most common among patients treated with DAPT and undergoing surgery.

In the *BRIDGE* study (Maintenance of Platelet Inhibition With Cangrelor After Discontinuation of Thienopyridines in Patients Undergoing Surgery), which assessed platelet inhibition in patients who had discontinued thienopyridine therapy before cardiac surgery, cangrelor resulted in higher rate of maintained platelet inhibition than placebo [49], likely due to the presence of P2Y₁₂ receptors which can be inhibited by cangrelor. Although the safety and efficacy of bridging requires further investigation [50], at present it is recommended to start cangrelor infusion at a dose 0.75 μ g/kg/min should within 72 h following discontinuation of an oral P2Y₁₂ antagonist (prasugrel: 7 days

before surgery, clopidogrel: 5 days before surgery, and ticagrelor: 3–5 days before surgery). The infusion should be continued for a minimum of 48 h and a maximum of 7 days. Importantly, cangrelor infusion should be stopped 1–6 h before the surgery, and re-initiated after the surgery only if oral P2Y₁₂ administration is impossible. If oral administration is possible, clopidogrel LD (300 mg – 600 mg) is a P2Y₁₂ antagonist of choice, whereas ticagrelor and prasugrel are discouraged [7].

3.2.7. Time-point of switch

3.2.7.1. Clopidogrel to prasugrel or ticagrelor. Because in patients treated with clopidogrel a part of P2Y₁₂ receptors remain unoccupied, in the early phase both prasugrel LD and ticagrelor LD may be administered regardless of the timing of the last dose of clopidogrel [7]. Beyond the early phase, due to practical reasons it is recommended to administer the MD of prasugrel or ticagrelor 24 h after the last dose of clopidogrel [7].

3.2.7.2. Prasugrel or ticagrelor to clopidogrel. In the early phase, clopidogrel LD should be administered 24 h after the last dose of prasugrel or ticagrelor, since this timeframe allows the new, uninhibited platelets to enter the circulation, therefore increasing the number of P2Y₁₂ receptors to be occupied by clopidogrel. Beyond the early phase, clopidogrel MD should be administered 24 h after the last dose of prasugrel, and clopidogrel LD – 24 h after the last dose of ticagrelor, mostly due to practical reasons.

To conclude, prasugrel LD and ticagrelor LD may be administered regardless of the timing of the last dose of clopidogrel only in the early phase, whereas all other types of switch may be conducted 24 h after the last dose of the previous oral P2Y₁₂ antagonist.

3.2.7.3. Controversial clinical scenarios. While the consensus greatly helps to guide switching between P2Y₁₂ antagonists, a number of controversial clinical scenarios remain, where the evidence regarding the optimal switch strategy is scarce. These scenarios include (i) an ischaemic event, (ii) a bleeding event or risk thereof, and (iii) development of contraindications to the current P2Y₁₂ antagonist. Here we elaborate on these scenarios and propose an algorithm on how to tailor antiplatelet therapy in patients who presented with an ischaemic or bleeding event while being treated with DAPT after AMI or after elective PCI in course of SCAD. The algorithm is presented in Fig. 3.

3.3. Ischaemic event

Three major risk factors of ischaemic events (e.g. AMI, stent thrombosis, urgent revascularization) in patients on DAPT are (i) procedure-related (stent underexpansion, malapposition, fracture), (ii) patient-related (non-compliance), and (iii) therapy-related (inadequate platelet inhibition, HTPR) [51]. Inadequate platelet inhibition may result from either intrinsic (comorbidities, genetic polymorphisms) or extrinsic factors (cigarette smoking, drug-drug interactions) [14]. Therefore, if incorrect stent insertion and non-compliance are unlikely, it is crucial to confirm HTPR in patients experiencing recurrent ischaemic events. In patients treated with clopidogrel, the PREDICT score (Platelet Aggregation after Deployment of Intracoronary Stent) can be used to estimate HTPR by easily available patient details (reduced left ventricle ejection fraction, chronic kidney disease, diabetes, ACS at admission or age > 65 years) [52]. In turn, in patients treated with ticagrelor and prasugrel, ADP-related platelet function tests such as MEA or VerifyNow might be considered a valuable tool to confirm HTPR [14].

If HTPR is confirmed, interactions with drugs which affect the antiplatelet efficacy of P2Y₁₂ antagonists should be considered, such asazole antifungals (ketoconazole, fluconazole), calcium channel blockers, lipophilic statins, morphine, vitamin K antagonists, protein

pump inhibitors [53,54]. Although ticagrelor and prasugrel are preferred over clopidogrel in patients after AMI, some patients are still discharged on clopidogrel without PFT prior to discharge, for example due to financial constraints. Given the high proportion of patients not responding to clopidogrel, as well as superiority of novel P2Y₁₂ antagonist over clopidogrel, patients treated with clopidogrel following AMI who experienced recurrent ischaemic event should urgently switch to prasugrel or ticagrelor. Efforts should be made to inform the patients about the risk of recurrent ischaemic event, including recurrent AMI by continuation of clopidogrel treatment [2]. Moreover, one should keep in mind that cross-unresponsiveness may be observed between clopidogrel and prasugrel [55]. Of note, HTPR complicated by stent thrombosis has also been observed on ticagrelor [56,57]. Therefore, PFT seems to be a valuable tool not only to identify patients with HTPR, but also to confirm the adequate response to therapy following the switch of a P2Y₁₂ antagonist.

Although clopidogrel is the standard treatment for patients with SCAD patients undergoing PCI, prasugrel or ticagrelor may be considered instead of clopidogrel for patients with an ischaemic event during DAPT, taking into account the ischaemic risk (high SYNTAX score, complex PCI, recurrent event) and bleeding (PRECISE-DAPT score) risks [2]. Whereas in patients with ischaemic risk prevailing bleeding risk (PRECISE-DAPT < 25), ticagrelor or prasugrel may be considered, for patients with bleeding risk prevailing ischaemic risk (PRECISE-DAPT ≥ 25), double MD of clopidogrel may represent less efficient, however safer alternative [58].

3.4. Bleeding event

Patients treated with DAPT may experience bleeding (i) as a side effect of DAPT, or (ii) due to surgery. Bleeding as a side effect of DAPT most frequently results from excessive platelet inhibition, since overdosing of the P2Y₁₂ antagonist hardly leads to clinically overt bleeding [59]. Since bleeding may be unrelated to antiplatelet therapy, for example in case of patients with concomitant gastric ulcers or hemorrhoids, PFT might be taken into consideration to differentiate patients with truly low PR from those with adequate response to therapy. In patients with active bleeding, the benefits of antiplatelet therapy disruption should always be weighed against the risks of stent thrombosis and therefore considered as a temporary measure [60]. In case of truly low PR, drug-drug interactions should be considered, such as concomitant use of nonsteroidal anti-inflammatory drug or selective serotonin reuptake inhibitors, known to increase the risk of bleeding [53]. If interactions are unlikely, de-escalation of therapy is recommended, especially in patients with intracranial haemorrhage or recurrent bleeding [2]. This should start with a clopidogrel MD regimen (75 mg), unless the therapy has been disrupted for ≥ 5 days, when a 300-mg LD might be used [2]. Following de-escalation, PFT should be considered to confirm adequate response to therapy.

Prior to surgery, either the DAPT may be temporarily interrupted, or cangrelor may be used as a “bridging therapy”, however at a different dose than during PCI (0.75 µg/kg/min infusion without a bolus) [7]. Moreover, PFT may be considered to guide the decision on the timing of surgery in patients who have recently received P2Y₁₂ antagonists [61]. Notably, the *complete recovery of platelet function* and the *adequate recovery* following cessation of treatment with oral P2Y₁₂ antagonists are different terms. Whereas the complete recovery denotes entirely normal platelet function following treatment discontinuation [14], the adequate recovery is adequate platelet function to prevent increased bleeding risk in case of operation [62,63]. For example, the optimal cut-off for adequate recovery is 22–30 aggregation units (AU), compared to the cut-off 46 AU for complete recovery, when assessed with ADP-induced Multiplate Impedance Aggregometry (MEA) [14,62,63]. Pre-operative PFT allowed to decrease the waiting time for surgery by 50% without increased rate of bleeding in patients treated with clopidogrel and ticagrelor, which is particularly valuable in patients at high risk of

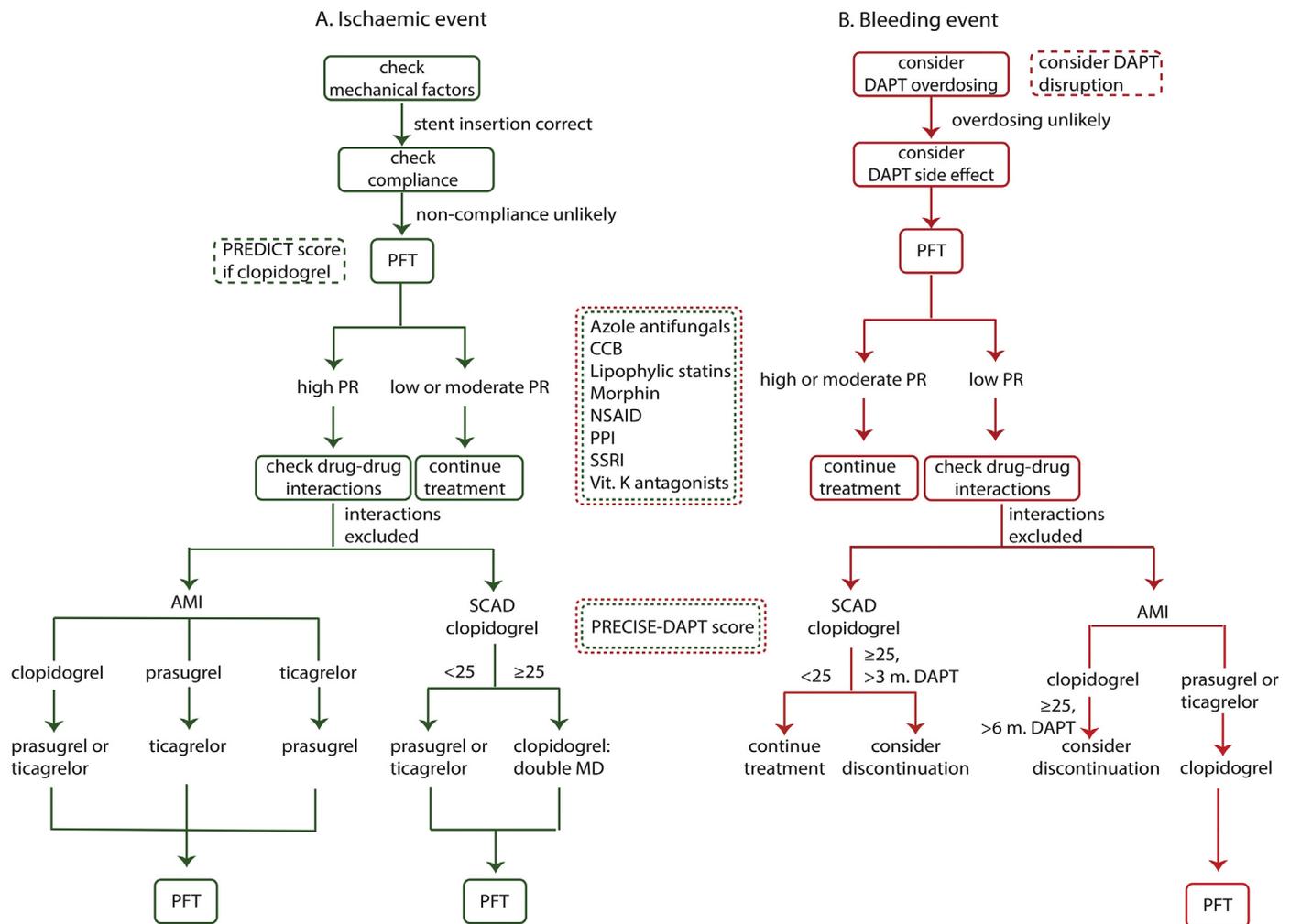


Fig. 3. Proposed algorithm on how to switch between P2Y₁₂ antagonists in complex clinical scenarios such as patients after AMI or after elective percutaneous coronary intervention in course of stable coronary artery disease who experienced (A) ischaemic event and (B) bleeding event while treated with dual antiplatelet therapy. AMI: acute myocardial infarction; CCB: calcium channel blockers; DAPT: dual antiplatelet therapy; NSAID: non-steroid anti-inflammatory drugs; PFT: platelet function testing; PPI: proton pump inhibitors; PR: platelet reactivity; SCAD: stable coronary artery disease; SSRI: selective serotonin reuptake inhibitors.

recurrent ischaemic events, who should be operated on as soon as possible to protect/rescue the myocardium.

Interestingly, the adequate recovery seems to differ between stable coronary artery disease (SCAD) and ACS patients. Whereas in SCAD patients it takes only 48 h to achieve adequate platelet function after ticagrelor and clopidogrel administration [64], in ACS patients at least 72 h of discontinuation is required [63]. Of note, 72 h after discontinuation as much as 25% patients who had been treated with ticagrelor have platelet aggregation below 22AU, indicating increased risk of bleeding [63]. In case of prasugrel, at least 5 days is required to achieve adequate platelet function, which has been hypothesized to result from a residual inhibitory effect of prasugrel on the megakaryocyte level [65]. To conclude, whereas the time to complete platelet recovery is established, time and cut-off points to adequate platelet recovery remain a matter of debate.

3.5. Development of contraindications to current P2Y₁₂ antagonist

Common contraindications to a current P2Y₁₂ antagonist include: (i) need for oral anticoagulation (ticagrelor, prasugrel), and (ii) age \geq 75 years, body weight $<$ 60 kg, stroke or TIA (prasugrel) [2]. In patients who develop a comorbidity requiring oral anticoagulation, in whom clopidogrel is the P2Y₁₂ antagonist of choice, the therapy should be de-escalated from prasugrel or ticagrelor to clopidogrel [2]. In the

late phase, clopidogrel may be started with a 300 mg LD regimen when switching from ticagrelor, and a routine 75 mg MD regimen when switching from prasugrel [7]. In (post-ACS) patients who experience a stroke or TIA on therapy with prasugrel, ticagrelor may be considered as a beneficial option for secondary stroke prevention [66]. Since the therapy modifications in patients who developed common contraindications are clear and do not require PFT, they are not presented in Fig. 3.

3.6. Practical implications for the optimal switch strategy

The recently published International Expert Consensus on Switching Platelet P2Y₁₂ Receptor-Inhibiting Therapies provided the first solid ground for the optimal switch strategy [7]. According to the consensus, in the early phase after PCI administration of a loading dose of a new P2Y₁₂ antagonist is recommended, regardless of the P2Y₁₂ antagonist chosen. On the contrary, in the late phase only switching from ticagrelor to thienopyridines (clopidogrel, prasugrel) requires administration of a loading dose of a new P2Y₁₂ antagonist. If switching from cangrelor to oral P2Y₁₂ antagonists, clopidogrel and prasugrel should be administered immediately after cangrelor discontinuation, whereas ticagrelor may be administered already at the start of cangrelor infusion. If switching from oral P2Y₁₂ antagonists to cangrelor, the cangrelor infusion should be initiated following wash-out of oral P2Y₁₂

antagonists, continued for maximum 7 days, and stopped 1–6 h before the surgery. In case of an ischaemic or a bleeding event on DAPT and in case of contraindications to current P2Y₁₂ antagonist, PFT may be considered to ensure efficient and safe treatment modification.

4. Conclusions

The availability of different P2Y₁₂ inhibitors provides clinicians with the ability to individualize and optimize antiplatelet therapy according to the changing clinical status. However, until now no large clinical trials supporting certain switching schemes were conducted and currently available recommendations have been established mostly based on the data from registries and pharmacodynamic studies, which lack power to draw firm conclusions on ischemic or bleeding outcomes. The recent International Expert Consensus provided the first recommendations on switching between the P2Y₁₂ antagonists, helping to choose the optimal switch strategy. However, in many situations the optimal switch strategy is arguable, and the decision should be made based on the pharmacological properties of P2Y₁₂ antagonists and individual patients thrombotic and bleeding risk. *The large-scale, randomized clinical trials would be of great help to match the most suitable switching strategies to specific groups of patients and determine the aspects of efficacy and safety of the available antiplatelet drugs.*

Declaration of interests

None.

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