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Review

Switching between $P2Y_{12}$ inhibitors: Rationale, methods, and expected consequences

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A B S T R A C T

The pharmacological and clinical differences of the three recommended oral $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, ticagrelor) enable physicians to switch from one agent to another that it is considered more appropriate in the specific clinical setting. Moreover, the recent availability of cangrelor, the only intravenous $P2Y_{12}$ inhibitor with a rapid onset and offset of its antiplatelet action, makes it necessary to switch from this agent to an oral $P2Y_{12}$ inhibitor for a continued platelet inhibition after percutaneous coronary intervention. Several pharmacodynamic studies have provided information on how to change drug, in terms of timing and dosage, without running the risk of a temporary impairment of platelet inhibition. In addition, several studies have assessed the impact of the switching between $P2Y_{12}$ inhibitors on clinical outcomes. Overall, these evidences have prompted the development of an extensive expert consensus document, have set the basis for recent practice guidelines recommendations, and have stimulated several systematic overviews. The present article provides a brief and schematic summary on the topic of switching between $P2Y_{12}$ inhibitors, focusing on three main practical issues: why and how to switch therapies and what are the clinical consequences of such strategy.

1. Introduction

Clopidogrel, prasugrel and ticagrelor are the oral inhibitors of the $P2Y_{12}$ platelet receptor most commonly used in current clinical practice for the prevention of atherothrombotic events after an acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI). However, those three antiplatelet agents have specific indications, contraindications, and side effects, different pharmacodynamic and clinical profiles, and also markedly distinctive costs. These differences enable physicians to switch from one agent to another that it is considered more appropriate in the specific clinical setting. Moreover, the recent availability of cangrelor, the only intravenous $P2Y_{12}$ inhibitor with a rapid onset and offset of its antiplatelet action, makes it necessary to switch from this agent to an oral $P2Y_{12}$ inhibitor for a continued platelet inhibition after PCI. Thus, considering that the mutual switching can occur between any of the three oral agents and between these latter and the intravenous agent, twelve possible combinations of switching among therapies can be envisaged.

Several pharmacodynamic studies have performed serial assessments of platelet inhibition after different modalities of switching for a specific combination, in order to provide information on how to change drug, in terms of timing and dosage, without running the risk of a temporary impairment of platelet inhibition. Indeed, pharmacological differences in the binding site, half-life, and speed of onset and offset of action might lead to drug interactions when switching from one $P2Y_{12}$ inhibitor to another. The potential drug-drug interactions, defined as a modification of the effect of a drug when administered with another drug, can cause a decreased or increased $P2Y_{12}$ platelet inhibition during the two-drug overlapping phase, prompting the need to identify an optimal switching strategy that can maintain adequate levels of platelet inhibition preventing thrombotic or bleeding complications. With regard to the safety of switching between $P2Y_{12}$ inhibitors, several studies have assessed the impact of such strategy on clinical outcomes. Overall, the relevant amount of pharmacodynamic and clinical data available on the switching between $P2Y_{12}$ inhibitors have prompted the development of an extensive expert consensus document, have set the basis for recent practice guidelines recommendations, and have stimulated several systematic overviews [1–4]. An updated comprehensive review of overall studies on the $P2Y_{12}$ inhibitors switching is available in this issue of the journal [4].

The present article provides a brief and schematic summary on the topic of switching between $P2Y_{12}$ inhibitors, focusing on three main practical issues: why and how to switch therapies and what are the clinical consequences of such strategy.

2. Why to switch between oral $P2Y_{12}$ inhibitors

There are no standardized and exhaustive recommendations on why switching between oral $P2Y_{12}$ inhibitors should be considered. However, several conditions occurring in clinical practice, summarized

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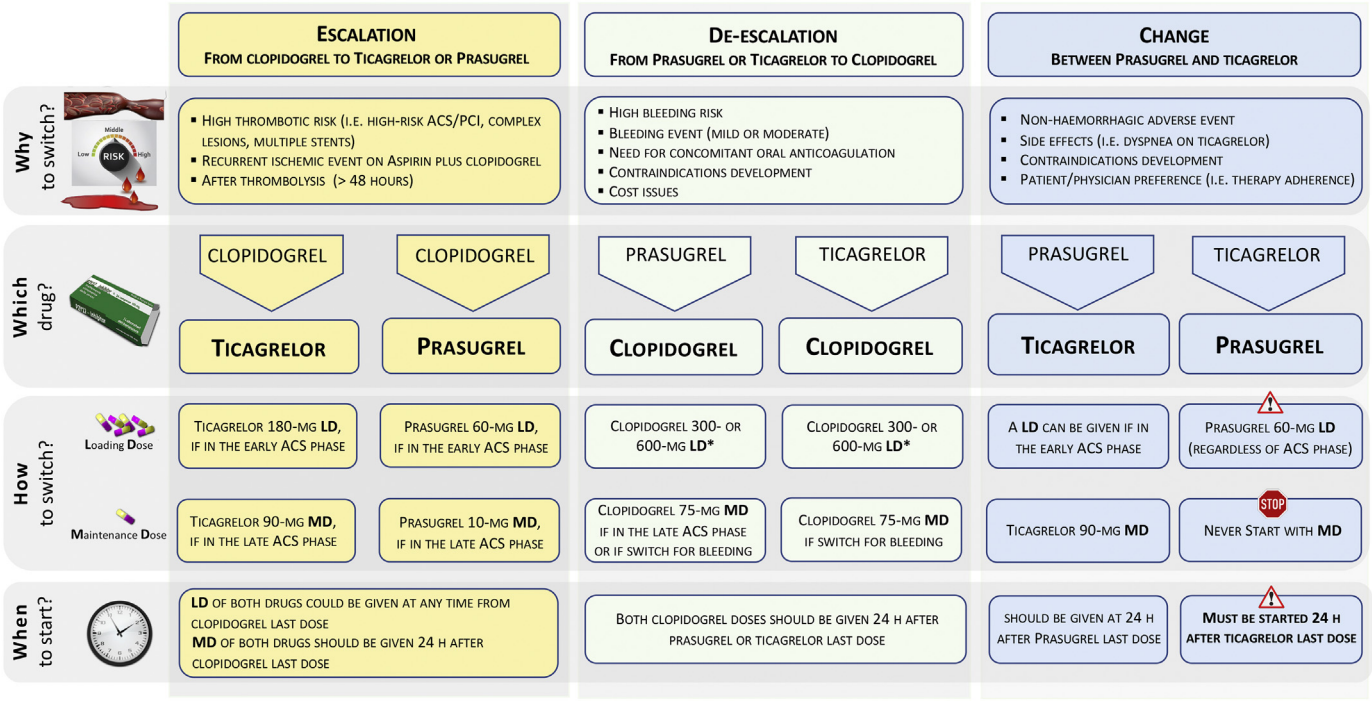

Fig. 1. Reasons and modalities for switching between oral $P2Y_{12}$ inhibitors. ACS: acute coronary syndrome; LD: loading dose; MD maintenance dose; PCI: percutaneous coronary intervention. *While a 600-mg clopidogrel loading dose should be the default strategy, a more conservative approach with a 300-mg dose could be reasonably considered if de-escalation occurs because of a particularly high bleeding risk or a bleeding event.

in Fig. 1, may reasonably drive a specific change from one drug to another based on the differential pharmacological and clinical characteristics of the $P2Y_{12}$ inhibitors.

An escalation of the oral $P2Y_{12}$ inhibition from the less potent clopidogrel to the more potent prasugrel or ticagrelor can occur when the thrombotic risk is considered as high and predominant over the bleeding risk to require enhanced platelet inhibition. Indeed, the escalation from clopidogrel to prasugrel or ticagrelor commonly occurs in patients with high-risk ACS undergoing PCI, who had received pretreatment with clopidogrel at the time of admission. Indeed, according to guidelines, clopidogrel is a treatment option in ACS patients only when prasugrel or ticagrelor are not available or are contraindicated [5]. Another condition that can lead to an escalation of therapy could be an ACS event occurring while on dual antiplatelet therapy (DAPT) with aspirin and clopidogrel. However, this latter represents a challenging scenario if a high-bleeding risk also coexists, in which case the escalation of $P2Y_{12}$ inhibition could be guided by a platelet function testing, and continuation of clopidogrel can be considered if an anatomical cause of the ACS event can be identified and corrected, as illustrated in an algorithm proposed in the review paper by Gasecka et al. in this issue of the journal [4]. Finally, a $P2Y_{12}$ inhibition escalation could occur in ACS patients treated with thrombolysis, on top of which clopidogrel is the standard of care and can be switched to prasugrel or ticagrelor 48 h after thrombolytic therapy.

The observation that the greatest anti-ischemic benefits of more potent agents, prasugrel or ticagrelor, are seen early, while most bleeding arise during chronic treatment with these drugs [6,7], has set the rational for de-escalating the $P2Y_{12}$-inhibiting therapy in the late ACS phase in order to achieve an optimal balance between ischemic benefit and bleeding risk. Despite currently there is no evidence for a uniform large-scale $P2Y_{12}$ de-escalation, such strategy may be considered in clinical practice for several reasons. Indeed, de-escalation of the oral $P2Y_{12}$ inhibition can be reasonable when the bleeding risk is considered to outweigh the benefits achieved from reductions in ischemic events, thus requiring a less pronounced platelet inhibition, or in case of a bleeding event occurring while on DAPT with aspirin plus prasugrel or ticagrelor. However, the management of DAPT during a bleeding event is challenging and controversial. In accordance with an algorithm proposed in current European guidelines, maintaining the DAPT with a switching from ticagrelor or prasugrel to clopidogrel is among the options to be considered in case of mild and moderate bleeding [2]. Moreover, the need for concomitant oral anticoagulation therapy or the development of specific contraindications prompt the switch from prasugrel or ticagrelor to clopidogrel. Finally, the reduced costs associated with a generic formulation of clopidogrel remain among the most important reasons for $P2Y_{12}$ inhibitors de-escalation.

Reasons for mutual switching between prasugrel and ticagrelor, defined as change, may include intolerable side effects, non-hemorrhagic adverse events, the development of contraindications, and adherence-related issues. In particular, ticagrelor-related dyspnea is among the main reason prompting the change from ticagrelor to prasugrel in clinical practice [8,9].

3. Why to switch between intravenous and oral $P2Y_{12}$ inhibitors

The switching from cangrelor to an oral $P2Y_{12}$ inhibitor occurs in patients undergoing PCI when cangrelor is used to achieve immediate potent platelet inhibition during the peri-PCI period. Because of the need to continue chronic $P2Y_{12}$ inhibition with an oral agent after cangrelor discontinuation, this type of switching is referred as transition [1].

The switching from an oral $P2Y_{12}$ inhibitor to cangrelor typically occur in the peri-surgery period, in order to maintain adequate level of platelet inhibition after oral $P2Y_{12}$ inhibitors interruption along with rapid platelets function recovery at the time of surgery. This modality of perioperative switching is defined as bridging [1].

4. How to switch between oral $P2Y_{12}$ inhibitors

A recent International Expert Consensus document on Switching Platelet $P2Y_{12}$ Receptor-Inhibiting Therapies has provided the modalities of switching between $P2Y_{12}$ inhibitors, which have been also

supported by the 2017 European guidelines focusing on dual antiplatelet therapy in coronary artery disease [1,2]. Those modalities are described below and summarized in Fig. 1 for all the possible combinations.

The escalation from clopidogrel to ticagrelor or prasugrel can be achieved with the loading dose (180- or 60-mg, respectively) or directly with the maintenance dose (90- or 10-mg, respectively) if it occurs in the acute or in the late phase of ACS and or/PCI, respectively. The ticagrelor or prasugrel doses can be administered at any time from the clopidogrel last loading or maintenance doses, as no drug-drug interactions occur with this escalation, regardless of the switching combination. However, in the late ACS phase, it is logistically practical to administer the ticagrelor or prasugrel maintenance doses at the time of the next scheduled dose of $P2Y_{12}$-inhibiting therapy (i.e., at about 24 h from the clopidogrel last dose). This escalation modality applies regardless of age and body weight.

Approaches on how to achieve a de-escalation from prasugrel or ticagrelor to clopidogrel have not been fully established. In particular, there was no consensus on switching with or without a clopidogrel loading dose, especially in case of de-escalation from prasugrel to clopidogrel [1]. Indeed, while the offset of prasugrel could be prolonged enough (7–10 days) to allow clopidogrel to reach its full antiplatelet effects during the waning time of prasugrel even if initiated with a 75-mg maintenance dose, ticagrelor has a relatively fast offset of action requiring a more rapid clopidogrel effect in order to avoid any significant gap in platelet inhibition. Therefore, the use of a clopidogrel loading dose should be considered when de-escalating from ticagrelor, regardless of the ACS phase (i.e., acute, early, or late). This latter recommendation was supported by the results of the SWAP (Switching Antiplatelet Therapy)-4 pharmacodynamic study, which showed that switching from ticagrelor to clopidogrel with a loading dose was associated with greater levels of platelet inhibition during the first 48 h compared with switching directly to a maintenance dose [10]. Differently, when switching from prasugrel, a clopidogrel loading dose should be used only in the early ACS phase, when platelet recovery after prasugrel discontinuation may be shorter and the unpredictable effect of clopidogrel may lead to a window of inadequate platelet inhibition. In the late phase of ACS and PCI, the de-escalation from prasugrel can be reasonably performed without a clopidogrel loading dose. Regarding the timing of clopidogrel administration, both the loading and maintenance doses should be given 24 h after last dose of prasugrel or ticagrelor. Indeed, in the SWAP-4 study the pharmacodynamic profiles did not differ according to timing (12 versus 24 h) of administration of the clopidogrel loading dose after ticagrelor discontinuation [10]. Finally, while a 600-mg clopidogrel loading dose should be the default strategy, a more conservative approach with a 300-mg dose could be reasonably considered if de-escalation occurs because of a particularly high bleeding risk or a bleeding event. In this latter scenario, the consensus suggested that the de-escalation from prasugrel or ticagrelor to clopidogrel could be achieved also without the need for a loading dose. However, considering the variable and unpredictable onset of clopidogrel effect, if switching occurs in the early ACS/PCI phase because of bleeding, the use of a 300-mg clopidogrel loading dose could represent a reasonable choice.

The change from ticagrelor to prasugrel has been associated to drug-drug interaction causing an increased platelet reactivity that can be overcome by starting always with a prasugrel loading dose (60-mg), regardless of the timing from the index event that required initiation of the $P2Y_{12}$-inhibitor. In addition, the prasugrel loading dose should be administered 24 h after the last maintenance dose of ticagrelor to allow some waning of ticagrelor plasma concentrations and new platelets with unoccupied receptors entering the systemic circulation. Indeed, if prasugrel is given when ticagrelor plasma concentration are still relevant, platelet receptors remain occupied and cannot be inhibited before the active metabolites of prasugrel are eliminated. Differently, no drug-drug interaction has been shown when changing from prasugrel to ticagrelor therapy, allowing a switch with the maintenance dose of ticagrelor (90-mg), which should be started at the time of the next $P2Y_{12}$ inhibitor scheduled dose. However, the administration of a ticagrelor loading dose given 24 h after the prasugrel last dose should be considered when the change from prasugrel to ticagrelor occurs in the acute phase of ACS.

5. How to switch between intravenous and oral $P2Y_{12}$ inhibitors

In the transition from cangrelor to clopidogrel or prasugrel, these latter should be administered immediately after the discontinuation of cangrelor infusion using a loading dose (600-mg clopidogrel or 60-mg prasugrel). When cangrelor is administered on top of a thienopyridine, if the pretreatment with this latter was shortly before the initiation of cangrelor or unknown, a loading dose at the end of the infusion should be considered. Differently, the transition to ticagrelor can occur with a loading dose (180 mg) given at any time before, during, or immediately after cangrelor infusion. The earlier administration of ticagrelor at the time of PCI is preferred over administration at the end of cangrelor infusion because it would cover for the potential gap in platelet inhibition during the transition phase.

For the bridging from oral $P2Y_{12}$ inhibitors to cangrelor in the presurgery setting, the infusion of cangrelor can be started 3 to 4 days after prasugrel and 2 to 3 days after clopidogrel or ticagrelor discontinuations to avoid unnecessary infusion during the time in which an adequate platelet inhibition still persists after oral $P2Y_{12}$ inhibitors interruption.

6. Clinical outcomes of switching between oral $P2Y_{12}$ inhibitors

There are no randomized trials specifically designed to assess the safety and efficacy of $P2Y_{12}$ inhibition escalation vs an initial treatment with a more potent P2Y12 antagonist. Subanalyses from randomized data are available only for the escalation from clopidogrel to ticagrelor, which did not affect the safety and efficacy of ticagrelor vs clopidogrel in the PLATO trial [6]. Such analysis is not available for the escalation from clopidogrel to prasugrel, as in the TRITON TIMI-38 approval trial comparing prasugrel vs clopidogrel in the PCI setting patients receiving clopidogrel before randomization were excluded [7]. Because of this lack of evidence on prasugrel, current European guidelines focusing on DAPT have only recommended (Class I B) the switching from clopidogrel to ticagrelor, to occur early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contraindications to ticagrelor exist [2]. However, the escalation from clopidogrel to prasugrel has been frequent in clinical practice, as reported in several registries, consistently showing no increase in major bleeding associated with switching from clopidogrel to prasugrel loading doses.

Clinical outcomes following $P2Y_{12}$ de-escalation after ACS derives from two recent randomized trials, which have assessed two strategies [11,12]: 1) switching from prasugrel to clopidogrel at one week after ACS by platelet function testing guidance [11]; 2) switching from prasugrel or ticagrelor to clopidogrel at one month after ACS without platelet function testing [12]. Both de-escalation modalities have been associated with reduced events in net clinical outcomes analyses, driven by a reduction in bleeding without increase in ischemic events compared with the conventional 1-year prasugrel or ticagrelor treatment. However, available trials on $P2Y_{12}$ de-escalation were not powered to detect differences in ischemic outcomes, and no definitive conclusions can be drawn on the clinical efficacy of such switching possibility. For this reason, the 2018 European guidelines on myocardial revascularization recommended (Class IIb B) that $P2Y_{12}$ inhibitors de-escalation guided by platelet function testing may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for a 12-month potent platelet inhibition [5].

The clinical relevance of the change between the two more potent

$P2Y_{12}$ inhibitors has not been specifically explored, but no differences should be expected during the chronic therapy phase based on comparative data showing no differences between ticagrelor and prasugrel. However, the drug-drug interaction occurring during the changing phase from ticagrelor to prasugrel, leading to a temporary increased platelet reactivity, may be associated to detrimental clinical effects. This potential risk of the switching from ticagrelor to prasugrel can be minimized by starting always with the prasugrel loading dose given 24 after the last ticagrelor maintenance dose, as recommended and described above [1].

7. Clinical outcomes of switching between intravenous and oral $P2Y_{12}$ inhibitors

In a large randomized trial the transition from cangrelor to clopidogrel versus clopidogrel loading dose was associated with significantly reduced rate of ischemic events, driven by a reduction in stent thrombosis and myocardial infarction, with no significant increase in severe bleeding in patients undergoing PCI [13]. Differently, to date there are no studies investigating the comparative safety and efficacy of transitioning from cangrelor to prasugrel or ticagrelor versus initial treatment with these two latter oral agents in the PCI setting. The recent CANTIC (the Platelet Inhibition with CANgrelor and Crushed TICagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention) randomized pharmacodynamic study has shown that, in patients undergoing primary PCI for ST-elevation myocardial infarction (STEMI), cangrelor is an effective strategy to bridge the gap in platelet inhibition associated with the use of ticagrelor that was administered as a crushed formulation concomitant with cangrelor, without any apparent drug interaction [14]. Considering that an effective $P2Y_{12}$ inibition reached during PCI for STEMI has been proven to be beneficial [15], the use of cangrelor as a bridge of oral $P2Y_{12}$ inhibitors in the setting of STEMI might potentially improve outcomes. However, studies assessing the clinical safety and efficacy of cangrelor versus more potent oral $P2Y_{12}$ inhibitors in the setting of STEMI are still missing.

In a pharmacodynamic randomized trial among patients who discontinue $P2Y_{12}$ inhibitors before cardiac surgery, bridging with cangrelor consistently achieved and maintained platelet inhibition at levels known to be associated with a low risk of thrombotic events, with no differences in coronary artery bypass grafting-related bleeding compared with placebo [16]. However, clinical safety and efficacy outcomes associated with cangrelor bridging before surgery remain to be established yet.

8. Conclusions

In summary, several modalities have been clearly defined to support physicians in specific settings where it is considered clinically appropriate to switch from one $P2Y_{12}$ inhibitor to another. The rationale and potential practical advantages of routine $P2Y_{12}$ de-escalation in the late ACS phase have fueled particular interest in this latter strategy, which, however, needs further clinical investigation before being applied to patients without specific reasons for not continuing conventional treatment. Moreover, several studies are warranted to better clarify the role of a transition from cangrelor to more potent oral $P2Y_{12}$ inhibitors in the different clinical scenarios.

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