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# International Expert Consensus on Switching Platelet $P2Y_{12}$ Receptor–Inhibiting Therapies

**ABSTRACT:** Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor is the treatment of choice for the prevention of atherothrombotic events in patients with acute coronary syndromes and for those undergoing percutaneous coronary interventions. The availability of different oral $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, ticagrelor) has enabled physicians to contemplate switching among therapies because of specific clinical scenarios. The recent introduction of an intravenous $P2Y_{12}$ inhibitor (cangrelor) further adds to the multitude of modalities and settings in which switching therapies may occur. In clinical practice, it is not uncommon to switch $P2Y_{12}$ inhibitor, and switching may be attributed to a variety of factors. However, concerns about the safety of switching between these agents have emerged. Practice guidelines have not fully elaborated on how to switch therapies, leaving clinicians with limited guidance on when and how to switch therapies when needed. This prompted the development of this expert consensus document by key leaders from North America and Europe with expertise in basic, translational, and clinical sciences in the field of antiplatelet therapy. This expert consensus provides an overview of the pharmacology of $P2Y_{12}$ inhibitors, different modalities and definitions of switching, and available literature and recommendations for switching between $P2Y_{12}$ inhibitors.

**Dominick J. Angiolillo, MD, PhD**
**et al**

The full author list is available on page 1969.

**Correspondence to:** Dominick J. Angiolillo, MD, PhD, University of Florida College of Medicine–Jacksonville, 655 West 8th Street, Jacksonville, FL 32209. E-mail dominick.angiolillo@jax.ufl.edu

**Key Words:** drug interactions ■ hemorrhage ■ pharmacodynamics ■ platelet aggregation inhibitors ■ $P2Y_{12}$ receptor inhibitors ■ thrombosis



Dual antiplatelet therapy with aspirin and a platelet $P2Y_{12}$ receptor antagonist ($P2Y_{12}$ inhibitor) is the treatment of choice for the prevention of atherothrombotic events in patients with acute coronary syndromes (ACS) and for those undergoing percutaneous coronary intervention (PCI).[1,2] Clopidogrel, prasugrel, and ticagrelor are the most commonly used oral platelet $P2Y_{12}$ inhibitors; the use of ticlopidine, the first available $P2Y_{12}$ inhibitor, has been largely abandoned.[3] Clopidogrel is the only oral $P2Y_{12}$ inhibitor indicated for the treatment of patients with stable coronary artery disease.[1,2] Although all 3 agents have an indication for use in ACS, current guidelines support the preferential use of prasugrel and ticagrelor over clopidogrel because of their superior net clinical benefits.[1,2,4–6] Nevertheless, clopidogrel remains widely prescribed.[7,8]

The availability of different oral $P2Y_{12}$ inhibitors has enabled physicians to contemplate switching among therapies because of specific clinical scenarios.[9] The recent introduction of an intravenous $P2Y_{12}$ inhibitor (ie, cangrelor) further adds to the multitude of modalities and settings in which switching therapies may occur.[6] A variety of factors may contribute to the decision to switch, including the clinical setting, patient characteristics, concomitant therapies, costs, social issues, development of side effects, medication adherence, and patient/physician preference.[9]

Therefore, it is not uncommon to change $P2Y_{12}$ inhibitor. However, concerns about the safety of switching between these agents have emerged.

At present, data from large-scale clinical studies to guide the optimal approach to switching $P2Y_{12}$ inhibitors are limited, and most data are derived from pharmacodynamic studies. In turn, practice guidelines have not fully elaborated on how to switch therapies, leaving clinicians with limited guidance on when and how to switch therapies when needed, which prompted the development of this expert consensus document. Key leaders from North America and Europe with expertise in basic, translational, and clinical sciences in the field of antiplatelet therapy who have contributed to the scientific literature of switching antiplatelet therapies were identified by the document chairs (D.J.A. and M.J.P.). All invited experts agreed to partake in the development of this document and endorse the recommendations provided. This was an academic collaboration between the identified experts and was free from any type of industry support. This expert consensus provides an overview of the pharmacology of $P2Y_{12}$ inhibitors, different modalities and definitions of switching, available literature, and recommendations for switching between $P2Y_{12}$ inhibitors.

## PHARMACOLOGICAL PROPERTIES

Concerns surrounding the safety of switching between $P2Y_{12}$ inhibitors have emerged because of the potential for drug-drug interactions (DDIs). A DDI is defined as a modification of the effect of a drug when administered with another drug. In particular, because of a DDI, the effects of a $P2Y_{12}$ inhibitor can be decreased, leading to inadequate platelet inhibition and increasing the risk for thrombotic complications; alternatively, there may be a potential for overdosing as a result of an overlap in drug therapy that could lead to excessive platelet inhibition and predispose to bleeding complications. Although to date no studies have shown a clinical impact of DDIs occurring as a result of switching, there is robust evidence associating different levels of platelet reactivity with adverse clinical outcomes.[10,11] The potential for DDIs when switching $P2Y_{12}$ inhibitors rests on differences in their pharmacological properties. Key pharmacological properties to consider include drug half-life, the site and mechanism of $P2Y_{12}$ receptor binding, and the speeds of onset and offset of pharmacodynamic effects (Table 1).[3,6,9]

Clopidogrel, a second-generation thienopyridine, is a prodrug that is largely (up to 85%) hydrolyzed into an inactive metabolite by human carboxylesterase-1 after intestinal absorption.[12] The remaining prodrug (≈15%) requires a 2-step oxidation process with multiple hepatic cytochrome P-450 (CYP) isoenzymes, mainly CYP2C19, to generate the active thiol metabolite that irreversibly blocks the ADP-binding site on the $P2Y_{12}$ receptor (Figure 1). Prasugrel is a third-generation thienopyridine and is also a prodrug. However, the generation of the active metabolite of prasugrel is more efficient compared with clopidogrel because ultrarapid hydrolysis by human

**Table 1. Pharmacological Properties of $P2Y_{12}$ Receptor Inhibitors**

| | Clopidogrel | Prasugrel | Ticagrelor | Cangrelor |
|---|---|---|---|---|
| Receptor blockade | Irreversible | Irreversible | Reversible | Reversible |
| Prodrug | Yes | Yes | No | No |
| Half-life of parent drug | ≈6 h | <5 min | 6–12 h | 3–6 min |
| Half-life of active metabolite | 30 mins | Distribution half-life, 30–60 mins | 8–12 h | NA |
| | | Elimination half-life, 2–15 h | | |
| Binding site | ADP-binding site | ADP-binding site | Allosteric binding site | Undetermined* |
| Administration route | Oral | Oral | Oral | Intravenous |
| Frequency | Once daily | Once daily | Twice daily | Bolus plus infusion |
| Onset of action† | 2–8 h | 30 min–4 h | 30 min–4 h | ≈2 min |
| Offset of action | 5–10 d | 7–10 d | 3–5 d | 60 min |
| CYP drug interaction‡ | CYP2C19 | No | CYP3A | No |
| Approved settings | ACS (invasive and noninvasively managed), stable CAD, PCI, PAD, and ischemic stroke | ACS undergoing PCI | ACS (invasive or noninvasively managed) or history of MI | PCI in patients with or without ACS |

*ACS indicates acute coronary syndrome; CAD, coronary artery disease; CYP, cytochrome P450; MI, myocardial infarction; PAD, peripheral arterial disease; and PCI, percutaneous coronary intervention.*

**The binding site of cangrelor at the $P2Y_{12}$ receptor level is not clearly defined; nevertheless, cangrelor is associated with high levels of receptor occupancy, preventing ADP signaling.*

*†Indicates times after loading dose and bolus administration for oral and intravenous agents, respectively. Times for oral agents refer to clinically stable subjects and may be prolonged in patients with ST-segment–elevation myocardial infarction or treated with opioids.*

*‡Indicates clinically significant drug interactions.*

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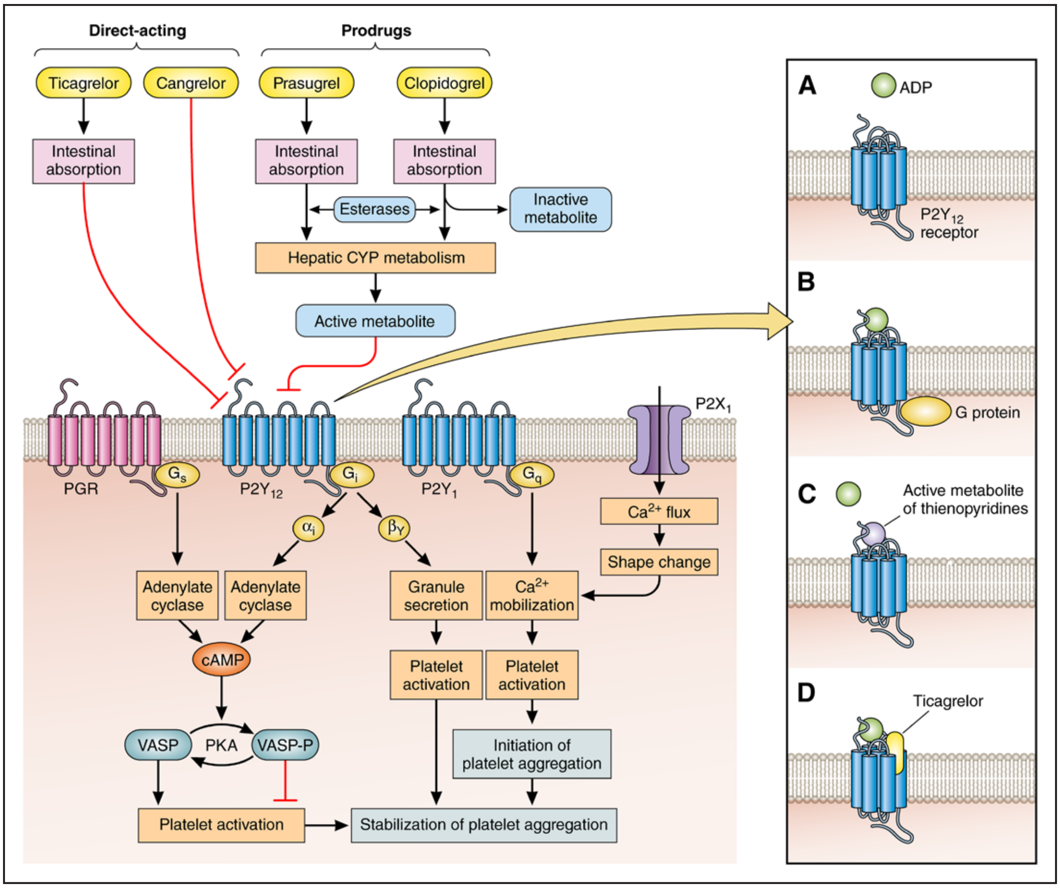


**Figure 1. Mechanisms of action and binding properties of $P2Y_{12}$ inhibitors.**
**Left**, Mechanism of action. Activation of the $P2Y_{12}$ receptor inhibits adenylyl cyclase, causing a decrease in cAMP and phosphorylated (P) vasodilator-stimulated phosphoprotein (VASP) levels, and activation of $P2Y_{12}$ causes an increase in intracellular $Ca^{2+}$ levels. These changes promote platelet aggregation by altering the ligand-binding properties of the glycoprotein IIb/IIIa receptor. Inhibition of the $P2Y_{12}$ receptor therefore suppresses platelet activation. Clopidogrel and prasugrel are oral prodrugs requiring hepatic metabolism to generate an active metabolite that irreversibly inhibits the $P2Y_{12}$ receptor. Ticagrelor is a direct-acting (no metabolism required) oral agent that reversibly inhibits the $P2Y_{12}$ receptor. Cangrelor is a direct-acting intravenous agent that reversibly inhibits the $P2Y_{12}$ receptor. **Right**, Binding properties. **A**, ADP binds to the $P2Y_{12}$ receptor, which (**B**) leads to a conformational change of the receptor and to G-protein activation. **C**, The active metabolite of thienopyridines occupies the ADP-binding site on the $P2Y_{12}$ receptor. Binding is irreversible, which renders the receptor nonfunctional for the life of the platelet. **D**, Ticagrelor binds reversibly to the $P2Y_{12}$ receptor at a site that is distinct from the ADP-binding site. CYP indicates cytochrome P450; PGR, prostaglandin receptor; and PKA, protein kinase A. Adapted from Rollini et al[9] with permission. Copyright ©2016, Mcmillan Publishers Ltd.

carboxylesterase-2 forms an intermediate metabolite, which subsequently requires only a single-step hepatic CYP oxidation to generate its active metabolite. The active metabolite of prasugrel also irreversibly blocks the ADP-binding site on the $P2Y_{12}$ receptor.[12] Although the active metabolite of prasugrel is equipotent to that derived from clopidogrel, its plasma concentration is higher, which translates into more prompt, potent, and predictable platelet inhibitory effects compared with clopidogrel.[12] The active metabolite of clopidogrel is unstable, has a very short half-life (≈30 minutes), and is rapidly eliminated from the circulation if it does not bind to the $P2Y_{12}$ receptor. The active metabolite of prasugrel is more stable, but plasma levels fall rapidly as a result of distribution to extravascular compartments (distribution half-life, 30–60 minutes), after which levels may be insufficient to achieve effective levels of $P2Y_{12}$ blockade.[12] These low levels of active metabolite are detectable in the circulation for an extended time compared with clopidogrel as a result of the much longer elimination half-life (2–15 hours).[12] Given the irreversible binding of the active metabolites, recovery time after treatment discontinuation approximates the life span of platelets. Although subject to variability, this is longer after prasugrel (7–10 days) compared with clopidogrel (5–7 days) discontinuation because of the enhanced level of platelet inhibition achieved (Figure 2A).[13,14]

Ticagrelor is an oral cyclopentyl-triazolopyrimidine that reversibly binds the $P2Y_{12}$ receptor.[15] It is a direct-acting agent and does not require hepatic metabolism

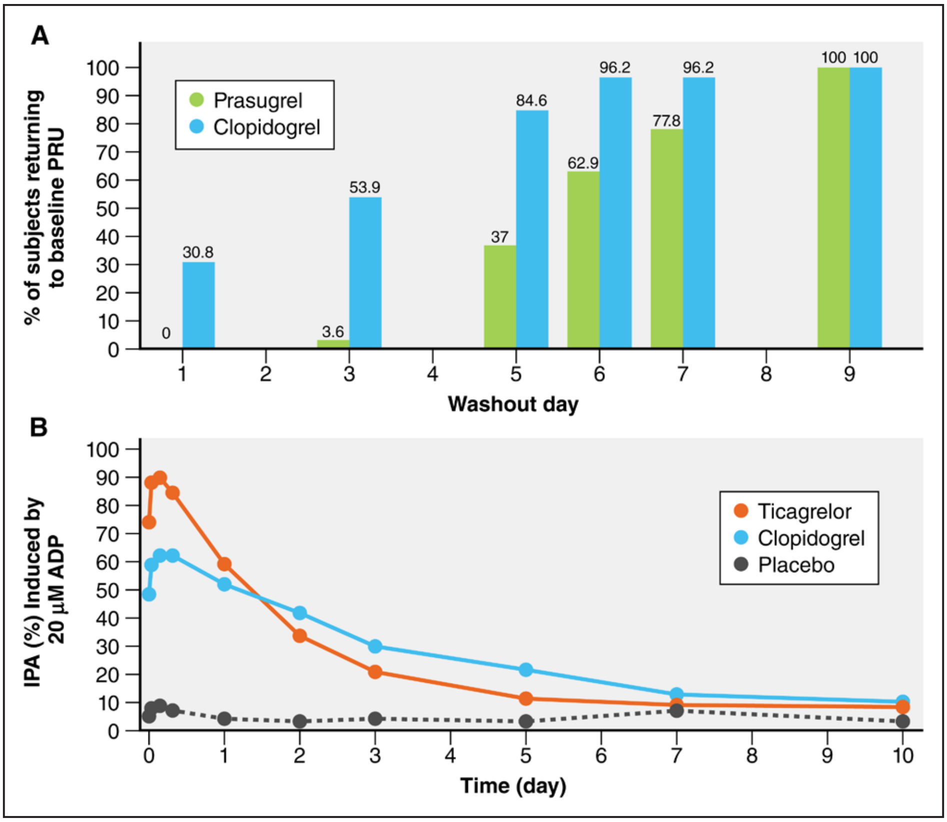


**Figure 2. Offset of antiplatelet effects of oral $P2Y_{12}$ inhibitors.**
**A**, Cumulative proportion of patients returning to baseline reactivity after thienopyridine discontinuation: the RECOVERY trial (Recovery of Platelet Function Following Discontinuation of Prasugrel or Clopidogrel Maintenance Dosing in Aspirin-Treated Subjects With Stable Coronary Disease). Baseline platelet reactivity defined as within 60 $P2Y_{12}$ reaction units (PRUs) of the reactivity measured before study drug exposure. Adapted from Price et al[14] with permission. Copyright ©2012, American College of Cardiology. **B**, Offset of inhibition of platelet aggregation (IPA) on ticagrelor, clopidogrel, and placebo: the ONSET/OFFSET study (A Study of the Onset and Offset of Antiplatelet Effects Comparing Ticagrelor, Clopidogrel, and Placebo With Aspirin). IPA after 20 μmol/L ADP (final extent) measured after last ticagrelor, clopidogrel, and placebo maintenance dose (day 0) and followed up for 10 days. Adapted from Gurbel al[16] with permission. Copyright ©2009, American Heart Association, Inc.

to exert its effect. However, ≈30% of the antiplatelet effect of ticagrelor derives from an active metabolite (AR-C124910XX) generated through CYP3A4/5 enzymes. This active metabolite has pharmacological properties similar to those of the parent compound.[15] Ticagrelor requires twice-daily dosing because of its reversible receptor binding and half-life of 6 to 12 hours. Ticagrelor reversibly binds to a distinct site on the $P2Y_{12}$ receptor and acts through a noncompetitive, allosteric mechanism to prevent G-protein–mediated signal transduction after ADP binding.[15] The pharmacodynamic effects of ticagrelor are more prompt, potent, and predictable compared with those of clopidogrel. However, because of its reversible binding and relatively short half-life, ticagrelor has a faster offset of antiplatelet effect (3–5 days) compared with thienopyridines[16] (Figure 2B).

Cangrelor is an intravenous ATP analog that directly and reversibly inhibits ADP binding to the $P2Y_{12}$ receptor in a dose-dependent manner, achieving immediate potent platelet inhibition after a bolus dose.[6,17] Although its binding site at the $P2Y_{12}$ receptor level is not clearly defined, cangrelor is associated with high levels of receptor occupancy and prevents ADP binding. Cangrelor is promptly inactivated through dephosphorylation by ectonucleotidase and has a very short plasma half-life (3–6 minutes). Therefore, recovery of platelet function is rapid (≈60 minutes) after discontinuation of cangrelor infusion.[6,17]

## SWITCHING MODALITIES AND DEFINITIONS

This expert consensus provides uniform definitions to describe the various modalities of switching of $P2Y_{12}$ inhibitors. In particular, switching can occur between the oral agents and between the oral agents and an intravenous agent. Moreover, the timing of switching with respect to the index event that led to the initiation of $P2Y_{12}$ inhibitor therapy may also vary. Ultimately, switching may occur between different classes of $P2Y_{12}$ inhibitors, which may have potential implications for the occurrence of DDI between the 2 overlapped



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**Table 2. Modalities of Switching Between $P2Y_{12}$ Receptor Inhibitors and Potential for DDI**

| Type of Pharmacodynamic Switch | Type of Drug Class Switch | Potential for DDI |
|---|---|---|
| Oral* | | |
| Escalation | | |
| Clopidogrel to prasugrel | Intraclass | No |
| Clopidogrel to ticagrelor | Interclass | No |
| De-escalation | | |
| Prasugrel to clopidogrel | Intraclass | No |
| Ticagrelor to clopidogrel | Interclass | Yes |
| Change | | |
| Prasugrel to ticagrelor | Interclass | No |
| Ticagrelor to prasugrel | Interclass | Yes |
| Intravenous | | |
| Bridge | | |
| Clopidogrel to cangrelor | Interclass | No |
| Prasugrel to cangrelor | Interclass | No |
| Ticagrelor to cangrelor | Interclass | No |
| Transition | | |
| Cangrelor to clopidogrel | Interclass | Yes |
| Cangrelor to prasugrel | Interclass | Yes |
| Cangrelor to ticagrelor | Interclass | No |

DDI indicates drug-drug interaction.

*Switching between oral agents may be classified according to relationship from the index event a defined as acute (<24 hours), early (1–≤30 days), late (>30 days–1 year), and very late (>1 year).

agents. Switching modalities between $P2Y_{12}$ inhibitors and their potential for DDI are summarized in Table 2.

## Switching Between Oral $P2Y_{12}$ Inhibitors

Prasugrel and ticagrelor are characterized by enhanced pharmacodynamic effects compared with clopidogrel.[3,6,12–16] Therefore, switching between oral $P2Y_{12}$ inhibitors may result in a variation from a less intensive to a more intensive agent (ie, clopidogrel to prasugrel or ticagrelor) or vice versa from a more intensive to a less intensive agent (ie, prasugrel or ticagrelor to clopidogrel). These modalities of switching are defined as escalation and de-escalation, respectively. Although studies comparing the pharmacodynamic effects of prasugrel versus ticagrelor have yielded some inconsistent findings, the overall levels of $P2Y_{12}$ inhibition are markedly reduced and not that dissimilar between these agents.[18] Switching between prasugrel and ticagrelor is referred to as change. Such terminology (escalation, de-escalation, and change) should be considered only when referring to the pharmacodynamic effects associated with switching and should not imply any clinical correlate (efficacy or safety).

Switching may be also classified according to the $P2Y_{12}$ inhibitor class. Two different classes of oral $P2Y_{12}$ inhibitors are available for clinical use: thienopyridine (ie, clopidogrel or prasugrel) and cyclopentyl-triazolopyrimidine (ie, ticagrelor).[3,6] In some circumstances, an interclass switch (ie, between agents from 2 different classes) may lead to a DDI, which is unlikely to occur from an intraclass switch (ie, between 2 different agents of the same class). Overall, escalation of therapy has not been associated with DDI, regardless of class. However, there is a potential for a DDI with de-escalation therapy, particularly when switching from ticagrelor to clopidogrel.[9,19] A DDI, with an increase in platelet reactivity, has been suggested when switching from ticagrelor to prasugrel but not from prasugrel to ticagrelor.[20,21]

Switching may occur at different times from the index event that led to initiation of oral $P2Y_{12}$-inhibiting treatment. A main concern with switching oral $P2Y_{12}$-inhibiting therapy is that if this is associated with inadequate platelet inhibition, it may lead to stent thrombosis.[10,11] Because thrombotic risk is highest in the early weeks after an ACS or PCI, the timing of switching from the index event may have therapeutic implications. Definitions from the Academic Research Consortium have been provided to define stent thrombosis according to timing of occurrence.[22] In line with the therapeutic implications associated with switching according to the time from PCI, this expert consensus believes that incorporating well-known and established definitions would be practical. Accordingly, the timing of switching with respect to the duration since the initiating event may be defined as acute (<24 hours), early (1–30 days), late (>30 days–1 year), or very late (>1 year).

## Switching to and From an Intravenous $P2Y_{12}$ Inhibitor

Cangrelor, the only available intravenous $P2Y_{12}$ inhibitor, provides more prompt and greater $P2Y_{12}$ inhibition than any of the oral agents.[17,23–27] Switching may occur from an oral agent to cangrelor or vice versa. Patients are typically switched from an oral $P2Y_{12}$ inhibitor to cangrelor while awaiting cardiac or noncardiac surgery. This modality of switching is defined as bridging. Patients are typically switched from cangrelor to an oral $P2Y_{12}$ inhibitor in the setting of PCI when cangrelor is used to achieve immediate potent platelet inhibition during the peri-PCI period. Because of the need to continue $P2Y_{12}$ inhibition with an oral agent after discontinuation of cangrelor, this type of switching is defined as transition. Because cangrelor is of a different class from all oral $P2Y_{12}$ inhibitors, all switches involving cangrelor are by definition interclass. Bridging from oral to intravenous $P2Y_{12}$-inhibiting therapy with cangrelor is associated with sustained $P2Y_{12}$ inhibitory effects and does not lead to a DDI.[28] However, transitioning from cangrelor to a thienopyridine (clopidogrel and prasugrel), but not ticagrelor, can be associated with a DDI.[26–31]

## SWITCHING BETWEEN ORAL $P2Y_{12}$ INHIBITORS

In this section, a summary of the available data from clinical trials, registries, and pharmacodynamic studies on escalation, de-escalation, and change in oral $P2Y_{12}$ inhibitors is provided.

### Escalation (Switching From Clopidogrel to Prasugrel or Ticagrelor)

Escalating from clopidogrel to prasugrel or ticagrelor therapy commonly occurs in patients presenting with an ACS, above all those undergoing PCI, who may have been pretreated with clopidogrel at the time of clinical presentation. This is particularly frequent among patients who get transferred to a PCI-capable center. Occurrence of an ACS while on clopidogrel is also a reason for escalating therapy. To date, most data on escalation therapy derive from subgroup analyses of large clinical trials, registries. and pharmacodynamic studies.

The TRITON-TIMI 38 trial (Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38) demonstrated the superiority of prasugrel over clopidogrel in reducing ischemic events, albeit at the expense of increased bleeding, including fatal bleeding, in patients with ACS undergoing PCI. However, this trial cannot address the impact of switching from clopidogrel to prasugrel because patients with previous exposure to a $P2Y_{12}$ inhibitor were excluded.[5] On the contrary, 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 tested the effects of administering prasugrel 30 mg at the time of diagnosis plus 30 mg after coronary angiography versus administering 60 mg after coronary angiography if PCI was indicated in patients with non–ST-segment–elevation myocardial infarction, allowed patients receiving a 75-mg maintenance dose (MD) of clopidogrel at the time of randomization to be enrolled.[32] However, pretreatment with prasugrel increased major bleeding complications without any ischemic benefit, with consistent findings regardless of clopidogrel pretreatment. The TRILOGY-ACS trial (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage ACS) assessed the impact of long-term use of prasugrel compared with clopidogrel in patients with non–ST-segment–elevation ACS selected for medical management without revascularization. Prasugrel was initiated with an MD, without a loading dose (LD), in ≈95% of the population; ≈70% of patients randomized to prasugrel had received clopidogrel administered as an LD. Although there were no differences in major bleeding complications between treatment groups, these results need to be interpreted with caution because the trial did not reach its primary efficacy end point.[33]

The PLATO trial (Study of Platelet Inhibition and Patient Outcomes) demonstrated the superiority of ticagrelor over clopidogrel in reducing ischemic events without an increase in the rate of overall major bleeding but with an increase in non–coronary artery bypass graft surgery–related bleeding across the spectrum of patients with ACS regardless of the planned management strategy (invasive or noninvasive).[4] Approximately 50% of patients randomized to ticagrelor were previously treated with clopidogrel, and the efficacy and safety of ticagrelor 180-mg LD followed by an MD of 90 mg twice daily were consistent regardless of previous clopidogrel exposure.[4] In the ATLANTIC trial (Administration of Ticagrelor in the Cath Laboratory or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery), which showed that prehospital administration of ticagrelor in patients with acute ST-segment–elevation myocardial infarction appeared to be safe but did not improve pre-PCI coronary reperfusion, patients who were on clopidogrel at the time of presentation were excluded.[34] The PEGASUS trial (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) evaluated the safety and efficacy of a long-term MD of ticagrelor 60 or 90 mg twice daily, initiated without an LD, compared with placebo in patients with a myocardial infarction in the previous 1 to 3 years. Treatment with ticagrelor significantly reduced ischemic events, albeit at the expense of increased major bleeding.[35] Approximately one third of patients were on a $P2Y_{12}$ inhibitor (mostly clopidogrel) at the time of randomization.

A number of registries have evaluated escalating from clopidogrel to prasugrel or ticagrelor, showing a prevalence that varied from 5% to 50%, depending on the clinical setting and the period of observation (in-hospital versus after discharge; Table I in the online-only Data Supplement).[36–47] The reasons for switching included primarily clinical factors such as ST-segment–elevation myocardial infarction presentation, in-hospital reinfarction, high-risk angiographic characteristics, younger age, higher body weight, sex, and socioeconomic factors. In the majority of cases, the switch occurred in the catheterization laboratory at the time of or immediately after PCI. Although registries did not identify any major safety concerns associated with switching, these findings should be interpreted with caution because the studies were not designed or powered to assess clinical outcomes.

Many studies have been specifically conducted to provide insights into levels of platelet reactivity associated with switching from clopidogrel to prasugrel or ticagrelor (Figure 3). In the SWAP study (Switching Antiplatelet), conducted in patients receiving mainte-

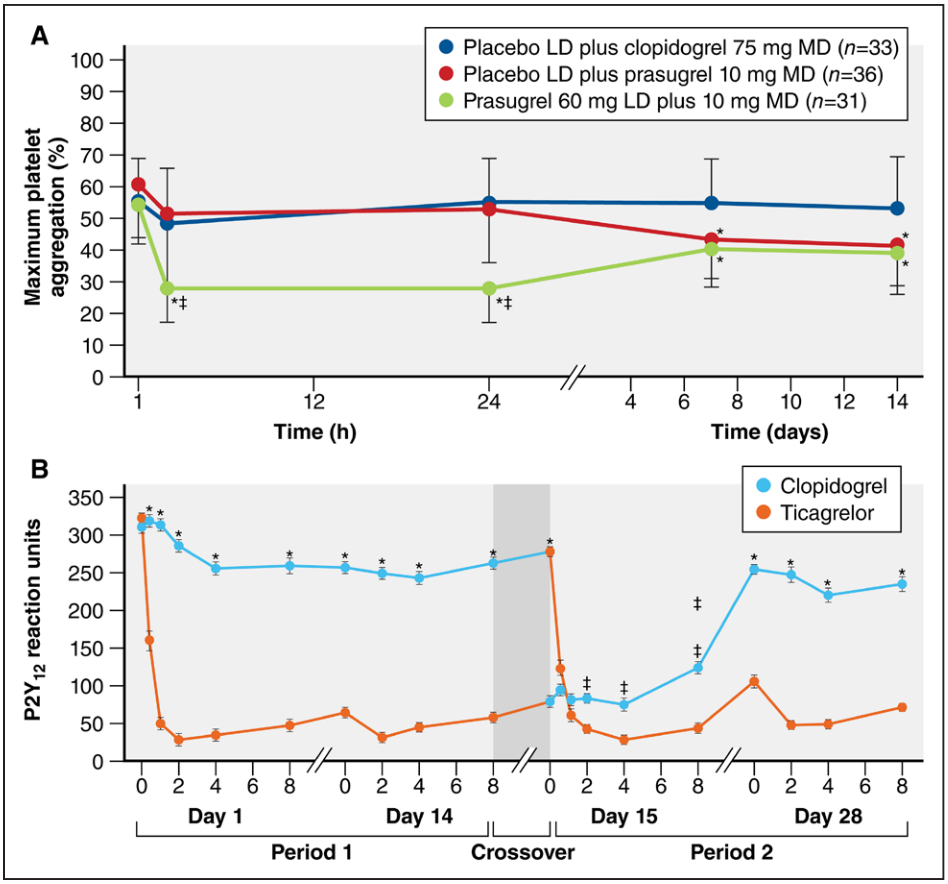


**Figure 3. Escalating $P2Y_{12}$ inhibiting therapy (switching from clopidogrel to prasugrel or ticagrelor).**
**A**, Pharmacodynamic profile of switching from clopidogrel to prasugrel therapy: the SWAP study (Switching Antiplatelet). Time course of platelet inhibition as measured with maximum platelet aggregation in response to 20 μmol/L ADP in patients with an acute coronary syndrome whose therapy was switched from clopidogrel to prasugrel. Patients were randomly assigned to 1 of the 3 study groups. **P*<0.0001 vs results with 75-mg maintenance dose (MD) of clopidogrel. ‡*P*<0.0001 vs results with 10-mg MD of prasugrel. **B**, Pharmacodynamic profile of switching between clopidogrel and ticagrelor therapy: results from the RESPOND study (Response to Ticagrelor in Clopidogrel Nonresponders and Responders and the Effect of Switching Therapies). $P2Y_{12}$ reaction units in clopidogrel-nonresponsive patients before and after crossover. Patients treated with ticagrelor in period 1 received a 600-mg clopidogrel loading dose (LD) followed by 75-mg daily maintenance therapy in period 2; patients treated with clopidogrel in period 1 received a 180-mg ticagrelor LD followed by 90-mg twice-daily maintenance therapy in period 2. **P*<0.0001. ‡*P*<0.05. Adapted from Rollini et al[9] with permission. Copyright ©2016, Mcmillan Publishers Ltd.

nance clopidogrel therapy after an ACS event, escalation from clopidogrel to prasugrel was associated with further reduction in platelet reactivity within 2 hours with the administration of a 60-mg prasugrel LD and by 1 week with 10-mg prasugrel as an MD (Figure 3A).[48] In the RESPOND study (Response to Ticagrelor in Clopidogrel Nonresponders and Responders and the Effect of Switching Therapies), conducted among patients with stable coronary artery disease, ticagrelor therapy (180-mg LD followed by MD) overcame nonresponsiveness to clopidogrel, and its antiplatelet effect was the same in clopidogrel responders and nonresponders (Figure 3B).[49] Many other studies exploring the pharmacodynamic profiles of switching from clopidogrel to prasugrel or ticagrelor have been conducted (Tables II and III in the online-only Data Supplement).[18,48–66] All studies have consistently shown enhanced platelet inhibition when escalating from clopidogrel to prasugrel or ticagrelor, regardless of clinical setting, as well as a reduction in rates of high on-treatment platelet reactivity (HPR),[18,48–70] a well-defined marker of risk of ischemic recurrences, including stent thrombosis.[10,11] These effects are achieved more promptly after administration of an LD compared with an MD regimen. These pharmacodynamic studies did not suggest any type of DDI or concerns of overdosing. This may be attributed to the fact that in patients treated with clopidogrel, even after an LD, a substantial number of $P2Y_{12}$ receptors remain uninhibited, allowing additional blockade by the administration of an LD of prasugrel or ticagrelor. The degree of $P2Y_{12}$ receptor blockade after prasugrel or ticagrelor administration is similar regardless of previous exposure to clopidogrel.

## De-escalation (Switching From Prasugrel or Ticagrelor to Clopidogrel)

Despite the evidence for the sustained efficacy and safety of prasugrel and ticagrelor with long-term treatment, many physicians limit treatment duration with these agents to the early weeks or months after the index event.[36–41] Reduced costs associated with a generic formulation of clopidogrel and concerns about increased risk of bleeding with prasugrel and ticagrelor remain the most important reasons for de-escalation. Nonbleeding side effects such as dyspnea also represent a potential reason for interrupting ticagrelor therapy.[4,35,71,72]

Overall, registry data indicate that the prevalence of in-hospital de-escalation ranges from 5% to 14% (Table I in the online-only Data Supplement).[36–41] These patients are less likely to be privately insured and have risk factors associated with increased bleeding risk such as older age, lower body weight, previous transient ischemic attack/stroke, in-hospital treatment with coronary artery bypass graft surgery, atrial fibrillation/flutter, and use of oral anticoagulants (OACs).[36–41] Switching between $P2Y_{12}$ inhibitors after hospital discharge occurs in 5% to 8% of patients, with most cases represented by de-escalation.[45] The SCOPE registry (Switching From Clopidogrel to New Oral Antiplatelet Agents During Percutaneous Coronary Intervention) showed that de-escalation of $P2Y_{12}$ inhibitors early after the index event in patients with ACS was associated with an increased risk of recurrent ischemic events with no differences in bleeding.[47] These findings are likely attributed to the increase in platelet reactivity and HPR rates, with patients being particularly vulnerable if de-escalation occurs too soon after the acute event.

Recently, randomized trials of de-escalation have been reported (Table I in the online-only Data Supplement).[73,74] The randomized TOPIC trial (Timing of Optimal Platelet Inhibition After Acute Coronary Syndrome) showed that in patients who have been event free for the first month after an ACS on a combination of aspirin plus a new-generation $P2Y_{12}$ inhibitor, de-escalation to aspirin plus clopidogrel was associated with reduced bleeding complications, mostly minor.[73] Although this study did not show any differences in ischemic events between groups, play of chance cannot be ruled out given the limited sample size of the trial. The TROPICAL-ACS trial (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for ACS) randomized patients with ACS undergoing PCI to either standard treatment with prasugrel for 12 months or a de-escalation regimen (1 week of prasugrel followed by 1 week of clopidogrel and platelet function testing–guided maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge).[74] The trial showed that a strategy of guided de-escalation of antiplatelet treatment was noninferior to standard treatment with prasugrel at 1 year in terms of net clinical benefit. The strategy did not show any increase in ischemic events, although there was a numeric but not statistically significant reduction in bleeding. The moderate impact on bleeding risk reduction could be explained by the considerably high percentage of patients (40%) who required escalation back to prasugrel therapy because of developing HPR after de-escalation. Thus far, TROPICAL-ACS is the only randomized trial using results of platelet function testing to adjust antiplatelet therapy (escalation or de-escalation) to meet its primary end point.[53,75–77] There are limited data assessing the clinical impact of escalation and de-escalation of antiplatelet therapy on the basis of the results of genetic testing, which is currently being evaluated in several randomized trials, including the use of rapid genetic testing.[78]

Overall, there is a paucity of studies assessing the pharmacodynamic effects associated with de-escalation to clopidogrel therapy that have consistently shown an increase in platelet reactivity and HPR rates, with some reporting lower bleeding events (Table IV in the online-only Data Supplement).[19,49,51,52,56,79,80] However, these findings, as well as the absence of increased thrombotic events despite a higher rate of patients developing HPR, should be interpreted with caution because none of these studies were powered for clinical outcomes. It is important to note that although switching from prasugrel or ticagrelor to clopidogrel is intuitively associated with an increase in platelet reactivity and HPR rates, the different speed of offset of the drugs may have important therapeutic implications, particularly with regard to the timing of clopidogrel administration and whether it should be given as an LD.[9,19] The rationale for switching should further influence whether an LD should be given, especially if there are concerns for bleeding.

## Change (Switching Between Prasugrel and Ticagrelor)

To date, there is limited information on switching between the newer-generation $P2Y_{12}$ inhibitors prasugrel and ticagrelor. The few available registry data indicate that the rate of switching between these agents ranges from 2% to 4% (Table I in the online-only Data Supplement).[36–39] Although ticagrelor can be administered in patients with ACS upstream before the coronary anatomy is known, physicians might consider switching to prasugrel because of its once-daily administration, which may improve adherence. Another reason to consider switching from ticagrelor to prasugrel is ticagrelor-associated dyspnea. Data from real-world clinical practice show that some patients may be treated with prasugrel despite having a relative or absolute contraindication but are candidates for ticagrelor therapy and may therefore switch treatment. These include patients with ACS who are pretreated with prasugrel before their coronary anatomy is defined but do not undergo PCI and those who have a previous cerebrovascular event.[36,39,41]

There are limited studies on the pharmacodynamic effects associated with change between newer $P2Y_{12}$ inhibitors.[20,21] The SWAP-2 study investigated the pharmacodynamic effects of switching from ticagrelor to prasugrel. In this study, patients were switched to prasugrel (with or without a 60-mg LD) 12 hours after the last MD of ticagrelor.[20] Platelet reactivity was higher in patients treated with prasugrel compared with patients treated with ticagrelor at 7 days, not meeting the noninferiority primary end point. Moreover, at 24 hours and even more so at 48 hours, platelet reactivity increased in patients switched to prasugrel compared with preswitch levels, and the use of an LD of prasugrel appeared to be essential to mitigate the increase in platelet reactivity after switching (Figure 4A).[20] The mechanisms for these observations remain unknown but might be the result of prolonged binding of ticagrelor and its major metabolite to the $P2Y_{12}$ receptor after plasma levels have fallen, which may potentially impede the active metabolites of thienopyridines to access their binding site. These changes may also explain why, despite being a reversible agent with an 8- to 12 hour half-life, ticagrelor has effects that may persist for several days after drug discontinuation.[16] For these reasons, it has been suggested that switching at a later time after MD (eg, after 24 hours) should limit increases in platelet reactivity by providing more time for $P2Y_{12}$ receptor blockade by ticagrelor to decline.

The SWAP-3 study investigated the pharmacodynamic effects of switching from prasugrel to ticagrelor.[21] The study showed that in patients who were on maintenance prasugrel therapy, changing to ticagrelor was associated with a transient reduction in platelet reactivity. These pharmacodynamic findings were observed as early as 2 hours after switching therapy, without any signs of DDI during the entire study time course and with no increase in HPR rates. Of note, these findings were observed when switching to ticagrelor with the 90-mg (not 60-mg) dosing regimen and occurred regardless of the use of an LD (Figure 4B).[21]

## SWITCHING BETWEEN INTRAVENOUS AND ORAL $P2Y_{12}$ INHIBITORS

### Bridging From Oral $P2Y_{12}$ Inhibitors to Cangrelor

Although cangrelor is being used in real-world clinical practice as a bridging strategy, there are limited data to support the safety and efficacy of this approach.[81] The BRIDGE trial (Maintenance of Platelet Inhibition With Cangrelor After Discontinuation of Thienopyridines in Patients Undergoing Surgery) showed that among patients who discontinue thienopyridine therapy before cardiac surgery, the use of cangrelor compared with placebo resulted in a higher rate of maintenance of platelet inhibition.[28] The dose of cangrelor used for bridging (0.75–$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion without a bolus) derives from a dose-finding study that identified levels of platelet inhibition similar to those achieved in patients with a good response to clopidogrel and is substantially lower than that used in PCI (30–μg/kg bolus and 4–$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion). The pharmacodynamic results from the BRIDGE study do not suggest any type of DDI, likely because there are still unoccupied receptors in patients treated with oral $P2Y_{12}$ inhibitors that can be bound and inhibited by cangrelor. This is in line with in vitro and ex vivo investigations showing no interaction when cangrelor is administered on top of thienopyridines or ticagrelor and is associated with enhanced antiplatelet effects.[24–27,30,82]

### Transition From Cangrelor to Oral $P2Y_{12}$ Inhibitors

Cangrelor was approved for clinical use on the basis of the results of the CHAMPION PHOENIX trial (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition), which showed that cangrelor significantly reduced the 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.[83] In patients treated with cangrelor, a clopidogrel LD was administered immediately after discontinuation of cangrelor infusion. This approach was used because pharmacodynamic studies with cangrelor demonstrated a rapid platelet inhibitory effect during cangrelor infusion and a rapid offset of action after treatment discontinuation.[23] The approach of administering clopidogrel after cangrelor was stopped was used across the cangrelor trial development program to avoid a potential DDI between cangrelor and clopidogrel, as described later. To date, no clinical outcomes study has investigated the safety and efficacy of cangrelor in patients subsequently treated with prasugrel or ticagrelor, although single-center observational data have been published.[84,85]

Given the different pharmacological properties of cangrelor and the oral $P2Y_{12}$ inhibitors, several studies have investigated the potential for DDI when these agents are concomitantly administered (Supplemental Table V in the online-only Data Supplement).[23–31] These potential DDIs are concerning because they can result in reduced platelet inhibition and subsequent lack of protection from thrombotic complications in the peri-

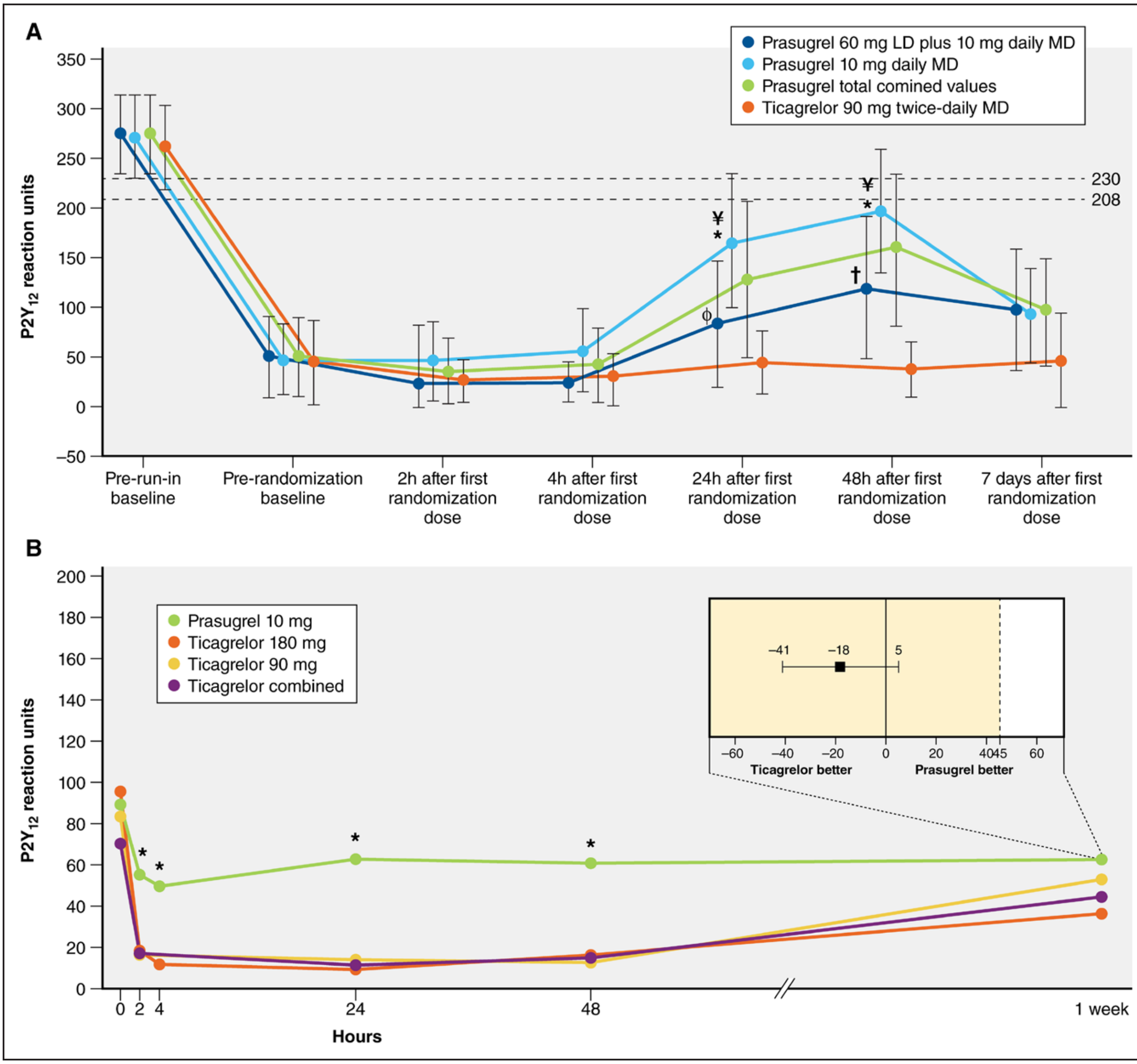


**Figure 4. Change between newer-generation oral $P2Y_{12}$ inhibitors (switching between prasugrel and ticagrelor).** **A**, Pharmacodynamic profile of switching from ticagrelor to prasugrel: the SWAP-2 study **(**Switching Antiplatelet 2). Time course of platelet inhibition as measured with $P2Y_{12}$ reaction units (PRUs) in patients with stable coronary artery disease. After the run-in phase with ticagrelor was completed, patients were randomly assigned to 1 of 3 regimens. **P*<0.001 for change from prerandomization baseline for prasugrel maintenance dose (MD) at 24 and 48 hours. ϕ*P*=0.002 for change from prerandomization baseline for prasugrel loading dose (LD) at 24 hours. †*P*<0.001 at 48 hours. ¥*P*<0.001 for the difference between the prasugrel MD group and the prasugrel LD group at 24 and 48 hours. Adapted from Angiolillo et al[20] with permission. Copyright ©2014, American College of Cardiology. **B**, Pharmacodynamic profile of switching from prasugrel to ticagrelor: the SWAP-3 study. Time course of platelet inhibition as measured with PRUs in patients with a recent acute coronary syndrome on maintenance prasugrel therapy. Patients were randomly assigned to 1 of 3 regimens. **P*<0.001 for the comparison of ticagrelor combined vs prasugrel 10 mg. The box in the top right corner represents the primary end point: 1-week PRU absolute difference and 2-sided 95% confidence interval between ticagrelor combined and prasugrel 10 mg (tinted area indicates zone of noninferiority. Adapted from Franchi et al[21] with permission. Copyright ©2016, American College of Cardiology.

PCI period. In a study conducted in healthy volunteers, clopidogrel administration during cangrelor infusion was associated with an impaired antiplatelet effect of clopidogrel after cangrelor discontinuation.[30] This reflects the fact that the clopidogrel active metabolite, like the prasugrel active metabolite, cannot bind to the $P2Y_{12}$ receptors if already largely occupied by cangrelor.[86] In turn, the plasma concentrations of the unbound thienopyridine active metabolites fall rapidly to subtherapeutic levels as a result of distribution to other compartments and systemic clearance. Therefore, after cangrelor infusion is stopped, when receptors become available for binding, most of the active metabolite of thienopyridines has already been eliminated from the circulation. In contradistinction, the antiplatelet effects of clopidogrel are not diminished when it is administered after cangrelor infusion because of the very fast offset of action of cangrelor and subsequent availability of $P2Y_{12}$ receptors for binding by clopidogrel active metabolite.[23,30,31] The transition from cangrelor to prasugrel is associated with transient recovery of platelet reactivity, in particular within 1 hour after cangrelor discontinuation.[27] However, it was observed that recovery of platelet function was attenuated when prasugrel was administered 30 minutes before the cangrelor infusion was stopped.[27] Conversely, administration of clopidogrel 30 minutes or 1 hour before cangrelor infusion discontinuation did not prevent recovery of platelet reactivity more effectively than administration at the end of the infusion.[31] Similar findings were observed when platelets were incubated with cangrelor before the addition of the active metabolites of either prasugrel or clopidogrel, when the ability of thienopyridines to inhibit platelet aggregation was strongly reduced.[82] However, the ExcelsiorLOAD2 study (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate–Advanced Loading Strategies) showed that a 60-mg LD of prasugrel given at the start of a 2-hour infusion of cangrelor was associated with sufficient platelet inhibition after cangrelor, with only rare cases of HPR.[87] These observations may be attributed to the relatively higher concentration and longer half-life of the active metabolite of prasugrel compared with that of clopidogrel.[12] However, whether similar findings would be observed with longer infusions of cangrelor (eg, up to 4 hours) is unknown.

Unlike that observed with thienopyridines, no interaction was shown for the transition from cangrelor to ticagrelor, allowing more versatile use of ticagrelor with respect to timing of administration in relation to the start of cangrelor therapy.[26] The presence of an interaction between thienopyridines, in particular clopidogrel, and cangrelor, but not between ticagrelor and cangrelor, is probably the result of the different half-lives of these drugs, as well as the different sites and types of binding to the $P2Y_{12}$ receptor.[6,12,15,17] Ticagrelor reversibly binds the $P2Y_{12}$ receptor at a site distinct from the ADP-binding site and has a half-life of 6 to 12 hours. Although it is unknown whether ticagrelor can bind with the $P2Y_{12}$ receptor during cangrelor infusion, its half-life (which exceeds that of the duration of cangrelor infusion) is such that drug is still systemically available to bind with the $P2Y_{12}$ receptor after discontinuation of cangrelor infusion. On the basis of these observations, ticagrelor can be administered before, during, or after cangrelor infusion.[26]

## $P2Y_{12}$ INHIBITORS: EXPERT CONSENSUS RECOMMENDATIONS ON SWITCHING

This expert consensus group developed recommendations on when and how to switch between $P2Y_{12}$ inhibitors, taking into consideration the pharmacological profiles of oral and intravenous $P2Y_{12}$ inhibitors; data from clinical trials, registries, and pharmacodynamic studies; and the potential for thrombotic complications based on the time elapsed from the index event leading to initiation of $P2Y_{12}$-inhibiting therapy. In line with the limited safety and efficacy data in this field, these recommendations are to be considered mostly consensus based rather than evidence based. In general, switching approaches that have shown to be associated with DDI should be avoided or minimized unless clinically necessary. The provided recommendations are to be considered as guidance for the practicing clinician, who may consider alternative approaches based on the clinical context of the patient. The considerations made here are proposed under the assumption that these patients are also, for the most part, treated with concomitant low-dose aspirin in line with guideline recommendations. The expert consensus recommendations on switching $P2Y_{12}$ inhibitors are described in detail in the following sections and summarized in Figures 5 and 6.

### Switching Between Oral $P2Y_{12}$ Inhibitors

#### *Escalation (Switching From Clopidogrel to Prasugrel or Ticagrelor)*

Escalation from clopidogrel to prasugrel or ticagrelor in the early, particularly acute, phase of treatment should occur with the use of a 60- or 180-mg LD, respectively. Administration of an LD regimen may occur regardless of the timing of the last dose of clopidogrel. This should be followed by standard MD regimens (prasugrel 10 mg daily or ticagrelor 90 mg twice-daily). Beyond the early phase, it is reasonable to escalate with a 10-mg daily or 90-mg twice-daily MD regimen of prasugrel or ticagrelor, respectively, without an LD. It is also reasonable and practical for the patient to start the new MD regimen at the time of the next scheduled dose of $P2Y_{12}$-inhibiting therapy (eg, ≈24 hours from last dose of clopidogrel). Similar considerations on timing of switching should apply for elderly or low-body-weight patients in whom a 5-mg MD of prasugrel is being used.

#### *De-Escalation (Switching From Prasugrel or Ticagrelor to Clopidogrel)*

There was a lack of group consensus on the appropriate approach to de-escalate from prasugrel to clopidogrel in the acute/early phase (ie, with an MD or an LD) given the limited data on therapy de-escalation. The pro-

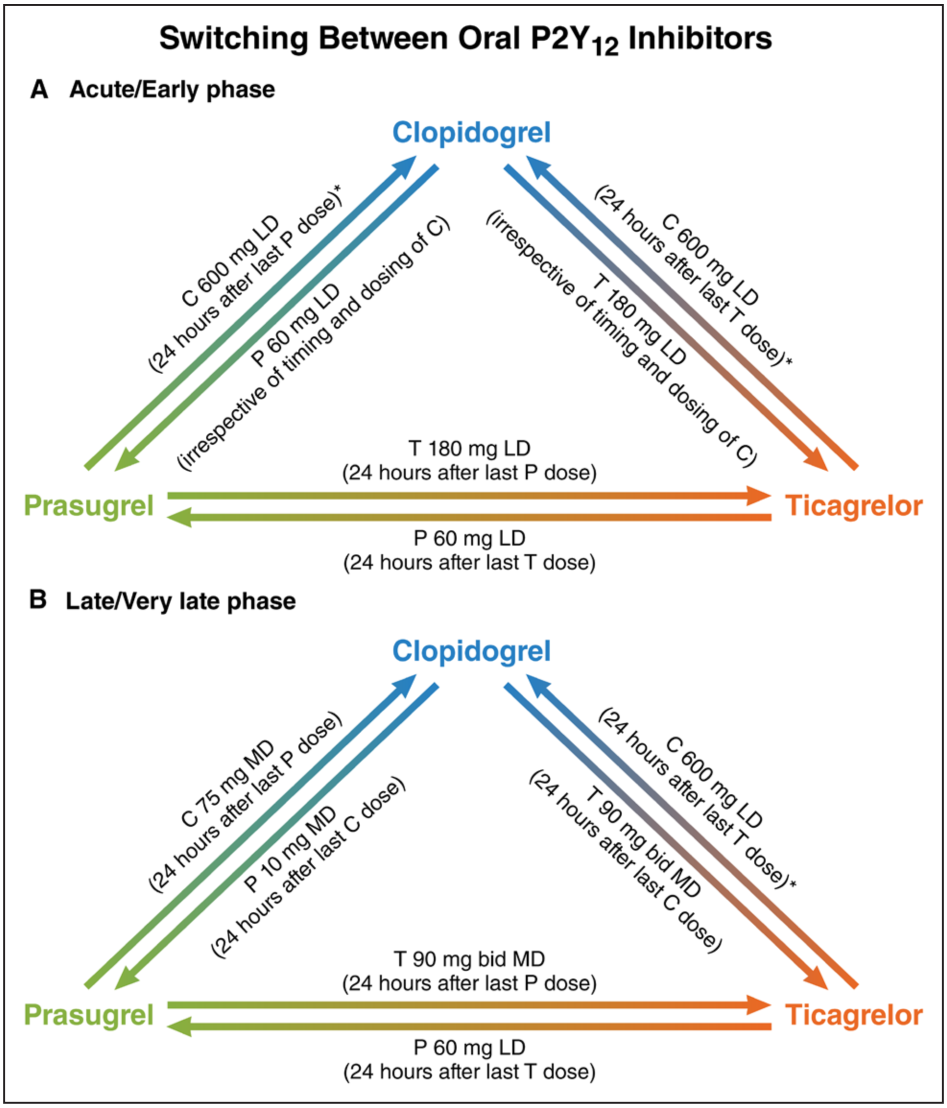


**Figure 5. Consensus recommendations on switching between oral P2Y$_{12}$ inhibitors.**
**A**, Switching between oral agents in the acute/early phase. In the acute/early phase (≤30 days from the index event), switching should occur with the administration of a loading dose (LD) in most cases, with the exception of patients who are de-escalating therapy because of bleeding or bleeding concerns, in whom a maintenance dose (MD) of clopidogrel (C) should be considered. Timing of switching should be 24 hours after the last dose of a given drug, with the exception of when escalating to prasugrel (P) or ticagrelor (T), when the LD can be given regardless of the timing and dosing of the previous clopidogrel regimen. *Consider de-escalation with clopidogrel 75-mg MD (24 hours after last prasugrel or ticagrelor dose) in patients with bleeding or bleeding concerns. **B**, Switching between oral agents in the late/very late phase. In the late/very late phase (>30 days from the index event), switching should occur with the administration of an MD 24 hours after the last dose of a given drug, with the exception of patients changing from ticagrelor to prasugrel therapy, for whom an LD should be considered. De-escalation from ticagrelor to clopidogrel should occur with administration of an LD 24 hours after the last dose of ticagrelor (but in patients in whom de-escalation occurs because of bleeding or bleeding concerns, an MD of clopidogrel should be considered). *Consider de-escalation with clopidogrel 75-mg MD (24 hours after last prasugrel or ticagrelor dose) in patients with bleeding or bleeding concerns.

longed offset of prasugrel (7–10 days) has the advantage of allowing clopidogrel to reach its full antiplatelet effects during this time even if initiated with a 75-mg MD regimen. Moreover, because of the high receptor occupancy rates induced by prasugrel, it may be argued that administration of an LD of clopidogrel would not provide further pharmacodynamic effects. These pharmacological considerations suggest that de-escalation with an MD might be appropriate. Switching from prasugrel to clopidogrel with a 75-mg MD is also a reasonable option in patients in whom switching occurs as a result of a bleeding event or concerns about bleeding. Therefore, defining the reason for de-escalation may have an impact on the strategy (LD versus MD) used.

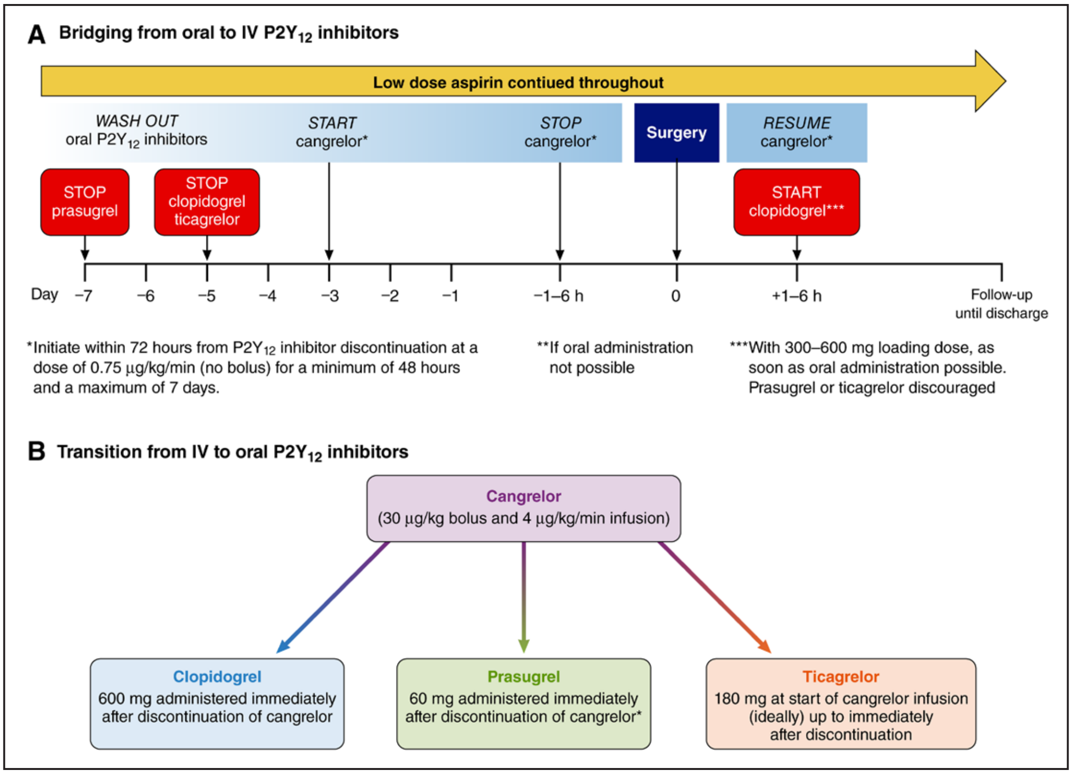


**Figure 6. Consensus recommendations on switching between oral and intravenous $P2Y_{12}$ inhibitors.**
**A**, Bridging from oral to intravenous agents. For both cardiac and noncardiac surgery, if withdrawal of $P2Y_{12}$-inhibiting therapy is needed, clopidogrel and ticagrelor should be discontinued for 5 days and prasugrel for 7 days. It is reasonable to start cangrelor bridging up to 3 to 4 days after prasugrel discontinuation and 2 to 3 days of clopidogrel and ticagrelor discontinuation. Platelet function testing may be considered to help guide timing of starting cangrelor infusion. After surgery, regardless of bridging strategy, clopidogrel should be resumed with a loading dose (LD) as soon as oral administration is possible and the risk of severe bleeding is acceptable (prasugrel and ticagrelor administration should be discouraged). If the use of oral $P2Y_{12}$-inhibiting therapy is not possible, postsurgery bridging with an intravenous agent should be considered. **B.** Transition from intravenous to oral agents. An LD should always be used when transitioning from cangrelor to an oral agent. In the case of thienopyridines (clopidogrel or prasugrel), this should be administered immediately after discontinuation of cangrelor infusion. Ticagrelor can be administered before, during, or immediately after cangrelor infusion, although earlier administration (eg, at the time of percutaneous coronary intervention) should be considered. *According to the package insert of the European Medical Agency, but not that of the US Food and Drug Administration, prasugrel may also be administered 30 minutes before infusion is stopped. Preliminary studies have shown that prasugrel given at the start of a 2-hour infusion of cangrelor results in sufficient platelet inhibition, but this strategy cannot be routinely recommended until more data are available.

However, it may also be argued that in the acute phase of treatment of patients with ACS, recovery of platelet function after discontinuation of prasugrel therapy may be shortened given their high platelet turnover rates, which may potentially not allow clopidogrel to reach its full platelet inhibitory effects before washout of prasugrel-mediated inhibition has been completed. Recovery of 37% and 63% of platelet function has been shown after 5 and 6 days, respectively, in patients with stable coronary artery disease.[14] Moreover, the onset of clopidogrel effect is variable, unpredictable, and often delayed. Therefore, in the early and, in particular, the acute phases of de-escalation, it may be also reasonable to administer a 600-mg LD of clopidogrel. This clopidogrel LD should be given at the time of the next scheduled dose of $P2Y_{12}$-inhibiting therapy (eg, ≈24 hours from last dose of prasugrel) for practical reasons and because this would allow some offset of the effects of prasugrel and allow new uninhibited platelets to be released into circulation. Beyond the early phase or in more stabilized patients, the use of a 75-mg MD of clopidogrel (without an LD) at the time of the next scheduled dose (eg, ≈24 hours from last dose of prasugrel) should be considered.

Because ticagrelor has a relatively fast offset of action, the use of a clopidogrel 600-mg LD should be considered when de-escalating from ticagrelor to avoid any significant gap in platelet inhibition, regardless of the timing of switching (ie, acute, early, or late), However, de-escalation to clopidogrel with an MD is a reasonable option, particularly in patients in whom switching occurs as a result of bleeding. Although the optimal timing of switching after the last dose of ticagrelor is unknown, waiting 24 hours after the last dose of ticagrelor should be considered because this not only exceeds the half-life of ticagrelor but also allows new platelets to be released into circulation and exposed to the active metabolite of clopidogrel, thus preventing a potential DDI. Furthermore, the level of platelet inhibition 24 hours after discontinuation of ticagrelor therapy is similar to the average level of inhibition provided by MD clopidogrel,[14] so a significant window of undertreatment is unlikely with this approach.

### *Change (Switching Between Prasugrel and Ticagrelor)*

On the basis of pharmacodynamic data suggesting a potential DDI, a 60-mg LD of prasugrel should always be used when changing from ticagrelor to prasugrel, regardless of timing (early or late), and switching with a 10-mg MD should be avoided.[20] Waiting 24 hours after the last MD of ticagrelor to administer the 60-mg LD of prasugrel should be considered because this allows more time for ticagrelor and its metabolite to be eliminated and new platelets to enter into systemic circulation. Pharmacodynamic studies do not suggest DDI when changing from prasugrel to ticagrelor therapy.[19] Therefore, this change can be performed with a standard 90-mg twice-daily MD dose regimen, without the need for an LD, which should be started at the time of the next scheduled dose (eg, ≈24 hours from last dose of prasugrel), particularly in stabilized patients. However, the use of an LD administered 24 hours after the last dose of prasugrel can be considered when the change occurs in the acute phase of patients with ACS.

## Switching Between Intravenous and Oral $P2Y_{12}$ Inhibitors

### *Bridging From Oral $P2Y_{12}$ Inhibitors to Cangrelor*

Because the effects of the oral agents persist with meaningful levels of $P2Y_{12}$ inhibition after drug discontinuation, it is reasonable to wait to start cangrelor bridging (0.75–$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion without a bolus) for up to 3 to 4 days after prasugrel discontinuation and 2 to 3 days of clopidogrel and ticagrelor discontinuation to minimize the duration of infusion. Platelet function testing might also help time the initiation of cangrelor bridging in an efficient fashion. For example, cangrelor infusion can be started once the pharmacodynamic effect is close to the threshold of HPR. This may also have cost implications linked to hospitalization and the drug and potentially may minimize the risk of bleeding complications associated with prolonged treatment with parenteral therapies.

### *Transition From Cangrelor to Oral $P2Y_{12}$ Inhibitors*

In patients undergoing PCI, cangrelor (30–μg/kg bolus and 4–$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion) should be initiated before PCI and continued for ≥2 hours or for the duration of the procedure, whichever is longer; the infusion can be continued for up to 4 hours at the discretion of the physician. Infusions up to 4 hours might be considered particularly in patients treated with opiates such as morphine (terminal half-life varies from 1.5–4.5 hours) and possibly in patients undergoing primary PCI, which are settings known to reduce the pharmacodynamic onset of oral antiplatelet agents.[88–91] These observations are likely attributed to impaired gastrointestinal motility and drug absorption, which can be accentuated in patients undergoing primary PCI.[92]

In the transition from cangrelor to a thienopyridine, the thienopyridine should be administered immediately after discontinuation of cangrelor with an LD (clopidogrel 600 mg or prasugrel 60 mg) to avoid a potential DDI.[93,94] According to the package insert of the European Medical Agency, but not that of the US Food and Drug Administration, prasugrel may also be administered 30 minutes before the infusion is stopped.[93,94] Although preliminary studies have shown that prasugrel given at the time a 2-hour infusion of cangrelor is started results in sufficient platelet inhibition,[87] this strategy cannot be routinely recommended until more data are available. Although cangrelor is approved for use in patients who have not received an oral $P2Y_{12}$ inhibitor before the PCI procedure, for those patients who have been pretreated with a thienopyridine, if the pretreatment was shortly before the initiation of cangrelor or unknown, an LD at the end of the infusion should be considered.

The US Food and Drug Administration indicates that ticagrelor can be administered before, during, or immediately after cangrelor infusion,[93,94] whereas the European Medical Agency indicates that ticagrelor should be administered immediately after discontinuation of cangrelor infusion or up to 30 minutes before the end of the infusion, Ticagrelor should be administered as a 180-mg LD. This expert consensus recommends that earlier administration of ticagrelor (eg, at the time of PCI) should be considered over administration at the end of cangrelor infusion because it would minimize the potential gap in platelet inhibition during the transition phase.

## SPECIAL CONSIDERATIONS

A number of settings represent clinical conundrums with regard to the management of antithrombotic therapy. Accordingly, there are a number of scenarios in which there may be a need to switch antiplatelet therapy but the modality to do this has not been studied. This expert consensus recognizes that there are some settings that may be unique and require specific recommendations.

- Patients undergoing cardiac and noncardiac surgery. Preoperative and postoperative management of antiplatelet therapy is described in detail


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elsewhere.[95] The decision to withdraw $P2Y_{12}$-inhibiting therapy should take into account the thrombotic and bleeding risks of the individual patient according to the specific surgery being performed and timing from PCI.[96] Similarly, the need for bridging should be individualized as described previously.[95,96] For patients with ACS requiring coronary artery bypass surgery, unless recent PCI was conducted, $P2Y_{12}$-inhibiting therapy should be withdrawn before surgery but restarted postoperatively if the bleeding risk is low. For both cardiac and noncardiac surgery, if withdrawal of $P2Y_{12}$-inhibiting therapy is warranted, clopidogrel and ticagrelor should be discontinued for 5 days and prasugrel for 7 days. If bridging with cangrelor, it is reasonable to wait up to 3 to 4 days after prasugrel discontinuation and 2 to 3 days after clopidogrel and ticagrelor discontinuation to minimize duration of cangrelor infusion. After noncardiac surgery, regardless of bridging strategy, clopidogrel should be resumed with an LD as soon as oral administration is possible and the risk of severe bleeding is acceptable. Prasugrel and ticagrelor administration should be discouraged in the early period after major noncardiac surgery when there is an ongoing risk of serious bleeding. If oral administration of clopidogrel is not possible, postsurgery bridging with an intravenous agent should be considered.

- Patients with bleeding or at high risk for bleeding complications. Management of bleeding complications in patients on dual antiplatelet therapy goes beyond the scope of this document and is described elsewhere.[97] In dual antiplatelet therapy–treated patients who develop a bleeding complication, there is commonly a desire for de-escalation therapy. This should start with an MD regimen (ie, clopidogrel 75 mg), unless there has been a gap of therapy for ≥5 days, in which case a 300-mg LD might be used. Similar approaches should be considered for patients at high risk for bleeding complications such as those who have or develop thrombocytopenia, patients who develop a cerebrovascular event, and elderly patients, among others.
- Switching after thrombolysis. Clopidogrel therapy is the standard of care in patients treated with thrombolytics who require $P2Y_{12}$ inhibitor therapy. Escalation of $P2Y_{12}$ inhibitors is discouraged within 24 hours of thrombolysis because the combination of lytics with potent platelet inhibitors (ie, glycoprotein IIb/IIIa inhibitors) increases bleeding[98]; after this duration, any escalation to a more potent regimen should occur with an LD regimen (prasugrel 60 mg or ticagrelor 180 mg).
- Patients requiring OAC. In patients requiring OAC who also undergo PCI requiring dual antiplatelet therapy, clopidogrel should be the $P2Y_{12}$ inhibitor of choice.[99,100] If patients are already on a newer-generation $P2Y_{12}$ inhibitor (eg, patients who already had PCI and develop atrial fibrillation requiring OAC), de-escalation therapy is recommended, and clopidogrel should be started with a 75-mg MD regimen. If patients are $P2Y_{12}$ inhibitor naïve, clopidogrel should be initiated with a 600-mg LD regimen (eg, patients with atrial fibrillation already on OAC who undergo PCI). Details of the management of PCI patients requiring OAC are given elsewhere.[99,100]
- Patients undergoing very late (>1 year) switch. De-escalation should occur with an MD regimen (no LD). Recently, a ticagrelor 60-mg twice-daily dosing regimen has been approved for post–myocardial infarction patients >1 year from their index event. When ticagrelor therapy is initiated for post–myocardial infarction patients >1 year from their index event, a switch should be made directly to 60-mg twice-daily MD (no LD) regardless of the prior $P2Y_{12}$ inhibitor used.[35]
- Patients on unknown therapy. It is not uncommon that patients are referred with unknown medication status. These patients should be treated as naïve, and an LD should be used.

## CONCLUSIONS

The current availability of a variety of $P2Y_{12}$ inhibitors provides clinicians with flexibility to optimize antiplatelet therapy for the individual patient. Although clinical data support the initiation and treatment of antiplatelet therapy with specific $P2Y_{12}$ inhibitors, clinical circumstances often arise that require the clinician to switch among the available therapies. Robust clinical outcomes data for specific switching strategies are lacking, but strategies can be guided by the different pharmacological profiles of these inhibitors, which may lead to DDIs that have potential implications for safety and efficacy. Therefore, this expert consensus document provides recommendations derived largely from pharmacodynamic and registry data, integrated with an understanding of the pharmacological principles of the agents involved. Ongoing dedicated studies will provide important insights into this topic.

## AUTHORS

Dominick J. Angiolillo, MD, PhD; Fabiana Rollini, MD; Robert F. Storey, MD; Deepak L. Bhatt, MD, MPH; Stefan James, MD, PhD; David J. Schneider, MD; Dirk Sibbing, MD; Derek Y.F. So, MD; Dietmar Trenk, PhD; Dimitrios Alexopoulos, MD; Paul A. Gurbel, MD; Willibald Hochholzer, MD; Leonardo De Luca, MD; Laurent Bonello, MD; Daniel Aradi, MD, PhD; Thomas Cuisset, MD, PhD; Udaya S. Tantry, PhD; Tracy Y. Wang, MD, MHS, MSc; Marco Valgimigli, MD, PhD; Ron Waksman, MD; Roxana Mehran, MD; Gilles Montalescot, MD; Francesco Franchi, MD; Matthew J. Price, MD

## DISCLOSURES

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Dr Bhatt discloses the following relationships: Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; chair: American Heart Association Quality Oversight Committee; Data Monitoring committees: Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, and Population Health Research Institute; honoraria: American College of Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org), Belvoir Publications (editor-in-chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (editor-in-chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor; associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), WebMD (CME steering committees); other: *Clinical Cardiology* (deputy editor), NCDR-ACTION Registry Steering Committee (chair), VA CART Research and Publications Committee (chair); research funding: Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, and The Medicines Company; royalties: Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); site coinvestigator: Biotronik, Boston Scientific, and St. Jude Medical (now Abbott); trustee: American College of Cardiology; and unfunded research: FlowCo, Merck, PLx Pharma, and Takeda. 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Dr Montalescot discloses the following relationships: research grants to the institution or consulting/lecture fees from Actelion, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Beth Israel Deaconess Medical, Brigham Women's Hospital, Cardiovascular Research Foundation, CCC, Celladon, CME Resources, Daiichi-Sankyo, Eli-Lilly, Europa, Elsevier, Fédération Française de Cardiologie, Gilead, ICAN, INSERM, Lead-Up, Menarini, Medtronic, MSD, Pfizer, Sanofi-Aventis, Servier, The Medicines Company, TIMI Study Group, and WebMD. Dr Price reports the following relationships: grants from Daiichi-Sankyo (to institution); consulting and speaking honoraria from AstraZeneca, Medtronic, The Medicines Company, St. Jude Medical, and Boston Scientific; and speaking honoraria from Chiesi USA and Abbott Vascular. Dr Schneider reports the following relationships: grants and honoraria from The Medicines Company, AstraZeneca, and Janssen Pharmaceuticals. Dr Sibbing reports the following relationships: speaker fees and honoraria for consulting from Eli Lilly, MSD, Pfizer, Daiichi Sankyo, Bayer Vital, AstraZeneca, and Roche Diagnostics, and research grants from Roche Diagnostics and Daiichi Sankyo. Dr So discloses the following relationships: Eli Lilly Canada, unrestricted grant support (physician-initiated grant); Astra Zeneca Canada, Advisory Board/honoraria; and Spartan Biosciences, unrestricted grant support (physician-initiated grant). Dr Storey discloses the following relationships: research grants, consultancy fees, and honoraria from AstraZeneca; research grants and consultancy fees from PlaqueTec; and consultancy fees from Actelion, Avacta, Bayer, Bristol Myers Squibb/Pfizer, Novartis, The Medicines Company, and ThermoFisher Scientific. Dr Tantry discloses the following relationships: honoraria from AstraZeneca, UptoDate, and Medicure. 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Dr Wang reports the following disclosures: research grants to the Duke Clinical Research Institute from AstraZeneca, Boston Scientific, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Gilead Sciences, Novartis, Pfizer, and Regeneron, as well as consulting or honoraria from Merck, Gilead, and Pfizer. Drs Franchi and Rollini report no conflicts.

## AFFILIATIONS

Division of Cardiology, University of Florida College of Medicine, Jacksonville (D.J.A., F.R., F.F.). Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, United Kingdom (R.F.S.). Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA (D.L.B.). Department of Medical Sciences, Cardiology and Uppsala Clinical Research Center, Uppsala University, Sweden (S.J.). Department of Medicine, Cardiology Unit, Cardiovascular Research Institute, University of Vermont, Burlington (D.J.S.). Department of Cardiology, Ludwig-Maximilians-Universität München, Germany (D.S.). DZHK (German Center for Cardiovascular Research), partner site Munich Heart Alliance, Germany (D.S.). Division of Cardiology, University of Ottawa Heart Institute, Ontario, Canada (D.Y.S.F.). Department of Cardiology & Angiology II, University Heart Center Freiburg-Bad Krozingen, Germany (D.T., W.H.). Second Department of Cardiology, National and Capodistrian University of Athens, Attikon University Hospital, Greece (D. Alexopoulos). Inova Center for Thrombosis Research and Drug Development, Inova Heart and Vascular Institute, Falls Church, VA (P.A.G., U.S.T.). Division of Cardiology, Laboratory of Interventional Cardiology, San Giovanni Evangelista Hospital, Tivoli-Rome, Italy (L.D.L.). Assistance Publique-Hôpitaux de Marseille, Department of Cardiology, Hôpital Nord, Marseille, France (L.B.). Mediterranean Academic Association for Research and Studies in Cardiology, Marseille, France (L.D.L.). Aix-Marseille University, INSERM UMRS 1076, Marseille, France (L.D.L.). Heart Center Balatonfüred and Semmelweis University Budapest, Hungary (D. Aradi). Department of Cardiology, CHU Timone, and Aix-Marseille Université, Faculté de Médecine, Marseille, France (T.C.). Duke Clinical Research Institute, Duke University Medical Center, Durham, NC (T.Y.W.). Swiss Cardiovascular Center Bern, Bern University Hospital, Switzerland (M.V.). Section of Interventional Cardiology, MedStar Washington Hospital Center, DC (R.W.). Icahn School of Medicine at Mount Sinai, New York City, NY (R.M.) Sorbonne Université Paris 6, ACTION Study Group, Hôpital Pitié-Salpêtrière, France (G.M.). Division of Cardiovascular Diseases, Scripps Clinic, La Jolla, CA (M.J.P.).

## FOOTNOTES

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