

Cardiac Diseases and Therapies ACUTE CORONARY SYNDROMES

ANTIPLATELET THERAPY SWITCHING CLINICIAN GUIDE

Data on switching antiplatelet therapies are primarily based on pharmacodynamic studies. These studies were not powered to assess the clinical impact of switching. Specifically designed studies evaluating the efficacy and safety with respect to clinical outcomes from switching are currently not available. Therefore, the following recommendations should be used as a guide only.

Risks of bleeding must be weighed against risk of coronary events within different time frames, as outlined in the table at the end. Underlying rationale for switching should also be considered.

Common reasons for switching include^{1,2}:

From clopidogrel to prasugrel/ticagrelor - high risk of coronary/stent thrombosis
- intolerance to clopidogrel

From prasugrel to clopidogrel - cost
- high bleeding risk
- requiring concurrent treatment with an oral anticoagulant
- decision for medical management

From prasugrel to ticagrelor - intolerance to prasugrel
- decision for medical management

From ticagrelor to clopidogrel - cost
- high bleeding risk
- requiring concurrent treatment with an oral anticoagulant

From ticagrelor to prasugrel - intolerance to ticagrelor (e.g. dyspnea, ventricular pauses)
- nonadherence to medications
- CYP3A4 drug interactions

General principles of switching:

Additional platelet inhibition was observed when switching from clopidogrel to prasugrel or ticagrelor.³⁻⁵ In contrast, reduction in platelet inhibition was seen when ticagrelor was switched to clopidogrel.⁵ When switching from prasugrel to ticagrelor and vice versa, ticagrelor demonstrated higher platelet inhibition.⁶ Drug interactions have been described when switching between P2Y₁₂ receptor inhibitors with different receptor-binding properties based on pharmacodynamic data (e.g. ticagrelor to prasugrel).⁷ Data from registries have not raised any major safety concerns, such as increased risk of bleeding, associated with switching between therapies; however they were not designed nor powered to assess clinical outcomes.⁷

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From	To	Recommendations ^{2,7}
Clopidogrel	Prasugrel	In the presence of high risk of coronary thrombosis, give a 60 mg loading dose of prasugrel, followed by the maintenance dose of 10 mg daily (irrespective of timing of the last dose of clopidogrel). <i>In the maintenance or low risk phase, there is generally no need to administer a loading dose of prasugrel; one can switch directly to prasugrel maintenance dose 24 hours after the last dose of clopidogrel. (Switching in the maintenance/low risk phase is not noted in the Canadian antiplatelet guidelines.)</i>
	Ticagrelor	In the presence of high risk of coronary thrombosis, give a 180 mg loading dose of ticagrelor, followed by the maintenance dose of 90 mg twice daily (irrespective of timing of the last dose of clopidogrel). <i>In the maintenance or low risk phase, there is generally no need to administer a loading dose of ticagrelor; one can switch directly to ticagrelor maintenance dose 24 hours after the last dose of clopidogrel. (Switching in the maintenance/low risk phase is not noted in the Canadian antiplatelet guidelines.)</i>
Prasugrel	Clopidogrel	There is generally NO need to administer a loading dose of clopidogrel; one can switch directly to clopidogrel maintenance dose of 75 mg daily 24 hours after the last dose of prasugrel.
	Ticagrelor	There is generally NO need to administer a loading dose of ticagrelor; one can switch directly to ticagrelor maintenance dose of 90 mg twice daily 24 hours after the last dose of prasugrel.
Ticagrelor	Clopidogrel	A loading dose of clopidogrel 300 mg is generally advisable, followed by the maintenance dose of 75 mg daily. Give the clopidogrel loading dose 12 hours after the last dose of ticagrelor. (This recommendation of clopidogrel 300 mg is different from the Canadian antiplatelet guidelines which suggest 600 mg.)
	Prasugrel	A loading dose of prasugrel 60 mg is generally advisable, followed by the maintenance dose of 10 mg daily. Give the prasugrel loading dose 12 hours after the last dose of ticagrelor.

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FROM CLOPIDOGREL to PRASUGREL

In the presence of high risk of coronary thrombosis, give a 60 mg loading dose of prasugrel, followed by the maintenance dose of 10 mg daily (irrespective of timing of the last dose of clopidogrel).

In the maintenance or low risk phase, there is generally no need to administer a loading dose of prasugrel; one can switch directly to prasugrel maintenance dose 24 hours after the last dose of clopidogrel.

For patients who are LOADED on clopidogrel during this hospital admission:

- In a prospective, observational, pharmacodynamic study of planned PCI for acute coronary syndromes (ACS) (n=80), patients received clopidogrel 300 mg loading dose (LD) and were given prasugrel LD ranging from 10 to 60 mg.⁸ The prasugrel 30 mg LD appeared to achieve a desirable level of platelet inhibition (although a 60 mg LD resulted in further platelet inhibition). No TIMI major bleeding events occurred during the study. However, this study was based on laboratory endpoints and not powered to assess clinical efficacy and safety.
- In a single-center, retrospective, cohort study of ACS patients undergoing PCI and who had received a 60 mg prasugrel LD before PCI (n=606), patients were categorized into those who had received clopidogrel preloading (300 or 600 mg) followed by prasugrel reloading (n=90) and prasugrel loading only (n=516).⁹ Prasugrel maintenance dose of 10 mg daily was administered after PCI in both groups. There was no significant difference in TIMI major bleeding, TIMI major or minor bleeding, the need for blood transfusion, and vascular complications between the clopidogrel-prasugrel LD group and prasugrel only LD group. All-cause and cardiac mortality were similar between the groups, but in-hospital major adverse cardiac events were greater in the clopidogrel-prasugrel LD group (5.6% vs 1.6%, p=0.031), mainly driven by a greater rate of urgent CABG. There were no cases of stent thrombosis. Thus, it is safe to reload prasugrel in patients at high ischemic risk who have received a loading dose with clopidogrel.
- The TRIPLET study was a multicenter, randomized, double-blind, double-dummy trial comparing the pharmacodynamic response of administering prasugrel LD added ≤ 24 hours to clopidogrel LD in ACS patients undergoing PCI (n=282).¹⁰ Patients were randomized to 3 LD strategies: placebo plus prasugrel 60 mg, clopidogrel 600 mg plus prasugrel 60 mg, or clopidogrel 600 mg plus prasugrel 30 mg. No significant differences in platelet reactivity were observed at any time point across the 3 groups. However, in the STEMI subgroup, at 2 hours after prasugrel LD, there was numerically less response to prasugrel 30 mg when added to clopidogrel 600 mg compared with prasugrel 60 mg added to either clopidogrel 600 mg or the placebo group. At 6 hours, the difference in platelet reactivity was negligible. Few bleeding events were observed regardless of treatment group. Platelet reactivity with prasugrel 60 mg LD added to clopidogrel 600 mg LD was not significantly different compared with prasugrel 60 mg LD alone, which suggests there is no additive pharmacodynamic effect of clopidogrel pretreatment.

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For patients who are ALREADY on clopidogrel prior to admission and a decision is made to switch to prasugrel:

- Based on pharmacodynamic studies, when a switch to prasugrel from maintenance clopidogrel therapy is initiated with a 60 mg LD, greater platelet inhibition is observed more quickly with a prasugrel LD than with no LD. The switch appears to be well tolerated without major safety events.
 - In patients with ACS, switching from clopidogrel to prasugrel is associated with a further reduction in maximum platelet aggregation (MPA) by 1 week using prasugrel 10 mg maintenance dose (MD) or prasugrel 60 mg LD + 10 mg MD (MPA 41.1% vs. 55.0%, $p < 0.0001$).³ However, higher platelet inhibition was achieved more quickly (within 2 hours) with the administration of a prasugrel LD. See Figure 1. Bleeding by TIMI criteria was reported in 12.5% of the clopidogrel group, 8.5% of the prasugrel MD group, and 13.6% of the prasugrel LD + MD group. All bleeding events were minimal by TIMI criteria and none needed medical or surgical intervention.
 - In healthy subjects, those administered a prasugrel 60 mg LD following the switch from clopidogrel 600 mg LD + 75 mg MD were observed to have a reduction in MPA within 30 minutes and a maximum effect at 2 hours, whereas subjects switched directly to the prasugrel 10 mg MD were observed to have a more modest reduction in MPA over the first 24 hours.⁴ See Figure 2. The incidence of bleeding events was similar regardless of whether subjects were switched to a prasugrel LD followed by MD or directly to a MD. Bleeding events were mild in severity.

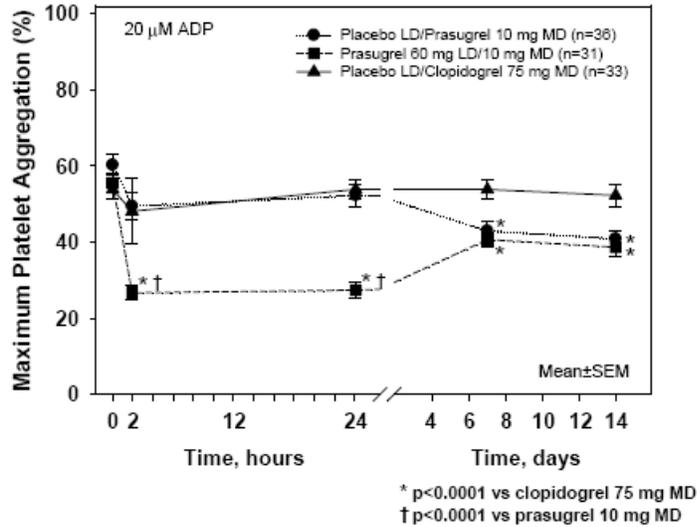
In the maintenance or low risk phase, there is generally no need to administer a loading dose of prasugrel; one can switch directly to prasugrel maintenance dose 24 hours after the last dose of clopidogrel.

- When switching from clopidogrel, a prasugrel LD achieves greater platelet inhibition compared to clopidogrel and more rapidly than with no LD. However, similar levels of platelet inhibition appear to be achieved at steady state regardless of whether a prasugrel LD was administered following the switch from clopidogrel. There appears to be no period in time that demonstrates a decrease in antiplatelet activity once a clopidogrel MD is stopped and switched directly to a prasugrel MD.^{3,4}
 - In patients with ACS, switching from clopidogrel to prasugrel is associated with a further reduction in MPA by 1 week using prasugrel 10 mg MD or prasugrel 60 mg LD + 10 mg MD (MPA 41.1% vs. 55.0%, $p < 0.0001$).³ See Figure 1.
 - In healthy subjects, MPA within 4 to 5 days of the switch was ~24% regardless of whether a subject received a prasugrel LD and was lower than that achieved with clopidogrel 75 mg MD.⁴ See Figure 2.
- Since there appears to be no loss of efficacy when clopidogrel MD is switched directly to prasugrel MD, and no clinical studies are available evaluating efficacy and safety, the risks of bleeding may outweigh the potential benefits of a prasugrel LD.

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Figure 1. MPA in Response to 20 μ M ADP Following a Switch from Clopidogrel to Prasugrel (With and Without a Prasugrel LD) in Patients with Recent ACS³



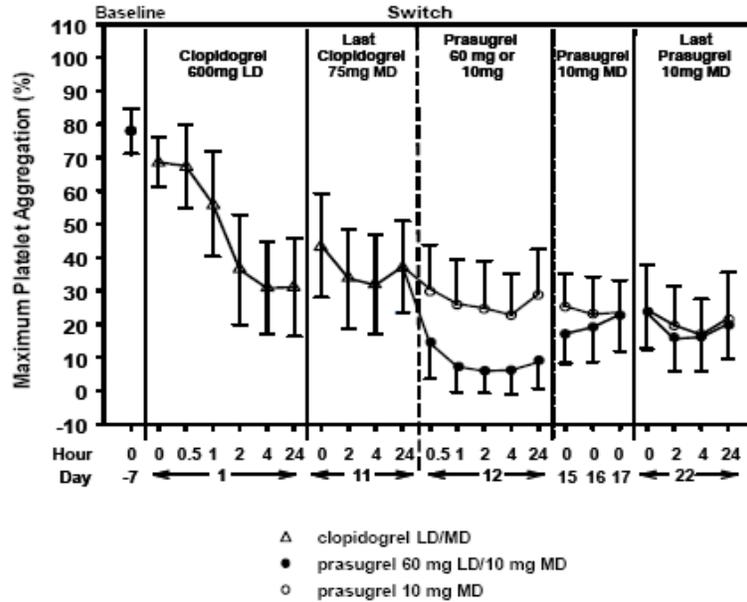
Note: Lower MPA value reflects greater inhibition of platelet aggregation.

Abbreviations: MPA = maximum platelet aggregation; μ M = micromolar; ADP = adenosine diphosphate; LD = loading dose; ACS = acute coronary syndrome; MD = maintenance dose; SEM = standard error of the mean

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Figure 2. MPA in Response to 20 μ M ADP Following a Switch from Clopidogrel to Prasugrel in Healthy Subjects⁴



Note: Lower MPA value reflects greater inhibition of platelet aggregation.

Abbreviations: MPA = maximum platelet aggregation; μ M = micromolar; ADP = adenosine diphosphate; LD = loading dose; MD = maintenance dose

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FROM CLOPIDOGREL to TICAGRELOR

In the presence of high risk of coronary thrombosis, give a 180 mg loading dose of ticagrelor, followed by the maintenance dose of 90 mg twice daily (irrespective of timing of the last dose of clopidogrel).

In the maintenance or low risk phase, there is generally no need to administer a loading dose of ticagrelor; one can switch directly to ticagrelor 90 mg twice daily maintenance dose 24 hours after the last dose of clopidogrel.

- The PLATO study design allowed for open-label clopidogrel to be administered before randomization and 46% of the ticagrelor group received clopidogrel in this way.¹¹ In the ticagrelor group, 20.6% of patients received clopidogrel 300 to 375 mg LD within 24 hours before or after randomization and 13.7% received 600 to 675 mg LD. The efficacy and safety of ticagrelor were consistent irrespective of prior clopidogrel exposure. Although the overall rates of major bleeding or fatal/life-threatening bleeding in this study were no different between the two groups (ticagrelor and clopidogrel), non-CABG-related major bleeding appeared to be higher in the ticagrelor group and there were also more cases of intracranial bleeding with ticagrelor.
- In a 2-way crossover study of stable coronary artery disease patients (n=98), switching from clopidogrel to ticagrelor in clopidogrel nonresponders resulted in a decrease in platelet aggregation from 59±9% to 35±11% (p<0.0001).⁵ These patients were treated with clopidogrel 600 mg LD + 14 days of 75 mg MD and then received ticagrelor 180 mg LD + 90 mg twice daily MD when they were switched over. One major and 3 minor bleeding events occurred during ticagrelor treatment (unclear whether these occurred after the switch from clopidogrel or during initial treatment with ticagrelor).
- The SHIFT-OVER study is a randomized, single-blinded, single-center trial of 50 ACS patients receiving aspirin and clopidogrel, who were randomly assigned to ticagrelor 90 mg twice daily MD (no LD) or 180 mg LD plus 90 mg twice daily MD.¹² Residual platelet aggregation was significantly reduced in both arms 2 hours after the first administration of ticagrelor (P<0.001). No difference in platelet aggregation was observed between groups. No major bleeding was observed in either group. Few minor bleeding events were reported within 30 days (n=9), but there was no statistically significant difference between the groups (p=0.064). Clopidogrel-resistant patients were excluded in the study. This study suggests that switching from clopidogrel to ticagrelor without a LD is feasible and the results may be of interest for the management of patients with high risk of bleeding.
- The product monograph for ticagrelor suggests that no ticagrelor LD needs to be given if switching from clopidogrel.¹³

FROM PRASUGREL to CLOPIDOGREL

There is generally NO need to administer a loading dose of clopidogrel; one can switch directly to clopidogrel maintenance dose of 75 mg daily 24 hours after the last dose of prasugrel.

- ACS patients on prasugrel 10 mg MD for 15 days and who display low on-treatment platelet reactivity and/or at high risk of bleeding were switched to clopidogrel 75 mg MD without LD (n=31).¹⁴ On-treatment platelet reactivity increased 10-fold with the switch from prasugrel to clopidogrel (p=0.0001) after 15 days, resulting in a much lower rate of patients with low on-treatment platelet reactivity (9.7% compared to 93.5% on prasugrel). The rate of patients with high on-treatment platelet reactivity increased from 0% with prasugrel to 29% (n=9)

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with clopidogrel. The rate of minor bleeding decreased after the switch from 32.2% to 9.7%; $p=0.03$.

- In the TOPIC study, 646 patients admitted with ACS requiring coronary intervention, on aspirin and ticagrelor/prasugrel and without adverse event at 1 month, were assigned to switch directly to aspirin and clopidogrel 75 mg daily with no LD or continuation of their dual antiplatelet regimen.¹⁵ 57% patients were on prasugrel at baseline. No significant difference was reported in ischemic endpoints, but there was less bleeding in the aspirin and clopidogrel group (4.0% vs 14.9%, $p<0.01$). However, the study was not powered for ischemic endpoints.
- In the TROPICAL-ACS trial of ACS patients with PCI ($n=2610$), patients were randomized to prasugrel for 12 months or a step-down regimen of 1 week prasugrel followed by 1 week clopidogrel 75 mg daily with no LD and platelet function testing-guided maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge.¹⁶ There was no increase in ischemic outcomes and no statistically significant difference in bleeding outcomes. This trial was also underpowered to assess ischemic outcomes.
- With prasugrel, platelet aggregation gradually returns to baseline values over 5-9 days after discontinuation.¹⁷ This time frame enables clopidogrel to achieve its full antiplatelet effects even if administered at a 75 mg daily MD regimen. After repeated doses of clopidogrel 75 mg per day, inhibition of platelet aggregation reaches steady state between days 3 to 7 of therapy.¹⁸ Waiting 24 h after the last MD of prasugrel is given to patients before administering clopidogrel should be considered, as this approach would allow enough time for new platelets to be released into the circulation and be exposed to the active metabolite of clopidogrel.¹⁹

FROM PRASUGREL to TICAGRELOR

There is generally NO need to administer a loading dose of ticagrelor; one can switch directly to ticagrelor maintenance dose of 90 mg twice daily 24 hours after the last dose of prasugrel.

- With prasugrel, platelet aggregation gradually returns to baseline values over 5-9 days after discontinuation.¹⁷ Platelet inhibition with ticagrelor reaches steady state after 2 to 3 days.²⁰
- In a prospective study, ACS patients ($n=44$) with high on-treatment platelet reactivity while on clopidogrel post-PCI were randomized to prasugrel 10 mg MD or ticagrelor 90 mg twice daily MD for 15 days and then switched over to the alternative treatment without loading for another 15 days.⁶ Platelet reactivity was lower with ticagrelor than prasugrel (32.9 vs. 101.3 platelet reactivity units, $p<0.001$). No major bleeding occurred; however, a total of 4 patients reported minimal bleeding events. Data for the pre-crossover and post-crossover periods are shown in Figure 3.
- In a prospective, randomized, open-label study of ACS patients who underwent PCI on maintenance dual antiplatelet therapy with aspirin and prasugrel (10 mg daily) for at least 14 days ($n=82$), patients were randomized to continue prasugrel 10 mg daily or switch to ticagrelor 90 mg twice daily, with or without a 180 mg LD for 1 week.²¹ After switching to ticagrelor, platelet reactivity decreased as early as 2 h after drug administration which persisted up to 48 h, and then there was an increase in platelet reactivity from 48 h to 1 week. The primary endpoint of noninferiority with respect to platelet reactivity of combined ticagrelor groups versus prasugrel at 1 week was met. Similar levels of platelet reactivity were seen irrespective of the use of a ticagrelor LD at any time point. See Figure 4. No bleeding complications were observed.

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Figure 3. Platelet Reactivity by Treatment Sequence of Prasugrel and Ticagrelor in ACS patients⁶

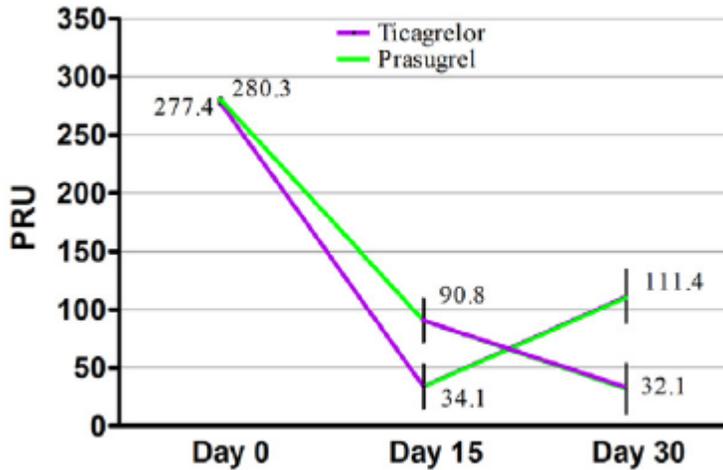
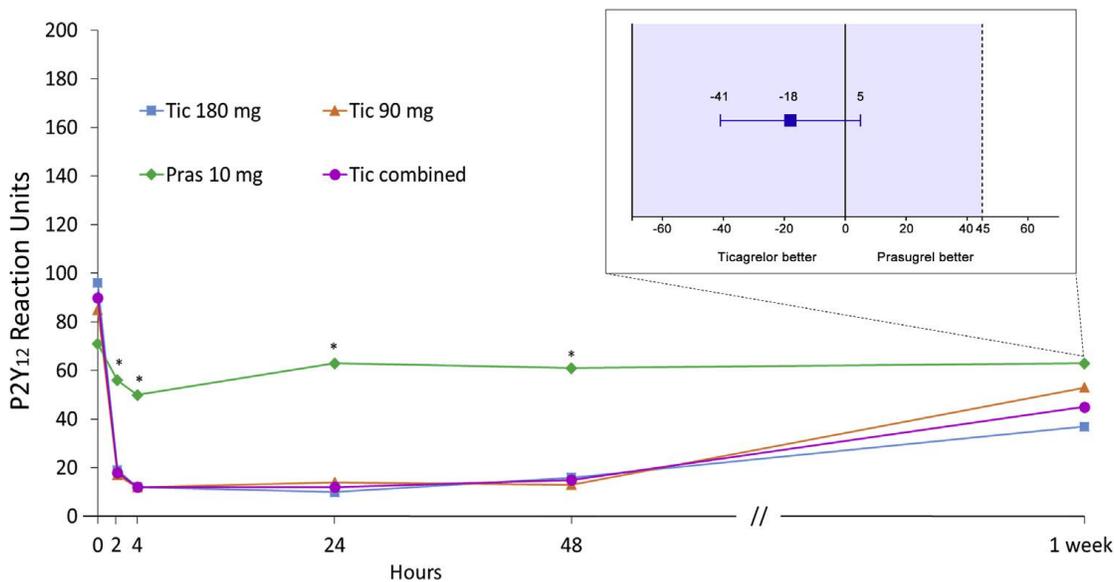


Figure 4. Platelet Reactivity Following a Switch from Prasugrel to Ticagrelor (With and Without a Ticagrelor LD) in Patients with ACS who Underwent PCI²¹



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FROM TICAGRELOR *to* CLOPIDOGREL

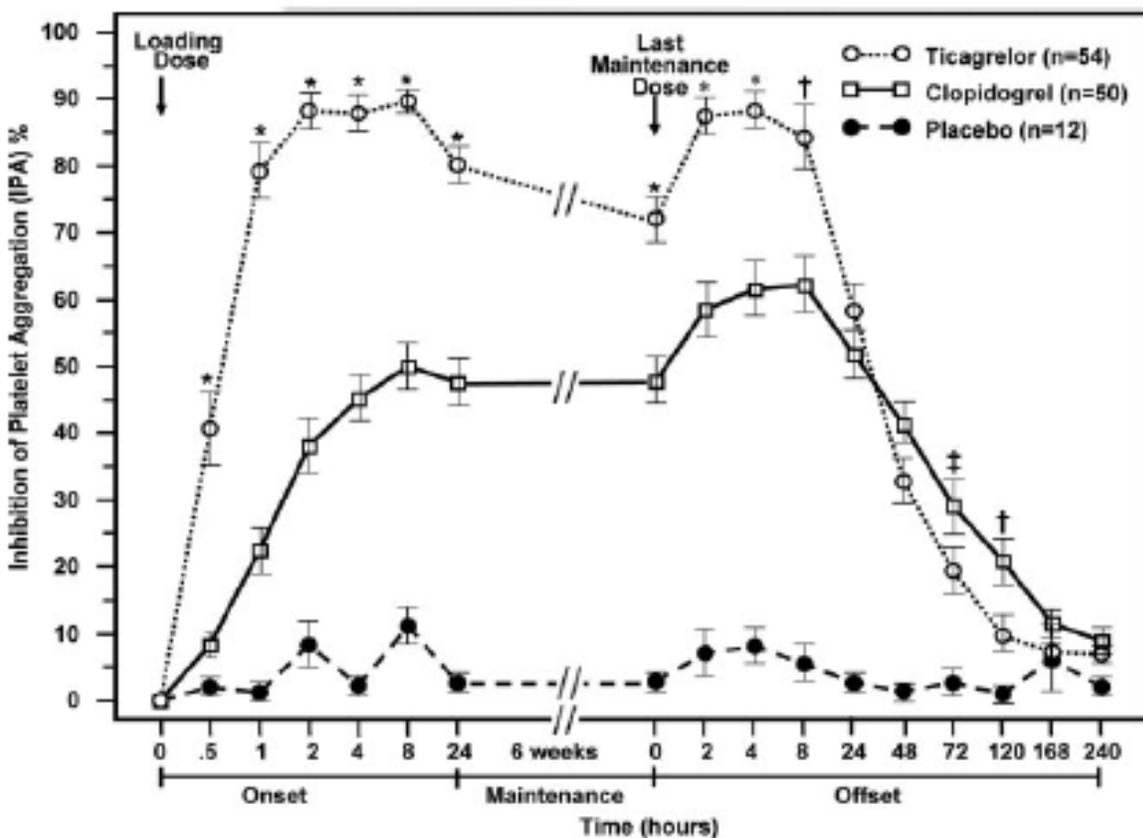
A loading dose of clopidogrel 300 mg is generally advisable, followed by the maintenance dose of 75 mg daily. Give the clopidogrel loading dose 12 hours after the last dose of ticagrelor.

- Based on pharmacokinetics, ticagrelor has a quick offset. It has been demonstrated in the ONSET/OFFSET study that by 3 days, platelet inhibition of ticagrelor was comparable to that of clopidogrel at day 5 after discontinuation.²² Platelet inhibition on day 5 for ticagrelor was similar to clopidogrel on day 7 and did not differ from placebo ($p=NS$). See Figure 5. After repeated clopidogrel doses of 75 mg per day, inhibition of platelet aggregation with clopidogrel reaches steady state between days 3 to 7 of therapy.¹⁸
- In a 2-way crossover study of stable coronary artery disease patients ($n=98$), switching from ticagrelor to clopidogrel in clopidogrel nonresponders resulted in an increase in platelet aggregation from $36\pm 14\%$ to $56\pm 9\%$ ($p<0.0001$).⁵ These patients were treated with ticagrelor 180 mg LD + 14 days of 90 mg twice daily MD and then received clopidogrel 600 mg LD + 75 mg MD when they were switched over. No bleeding events occurred during clopidogrel treatment.
- In a study of ACS patients on ticagrelor who had an indication to switch to clopidogrel, patients were randomized to either clopidogrel 600 mg LD (administered 12 hours after the last ticagrelor dose) followed by 75 mg daily ($n=30$) or clopidogrel 75 mg daily (administered 12 hours after the last ticagrelor dose) with no LD ($n=30$).²³ All study patients had to receive a ticagrelor LD (180 mg) on admission followed by at least one day of maintenance therapy prior to being randomized. Platelet reactivity increased after transition to clopidogrel in both groups and at 72 hours there was no difference between the LD and no LD regimens. However, platelet reactivity at 48 hours was lower in the LD group. There was also a significant reduction in the incidence of high on-treatment platelet reactivity in the LD group compared to the no LD group (26.7% vs 56.7%, $p=0.02$). No differences in major adverse cardiac events or TIMI major bleeding were observed between the treatment strategies.

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Figure 5. Platelet Inhibition in Response to 20 μ M ADP by Protocol Time and Treatment for Ticagrelor and Clopidogrel²²



FROM TICAGRELOR to PRASUGREL

A loading dose of prasugrel 60 mg is generally advisable, followed by the maintenance dose of 10 mg daily. Give the prasugrel loading dose 12 hours after the last dose of ticagrelor.

- Based on pharmacokinetics, ticagrelor has a quick offset. It has been demonstrated in the ONSET/OFFSET study that by 3 days, platelet inhibition of ticagrelor was comparable to that of clopidogrel at day 5 after discontinuation.²² Platelet inhibition on day 5 for ticagrelor was similar to clopidogrel on day 7 and did not differ from placebo ($p=NS$). See Figure 5. Platelet inhibition with prasugrel reaches steady state between days 3 to 5 of therapy.^{24,25}
- In a prospective study, ACS patients ($n=44$) with high on-treatment platelet reactivity while on clopidogrel post-PCI were randomized to ticagrelor 90 mg twice daily MD or prasugrel 10 mg MD for 15 days and then switched over to the alternative treatment without loading for another 15 days.⁶ Platelet reactivity was lower with ticagrelor than prasugrel (32.9 vs. 101.3 platelet reactivity units, $p<0.001$). No major bleeding occurred; however, 4 patients in total reported minimal bleeding events. Data for the pre-crossover and post-crossover periods are shown in Figure 3.

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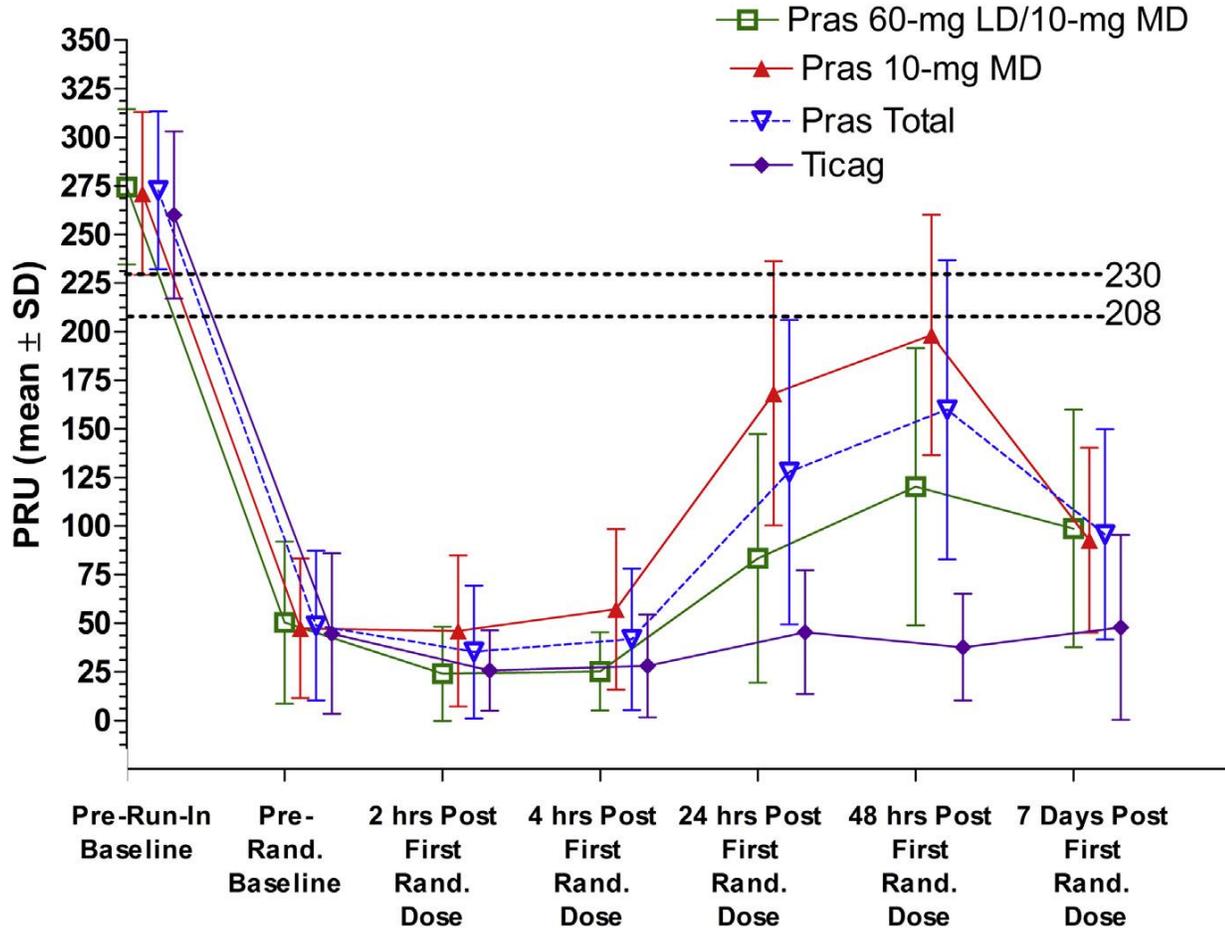
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- In a randomized, multicenter, open-label study, aspirin-treated patients with stable coronary disease (n=110) were randomized to continue ticagrelor or switch to prasugrel 10 mg once daily MD (with or without a 60 mg LD) after a 3- to 5-day run-in phase with ticagrelor 180 mg LD followed by a ticagrelor MD.²⁶ Platelet reactivity was significantly higher at 24 and 48 hours after switching to prasugrel versus continued therapy with ticagrelor, although to a lesser extent in those receiving a LD. At 7 days after randomization, platelet reactivity remained significantly greater in the combined prasugrel groups versus the ticagrelor group (mean \pm SD values of 95.6 ± 54.12 and 47.9 ± 47.59 , respectively), although it was lower at 7 days than at 24 or 48 hours. See Figure 6. More bleeding (primarily mild ecchymosis) tended to be observed in the ticagrelor group compared with the combined prasugrel groups (20% vs 11%).
- There may be a pharmacodynamic drug interaction between ticagrelor and prasugrel, as seen by the initial increase in platelet reactivity followed by a decrease at 7 days. This suggests that there may be a residual effect of ticagrelor (or its metabolite) on the P2Y₁₂ receptor. It is possible that a greater number of P2Y₁₂ receptors are occupied with ticagrelor than with clopidogrel, thereby preventing the active metabolite of prasugrel from binding to the receptor during the immediate switching phase. The prasugrel-active metabolite may not be able to bind to the receptor until ticagrelor dissociates. Also, ticagrelor may cause a change in receptor conformation that prevents prasugrel-active metabolite binding. This could explain the delay in platelet inhibition in the prasugrel groups in the study. The potential for a prolonged receptor interaction is consistent with the observation of a persistent (at least 72 hours) antiplatelet effect with ticagrelor during the offset phase, although some data suggest that ticagrelor binds to a receptor site different from (and noncompetitive with) the thienopyridines.²⁶

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Figure 6. Platelet Reactivity Following a Switch from Ticagrelor to Prasugrel (With and Without a Prasugrel LD) in Patients with Stable Coronary Disease²⁶



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PREFERRED ANTIPLATELET BASED ON RISK/BENEFIT AND TIMELINE POST-ACS

		0 - 5 Days	5 - 30 Days	30 - 180 Days	180 - 360 Days	> 360 days
Acute Coronary Occlusion (STEMI)		prasugrel	prasugrel	prasugrel	prasugrel/clopidogrel / none	none
	High Bleeding Risk ^a	clopidogrel	clopidogrel	clopidogrel	none	none
Acute Coronary Syndromes (ACS) (NSTEMI)		prasugrel/ticagrelor	prasugrel/ticagrelor	prasugrel/ticagrelor	prasugrel/ticagrelor/clopidogrel/none	none
	High Bleeding Risk ^a	clopidogrel	clopidogrel	clopidogrel	none	none
Post-PCI	High Risk of Stent Thrombosis	prasugrel/ticagrelor	prasugrel/ticagrelor	prasugrel/ticagrelor	prasugrel/ticagrelor/clopidogrel/none	none
	High Bleeding Risk ^a ; Compliance	clopidogrel	clopidogrel	clopidogrel	none	none
2° Prevention	Greater than 360 days post ACS	none	none	none	none	none
1° Prevention	No ACS, no PCI	none	none	none	none	none

a - High bleeding risk is defined as:

- History of stroke or TIA
- Age ≥ 75 years old
- Weight < 60 kg
- Other risk factors, such as recent trauma and previous bleed

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Notice to Healthcare Providers:

The Pharmacotherapy Handbook is intended to be used as a tool to aid in the appropriate prescribing and administration of cardiovascular formulary agents.

This information in this Handbook is intended for use by and with experienced physicians and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about Cardiovascular illness and the treatments in question.

Due to the rapidly changing nature of cardiovascular treatments and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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