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.\(^1\) 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:**

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

From prasugrel to clopidogrel – cost
- high bleeding risk
- decision for medical management

From ticagrelor to clopidogrel – high bleeding risk
- cost

**General pharmacodynamic principles of switching:**

Based on several pharmacodynamic studies, when switching from one antiplatelet to another, platelet inhibition at the new steady state is independent from the effects of the previous antiplatelet (i.e. no carryover, additive, or synergistic effect is noted at steady state). Additional platelet inhibition was observed when switching from clopidogrel to prasugrel or ticagrelor.\(^2\)-\(^4\) In contrast, reduction in platelet inhibition was seen when ticagrelor was switched to clopidogrel.\(^4\) When switching from prasugrel to ticagrelor and vice versa, ticagrelor demonstrated higher platelet inhibition.\(^5\)

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>Prasugrel</td>
<td><strong>For patients who are LOADED on clopidogrel during this hospital admission:</strong> A loading dose of prasugrel 60 mg is generally advisable in the presence of high risk of stent thrombosis. <strong>For patients who are ALREADY on clopidogrel prior to admission and a decision is made to switch to prasugrel:</strong> In the presence of high risk of stent thrombosis, give a 60 mg loading dose of prasugrel, followed by the maintenance dose of 10 mg daily. If the early increased effect is not required (i.e. switching due to intolerance to clopidogrel), there is generally no need to administer a loading dose of prasugrel; one can switch directly to the maintenance dose of prasugrel at the next scheduled clopidogrel</td>
</tr>
</tbody>
</table>
Cardiac Diseases and Therapies
ACUTE CORONARY SYNDROMES

ANTIPLATELET THERAPY SWITCHING CLINICIAN GUIDE

dose.

**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.

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 following the last dose of clopidogrel.

**Prasugrel**
There is generally NO need to administer a loading dose of clopidogrel; one can switch directly to the maintenance dose of clopidogrel at the next scheduled prasugrel dose.

**Ticagrelor**
There is generally NO need to administer a loading dose of ticagrelor; ticagrelor can be switched directly to the maintenance dose at the next scheduled prasugrel dose.

In the acute phase where there’s a high risk of coronary thrombosis, give a 180 mg loading dose of ticagrelor, followed by the maintenance dose of 90 mg twice daily.

**Clopidogrel**
A loading dose of clopidogrel 300 mg is generally advisable in the presence of high risk of coronary thrombosis due to the quick offset of ticagrelor.

**Prasugrel**
A loading dose of prasugrel 60 mg is generally advisable in the presence of high risk of stent thrombosis due to the quick offset of ticagrelor.
FROM CLOPIDOGREL to PRASUGREL

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

A loading dose of prasugrel 60 mg is generally advisable in the presence of high risk of stent thrombosis.

- 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. 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). 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.

- More information will be available with the publication of the TRIPLET study.

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

In the presence of high risk of stent thrombosis, give a 60 mg loading dose of prasugrel, followed by the maintenance dose of 10 mg daily.

- 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). 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. 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.\(^3\)

**If the early increased effect is not required (i.e. switching due to intolerance to clopidogrel), there is generally no need to administer a loading dose of prasugrel; one can switch directly to the maintenance dose of prasugrel at the next scheduled clopidogrel dose.**

- 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.\(^2,3\)
  - 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%, \(p<0.0001\)).\(^2\) 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.\(^3\) 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.

**Figure 1. MPA in Response to 20 \(\mu\)M ADP Following a Switch from Clopidogrel to Prasugrel (With and Without a Prasugrel LD) in Patients with Recent ACS\(^2\)**

![Graph showing MPA in response to ADP](image)

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

**Abbreviations:** MPA = maximum platelet aggregation; \(\mu\)M = micromolar; ADP = adenosine diphosphate; LD = loading dose; ACS = acute coronary syndrome; MD = maintenance dose; SEM = standard error of the mean.
Figure 2. MPA in Response to 20 μM ADP Following a Switch from Clopidogrel to Prasugrel in Healthy Subjects

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

Abbreviations: MPA = maximum platelet aggregation; μM = micromolar; ADP = adenosine diphosphate; LD = loading dose; MD = maintenance dose
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.9

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 following the last dose of clopidogrel.9

- 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.10 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. 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).4 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 product monograph for ticagrelor suggests that no ticagrelor LD needs to be given if switching from clopidogrel.11

FROM PRASUGREL to CLOPIDOGREL

There is generally NO need to administer a loading dose of clopidogrel; one can switch directly to the maintenance dose of clopidogrel at the next scheduled prasugrel dose.

- There are no data on switching from prasugrel to clopidogrel.

- With prasugrel, platelet aggregation gradually returns to baseline values over 5-9 days after discontinuation.12 After repeated doses of clopidogrel 75 mg per day, inhibition of platelet aggregation reaches steady state between days 3 to 7 of therapy.13

- Due to the long duration of antiplatelet effect with prasugrel, based on its irreversibility, it may not be necessary to load patients with clopidogrel when switching.

FROM PRASUGREL to TICAGRELOR

There is generally NO need to administer a loading dose of ticagrelor; ticagrelor can be switched directly to the maintenance dose at the next scheduled prasugrel dose.

In the acute phase where there’s a high risk of coronary thrombosis, give a 180 mg loading dose of ticagrelor, followed by the maintenance dose of 90 mg twice daily.

- With prasugrel, platelet aggregation gradually returns to baseline values over 5-9 days after discontinuation.12 Platelet inhibition with ticagrelor reaches steady state after 2 to 3 days.14

- 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.5 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.

- Due to the long duration of antiplatelet effect with prasugrel, based on its irreversibility, it may not be necessary to load patients with ticagrelor when switching. However, in the acute phase where there’s a high risk of coronary thrombosis, consider giving a 180 mg loading dose of ticagrelor, followed by the maintenance dose of 90 mg twice daily.

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

FROM TICAGRELOR to CLOPIDOGREL
A loading dose of clopidogrel 300 mg is generally advisable in the presence of high risk of coronary thrombosis due to the quick offset 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.\textsuperscript{15} Platelet inhibition on day 5 for ticagrelor was similar to clopidogrel on day 7 and did not differ from placebo (p=NS). See Figure 4. After repeated clopidogrel doses of 75 mg per day, inhibition of platelet aggregation with clopidogrel only reaches steady state between days 3 to 7 of therapy.\textsuperscript{13}

- 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±14% to 56±9% (p<0.0001).\textsuperscript{4} 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.
FROM TICAGRELOR to PRASUGREL

A loading dose of prasugrel 60 mg is generally advisable in the presence of high risk of stent thrombosis due to the quick offset 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.\(^ {15} \) Platelet inhibition on day 5 for ticagrelor was similar to clopidogrel on day 7 and did not differ from placebo (\( p=NS \)). See Figure 4. Platelet inhibition with prasugrel reaches steady state between days 3 to 5 of therapy.\(^ {16,17} \)

- 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.\(^5 \) 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.
REFERENCES


## ACUTE CORONARY SYNDROMES

### ANTIPLATELET THERAPY SWITCHING CLINICIAN GUIDE

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

<table>
<thead>
<tr>
<th></th>
<th>0 - 5 Days</th>
<th>5 - 30 Days</th>
<th>30 - 180 Days</th>
<th>180 - 360 Days</th>
<th>&gt; 360 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Coronary Occlusion (STEMI)</strong></td>
<td>prasugrel</td>
<td>prasugrel</td>
<td>prasugrel</td>
<td>prasugrel/clopidogrel/none</td>
<td>none</td>
</tr>
<tr>
<td>High Bleeding Risk&lt;sup&gt;a&lt;/sup&gt;</td>
<td>clopidogrel</td>
<td>clopidogrel</td>
<td>clopidogrel</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td><strong>Acute Coronary Syndromes (ACS) (NSTEMI)</strong></td>
<td>prasugrel/ticagrelor</td>
<td>prasugrel/ticagrelor</td>
<td>prasugrel/ticagrelor</td>
<td>prasugrel/ticagrelor/clopidogrel/none</td>
<td>none</td>
</tr>
<tr>
<td>High Bleeding Risk&lt;sup&gt;a&lt;/sup&gt;</td>
<td>clopidogrel</td>
<td>clopidogrel</td>
<td>clopidogrel</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td><strong>Post-PCI</strong></td>
<td>prasugrel/ticagrelor</td>
<td>prasugrel/ticagrelor</td>
<td>prasugrel/ticagrelor</td>
<td>prasugrel/ticagrelor/clopidogrel/none</td>
<td>none</td>
</tr>
<tr>
<td>High Bleeding Risk&lt;sup&gt;a&lt;/sup&gt;; Compliance</td>
<td>clopidogrel</td>
<td>clopidogrel</td>
<td>clopidogrel</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td><strong>2° Prevention</strong></td>
<td>Greater than 360 days post ACS</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td><strong>1° Prevention</strong></td>
<td>No ACS, no PCI</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> 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

**Prepared by:** Dr Paul Daly

**Approved by:** The Cardiovascular Subcommittee – October 2012; The Pharmacy & Therapeutics Committee – December 2012

CARDIOVASCULAR PHARMACOTHERAPY HANDBOOK
All contents copyright © University Health Network. All rights reserved
Terms and Conditions

Copyright © University Health Network, 2014. All rights reserved.
The contents of this Handbook are approved and endorsed by the UHN Cardiovascular Subcommittee of the Pharmacy and Therapeutics Committee.

1. Purpose of the Pharmacotherapy Handbook.

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.

Notice to non-Healthcare Providers:

Not Medical Advice. The information contained in the Handbook is not a substitute for professional medical advice, diagnosis or treatment. Never make changes to your medication, nor adjust your dose, without first consulting your health care provider. Always seek the advice of a physician or other qualified healthcare provider concerning questions you have regarding a medical condition, and before starting, stopping or modifying any treatment or medication. Never delay obtaining medical advice or disregard medical advice because of something you have or have not read in the Handbook. If you have, or suspect you have, a health problem, or if you experience an adverse side effect, please consult your doctor. If you have, or suspect you are experiencing a health emergency, please call 911 and/or promptly visit a Hospital Emergency Department in your area.

2. DISCLAIMER: UNIVERSITY HEALTH NETWORK MAKES NO WARRANTIES OR REPRESENTATIONS AS TO THE ACCURACY OF THE INFORMATION PROVIDED. THE INFORMATION CONTAINED IN OR PRESENTED IN THIS HANDBOOK COMES WITHOUT ANY REPRESENTATION OR WARRANTY OF ANY KIND, EXPRESSED OR IMPLIED. ANY IMPLIED WARRANTY OR CONDITION OF FITNESS FOR A PARTICULAR PURPOSE, MERCHANTABILITY OR OTHERWISE, INCLUDING BUT NOT LIMITED TO WARRANTIES OF NONINFRINGEMENT OF THIRD PARTY RIGHTS, AND FREEDOM FROM COMPUTER VIRUSES, IN RESPECT OF THE HANDBOOK IS EXPRESSLY DISCLAIMED.

3. Disclaimer. Neither UHN, as an entity, nor any of its staff or contractors cannot under any circumstance be held liable for consequences caused by or deriving from the use of the Handbook or any information contained in the Handbook. UHN is not liable for damages arising from use of the Handbook, or from third party websites (via hyperlinks) to which references are made in the Handbook. In no event shall UHN be liable for direct, indirect, consequential, special, exemplary, or other damages related to your use of the Handbook, regardless of how arising or the theory of liability whether arising in contract, tort, negligence or otherwise.

Your use of third-party websites is at your own risk and subject to the terms and conditions of use for such sites, including but not limited to the terms and conditions of http://pie.med.utoronto.ca/ on which this Handbook is housed.

4. Governing Law and Jurisdiction. Any action or claim arising from or related to your use of the Handbook shall be brought in the courts of, and governed exclusively by, the laws of Ontario, Canada and the applicable laws of Canada applicable therein, without regard to its conflicts of laws principles. Unless prohibited by applicable law, you expressly waive the right to participate in a class action proceeding.

Your comments on the usefulness of the resources contained in the Handbook are welcomed and may be forwarded to Amita Woods, Department of Pharmacy Services (amita.woods@uhn.ca).