One Year Outcome of Patients with Acute MI treated with primary angioplasty and randomized to Prasugrel vs. Ticagrelor: THE PRAGUE-18 Trial

Discussant

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Timeline of antiplatelet therapy after percutaneous coronary intervention

# Pharmacological Properties of P2Y12 Receptor Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
<th>Cangrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptor blockade</strong></td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</td>
<td>Reversible</td>
</tr>
<tr>
<td><strong>Pro-drug</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Half-life of parent drug</strong></td>
<td>~6 hours</td>
<td>&lt;5 min</td>
<td>6-12 hours</td>
<td>3-6 min</td>
</tr>
<tr>
<td><strong>Half-life of active metabolite</strong></td>
<td>30 mins</td>
<td>Distribution half-life: 30-60 mins Elimination half-life: 2-15 hours</td>
<td>8-12 hours</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Binding site</strong></td>
<td>ADP binding site</td>
<td>ADP binding site</td>
<td>Allosteric binding site</td>
<td>Undetermined*</td>
</tr>
<tr>
<td><strong>Administration route</strong></td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Once daily</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Bolus plus infusion</td>
</tr>
<tr>
<td><strong>Onset of action^</strong></td>
<td>2-8 hours</td>
<td>30 min-4 hours</td>
<td>30 min-4 hours</td>
<td>~2 min</td>
</tr>
<tr>
<td><strong>Offset of action</strong></td>
<td>5-10 days</td>
<td>7-10 days</td>
<td>3-5 days</td>
<td>60 min</td>
</tr>
<tr>
<td><strong>CYP drug interaction#</strong></td>
<td>CYP2C19</td>
<td>No</td>
<td>CYP3A</td>
<td>No</td>
</tr>
<tr>
<td><strong>Approved settings</strong></td>
<td>ACS (invasive and non-invasively managed), stable CAD PCI, PAD, and ischemic stroke</td>
<td>ACS undergoing PCI</td>
<td>ACS (invasive or non-invasively managed) or history of MI</td>
<td>PCI in patients with or without ACS</td>
</tr>
</tbody>
</table>

This study was designed to compare the efficacy and safety of Prasugrel and Ticagrelor in acute myocardial infarction treated with primary or immediate percutaneous coronary intervention.
Study Strengths

• Purely academic study, no industry support; important question

• Represents real-world---Patients had to cover the costs of Ticagrelor or Prasugrel after hospital discharge as per local healthcare regulations.

• Thus, some patients decided to switch after discharge to clopidogrel (fully covered by local healthcare). An important question to answer—regarding safety and efficacy of this common practice

• Excellent follow up of all patients
Why Switch from a Potent Agent to Clopidogrel?

• Overall, registry data indicate that the prevalence of in-hospital de-escalation ranges from 5% to 14% and from 5% to 8% after hospital discharge.

• 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.

• Non-bleeding side effects such as dyspnea also represent a potential reason for interrupting ticagrelor therapy.
Time distribution of economically motivated switches to clopidogrel after discharge

Motovska Z. Presented at AHA 2017
De-escalation

Conflicting findings have been observed on the clinical impact of de-escalation:

• SCOPE registry (observational; early de-escalation): increased ischemic recurrences with no differences in bleeding
• TOPIC trial (randomized; one-month de-escalation; non guided): reduced bleeding, no increase in ischemic events
• TROPICAL ACS trial (randomized; 1 week de-escalation; guided by PFT): no increase in ischemic events, trend toward reduced bleeding
De-escalation inevitably leads to an increase in platelet reactivity and HPR rates.

Offset of antiplatelet effects of oral P2Y12 inhibitors

RECOVERY trial

ONSET/OFFSET trial

Adapted from Price MJ et al. J Am Coll Cardiol 2012;59:2338-4

Adapted from Gurbel PA et al. Circulation 2009;120:2577-85
**Expert Consensus Recommendations on Switching**

**SWITCHING BETWEEN ORAL P2Y12 INHIBITORS**

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.

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.

What Does PRAGUE 18 add?

- Switching is common: 749/1230 (61%) patients enrolled in this trial switched to clopidogrel mostly within the first 90 days, and usually economically driven.
- Economically driven, physician directed de-escalation seems feasible, but the study is underpowered to evaluate safety and efficacy of this strategy.
- These observations (not randomized, confounders, etc.) require large randomized trials to evaluate the safety and efficacy of switching (de-escalation).