Switching between anti-platelet ADP receptor inhibitors

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Case #1

- 62 y/o male admitted with anterior wall STEMI
- Chest pain for 3 hours prior to arrival
- Risk factors: HTN, dyslipidemia
- In the ER receives aspirin, heparin and clopidogrel 600 mg
- Successful PCI performed with aspiration and DES implantation
The following day the patient should be treated with:

1. Clopidogrel 75 mg a day
2. Clopidogrel 150 mg a day for a week followed by 75 mg a day
3. Prasugrel 10 mg a day (without any loading)
4. Prasugrel 30 mg loading followed by 10 mg a day
5. Prasugrel 60 mg loading followed by 10 mg a day
6. Ticagrelor 180 mg loading followed by 90 mg bid
7. Ticagrelor 90 mg bid (without loading)
SWITCHING TO PRASUGREL

- Safe switch from clopidogrel LD (600-900 mg) → prasugrel MD (ACAPULCO, Thromb Haemost 2010).

- Safe switch from clopidogrel MD → prasugrel LD or MD. Switching to the LD provides faster onset of platelet inhibition (SWAP).

- No published data on clopidogrel LD → prasugrel LD switch; however, TRIPLET study partly addresses this question.
Prasugrel 10 mg MD vs. Clopidogrel 75 mg
MD: Higher IPA During Maintenance Dosing

The SWAP study

Switching from maintenance clopidogrel to prasugrel in 100 patients with ACS

Angiolillo et al, JACC 2010
Presented at EUROPCR 2012

**TRIPLET** – Switching from clopidogrel loading to prasugrel

**Time Course: Pharmacodynamic Population**

PRU (LS mean), PD population

% Inhibition (LS mean), PD population

ACS PCI patients

*P=NS at each time point vs. placebo/prasugrel 60 mg, **P=0.049 between the placebo/prasugrel 60 mg group and the clopidogrel 600 mg/prasugrel 60 mg group

LD=Loading Dose, LS=Least Square, PD=Pharmacodynamic, PRU=P2Y12 Reaction Units
Switching from prasugrel to clopidogrel

- ACS pts treated with prasugrel 10 mg for 2 wks
- Pts displaying low on-treatment platelet reactivity (by VerifyNow) or at high risk of bleeding were considered for switch to clopidogrel 75 mg

Kerneis et al, JACC CV Interv 2013
Switching drugs

- Switching from maintenance clopidogrel to prasugrel → more efficient and rapid platelet inhibition achieved by adding prasugrel loading dose

- Switching after clopidogrel loading dose may also require additional prasugrel loading of 30-60 mg
Ticagrelor – mode of action

P2Y12 receptor model
(Van Giezen et al, JTH 2009)

ADP binding site
Ticagrelor binding site
Ticagrelor - Onset / Offset Study, IPA to 5uM ADP

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Onset</th>
<th>Maintenance</th>
<th>Offset</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
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<td></td>
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<tr>
<td>4</td>
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<td></td>
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<td>8</td>
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<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
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<td></td>
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<tr>
<td>6 weeks</td>
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</tbody>
</table>

IPA %

- Ticagrelor (n=54)
- Clopidogrel (n=50)
- Placebo (n=12)

Gurbel PA et al. Circulation 2009
## Primary efficacy endpoint by clopidogrel loading dose

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio (95% CI)</th>
<th>Total Patients</th>
<th>KM % at Month 12</th>
<th>HR (95% CI)</th>
<th>p value (Interaction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel loading dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Pre-rand. + Study drug)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600 mg</td>
<td></td>
<td>9314</td>
<td>9.5</td>
<td>11.2</td>
<td>0.85 (0.74, 0.96)</td>
</tr>
<tr>
<td>300 mg</td>
<td></td>
<td>4091</td>
<td>8.0</td>
<td>9.5</td>
<td>0.83 (0.67, 1.03)</td>
</tr>
<tr>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
<td>2.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Ticagrelor better
- Clopidogrel better

### Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Ticagrelor (n=9,333)</th>
<th>Clopidogrel (n=9,291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel start-up, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel in hospital before randomisation</td>
<td>46.0</td>
<td>46.1</td>
</tr>
</tbody>
</table>
Switching drugs in the RESPOND study

Patients treated with ticagrelor in period 1 received a 600-mg clopidogrel load followed by 75-mg daily maint. therapy.

Patients treated with clopidogrel in period 1 received a 180-mg ticagrelor load followed by 90-mg twice daily maint. therapy.

41 patients non-responsive to clopidogrel

Gurbel et al, Circulation 2010
Switching drugs

- Switching from clopidogrel (loading or maintenance) to ticagrelor requires ticagrelor loading.

- Switching from ticagrelor to clopidogrel probably also requires loading because of differences in compounds and active sites.
THANK YOU