Optimising Crossover from Ticagrelor to Clopidogrel in Patients with Acute Coronary Syndrome [CAPITAL OPTI-CROSS]

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Disclosure

No relevant disclosures concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.
## Background – Guideline Recommendations

<table>
<thead>
<tr>
<th>STEMI</th>
<th></th>
<th></th>
<th>NSTE-ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>LOE</td>
<td>Recommendation</td>
<td>Class</td>
</tr>
</tbody>
</table>
| I     | B  | Loading dose as early as possible or at time of PCI:  
• clopidogrel 600 mg  
• prasugrel 60 mg  
• ticagrelor 180 mg |   | I  | Loading dose prior to PCI with stent:  
• Clopidogrel 600 mg  
• Ticagrelor 180 mg  
• Prasugrel 60 mg |
|       |    | It is reasonable to use ticagrelor in preference to clopidogrel for either ischemia-guided therapy or invasive management | IIa | B  | |
| I     | B  | P2Y12 inhibitor given for 1 year post-stent:  
• clopidogrel 75 mg daily  
• prasugrel 10 mg daily  
• ticagrelor 90 mg twice daily |   |   | |

Circulation 2013;127:529-555  
Circulation 2014; 130:e344-426
PLATO – Ticagrelor vs. Clopidogrel

Composite of cardiovascular death, myocardial infarction, or stroke

PLATO – Ticagrelor vs. Clopidogrel

Ticagrelor
Clopidogrel

Cumulative Incidence of Major Bleeding (%)

No. at Risk
Ticagrelor 9235 7246 6826 6545 5129 3783 3433
Clopidogrel 9186 7305 6930 6670 5209 3841 3479

P = 0.43

Major bleeding

# Background – PK/PD Parameters

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel (Plavix)</th>
<th>Ticagrelor (Brilinta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CYP isoenzymes - metabolism</td>
<td>2C19, 2C9, 3A, 2B6, 1A2</td>
<td>3A4/5</td>
</tr>
<tr>
<td>% Platelet Inhibition</td>
<td>30-50%</td>
<td>80-90%</td>
</tr>
<tr>
<td>Half-life</td>
<td>~6 hours</td>
<td>8-12 hours</td>
</tr>
<tr>
<td>Onset of action after loading dose</td>
<td>300 mg: 6 hours 600 mg: 4 hours</td>
<td>1.5 hours</td>
</tr>
<tr>
<td>Offset of action</td>
<td>5 days</td>
<td>3 days offset; label states should be held for 5 days before surgery</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Active pathological bleeding</td>
<td>Severe hepatic impairment, active bleeding</td>
</tr>
<tr>
<td>Precautions</td>
<td>CYP 2c19 polymorphisms</td>
<td>Severe dyspnea at baseline, moderate hepatic impairment, ASA dose &lt; 100 mg, risk of bradycardia</td>
</tr>
</tbody>
</table>

Cardiovasc Ther 2009; 27:259-74
Clopidogrel and Ticagrelor – Binding Properties

<table>
<thead>
<tr>
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<th>Clopidogrel (Plavix)</th>
<th>Ticagrelor (Brilinta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of binding</td>
<td>Competitive</td>
<td>Noncompetitive</td>
</tr>
<tr>
<td>Receptor inhibition</td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
</tbody>
</table>

**Diagram**

- **a**: ADP binding to the P2Y12 receptor
- **b**: G protein coupled with the receptor
- **c**: Clopidogrel binds to the receptor
- **d**: Ticagrelor binding to the receptor
Platelet reactivity is measured as a function of an increase in light transmission through whole blood as platelets are activated by ADP. Greater PRU = higher reactivity.
Background – Platelet Function Testing

2014 AHA/ACC Non-STE ACS Guidelines

6.2.3. Platelet Function and Genetic Phenotype Testing
Although higher platelet reactivity has been associated with a greater incidence of adverse events in patients undergoing stent implantation, a strategy of adjusting antiplatelet therapy based on routine platelet function testing has not been beneficial in reducing ischemic complications. Similarly, a strategy of routine genetic phenotype testing has also not been beneficial and thus is not recommended. A more detailed discussion of these issues and current recommendations about platelet function testing and genetic testing are in the 2011 PCI CPG.

2013 ACCF/AHA STEMI Guidelines

12.4. Antithrombotic Therapy
The optimum choice of P2Y12 receptor inhibitor and anticoagulant agents for patients with STEMI can be challenging. Individual genetic variability in drug absorption, metabolism, and effectiveness has been highlighted by the experience with clopidogrel in patients with ACS (285,637). The risks of bleeding also may vary across racial and ethnic groups (12). The roles of platelet function testing and genetic screening for clopidogrel metabolism in the acute phase of STEMI care are uncertain (289), especially with the availability of alternative P2Y12 receptor inhibitors. More information specific to patients with STEMI is needed with regard to the use of prasugrel, ticagrelor, novel factor Xa and IIa antagonists, and platelet protease--activated receptor 1 antagonists (638,639).
A randomised study for optimising crossover from ticagrelor to clopidogrel in patients with acute coronary syndrome [CAPITAL OPTI-CROSS]

**Study Design**

**Objective**
- Evaluate the pharmacodynamic effects of bolus versus no bolus clopidogrel in patients with ACS requiring a switch from ticagrelor to clopidogrel

**Study Design**
- Prospective, randomized, single-center, open-label study

**Treatment Groups**
- **Bolus group**: clopidogrel 600 mg bolus → clopidogrel 75 mg daily (n=30)
- **No bolus group**: clopidogrel 75 mg daily (n=30)

**Platelet reactivity testing**
- VerifyNow P2Y12 Assay
- At baseline, 12 h, 24 h, 48 h, 54 h, 60 h, 72 h

Thromb Haemost 2017; 117:303-310
Study Endpoints

Primary

Platelet Inhibition
• Platelet reactivity units (PRU) 72 hours after initiation of treatment

Secondary

Pharmacodynamic
• Compare mean PRUs at different time points
• Proportion of patients with high on-treatment platelet reactivity (HPR)

Efficacy
• 30-day major cardiovascular event composite*

Safety
• 30-day TIMI major and minor bleeding

*Cardiovascular death, recurrent MI, target vessel revascularization, or stroke; each component of the composite
## Study Design

### Inclusion Criteria
- > 18 years of age
- Admitted with ACS
- Initially treated with bolus ticagrelor 180 mg and at least 1 day of maintenance therapy prior to randomization

### Exclusion Criteria
- Active bleeding
- Clopidogrel intolerance
- Thrombocytopenia (platelet count < 100,000)
- Hematocrit < 30%
- Treatment with glycoprotein IIb/IIIa inhibitor in preceding 24 hours
- Inability to give informed consent
- Planned discharge prior to completion of study
Statistical Analysis

- PRU comparison
  - continuous variable over first 72 hours post-switching using mixed-model repeated measures analysis
- Freedom from HPR – estimated using Kaplan-Meier method
  - HPR defined as PRU ≥ 208
  - LPR defined as PRU < 85
- Assumed a standard deviation of 60, at 80% power, 48 patients required for enrollment
- Statistical significance defined as p < 0.05

Thromb Haemost 2017; 117:303-310
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bolus (n=30)</th>
<th>No Bolus (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male – n (%)</td>
<td>24 (80%)</td>
<td>15 (50%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age – years (SD)</td>
<td>70 (14)</td>
<td>69 (13)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension – n (%)</td>
<td>21 (70%)</td>
<td>19 (63.3%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes – n (%)</td>
<td>11 (36.7%)</td>
<td>13 (43.3%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Dyslipidemia – n (%)</td>
<td>10 (33.3%)</td>
<td>15 (50%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Smoking – n (%)</td>
<td>11 (36.7%)</td>
<td>17 (56.7%)</td>
<td>0.1</td>
</tr>
<tr>
<td>MI – n (%)</td>
<td>13 (43.3%)</td>
<td>8 (26.7%)</td>
<td>0.3</td>
</tr>
<tr>
<td>CABG – n (%)</td>
<td>1 (3.3%)</td>
<td>3 (10%)</td>
<td>0.7</td>
</tr>
<tr>
<td>PCI – n (%)</td>
<td>10 (33.3%)</td>
<td>5 (16.7%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Stroke – n (%)</td>
<td>5 (16.7%)</td>
<td>3 (10%)</td>
<td>0.7</td>
</tr>
<tr>
<td>CKD – n (%)</td>
<td>2 (6.7%)</td>
<td>2 (6.7%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bolus (n=30)</th>
<th>No Bolus (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI – n (%)</td>
<td>20 (66.7%)</td>
<td>19 (63.3%)</td>
<td>0.9</td>
</tr>
<tr>
<td>NSTEMI – n (%)</td>
<td>10 (33.3%)</td>
<td>11 (36.7%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Days on ticagrelor - (IQR)</td>
<td>1 (1-2)</td>
<td>2 (1-3.75)</td>
<td>0.7</td>
</tr>
<tr>
<td>Baseline PRU</td>
<td>47.5 ± 50.4</td>
<td>60.6 ± 54.8</td>
<td>0.34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initial Management</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percutaneous revascularization</td>
<td>45 (75%)</td>
</tr>
<tr>
<td>Medically managed</td>
<td>12 (20%)</td>
</tr>
<tr>
<td>Surgical revascularization</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

Thromb Haemost 2017; 117:303-310
## Indications to Switch to Clopidogrel

<table>
<thead>
<tr>
<th>Indication for Switch</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple therapy</td>
<td>24 (40%)</td>
</tr>
<tr>
<td>Increased bleeding risk</td>
<td>10 (16.7%)</td>
</tr>
<tr>
<td>Drug cost</td>
<td>9 (15%)</td>
</tr>
<tr>
<td>Need for CABG</td>
<td>7 (11.7%)</td>
</tr>
<tr>
<td>Compliance concerns</td>
<td>7 (11.7%)</td>
</tr>
<tr>
<td>Intolerance to ticagrelor</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>
Pharmacodynamic Results

• No difference between PRU values at 72 hours post-randomization between bolus and no bolus groups
  ○ 165.8 ± 71.0 and 184.1 ± 67.7; p=0.19
• Relative to pre-switching values, PRU increased over 72 hours in both treatment groups
Pharmacodynamic Results

- PRU at 48 hours bolus vs. no bolus group
  - $114.1 \pm 73.1$ vs. $165.1 \pm 70.5$; $p=0.0076$

Mean PRUs at specified time points

Thromb Haemost 2017; 117:303-310
Pharmacodynamic Results

- Incidence of HPR higher in no bolus group over first 72 hours

**Prevalence of HPR Over Time**

![Graph showing the prevalence of HPR over time with different post-transition time (hours) and the percentage of patients with HPR. The graph includes a line for the no bolus group and another for the bolus group. The hazard ratio (HR) is 0.37 with a 95% confidence interval (CI) of 0.15-0.79, and the p-value is 0.02.](image-url)
Pharmacodynamic Results

- HPR occurred more frequently in patients not receiving clopidogrel bolus overall (56.7% vs. 26.7%; p=0.02)

Number of Patients with PRU >208 at Various Time Points

- Time post-randomization (hours):
  - baseline
  - 12h
  - 24h
  - 48h
  - 54h
  - 60h
  - 72h

- Comparison between Bolus and No Bolus groups:
  - Baseline: p=ns
  - 12h: p=ns
  - 24h: p=ns
  - 48h: p=ns
  - 54h: p=ns
  - 60h: p=ns
  - 72h: p=ns

Thromb Haemost 2017; 117:303-310
Pharmacodynamic Results

- No significant difference in the incidence of LPR at various time points
- Incidence of LPR decreases over time following the switch to clopidogrel, corresponding to an increased PRU
## Secondary Clinical Results

<table>
<thead>
<tr>
<th>Secondary Clinical Endpoints</th>
<th>Bolus (n=29)*</th>
<th>No Bolus (n=28)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE – n (%)</td>
<td>1 (3.4%)</td>
<td>1 (3.6%)</td>
<td>0.9</td>
</tr>
<tr>
<td>CV mortality – n (%)</td>
<td>0</td>
<td>1 (3.6%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Re-infarction – n (%)</td>
<td>1 (3.4%)</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Urgent revascularization – n (%)</td>
<td>1 (3.4%)</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Stroke – n (%)</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Stent thrombosis – n (%)</td>
<td>1 (3.4%)</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>30-day all cause mortality – n (%)</td>
<td>1 (3.4%)</td>
<td>1 (3.6%)</td>
<td>0.9</td>
</tr>
<tr>
<td>TIMI major bleed – n (%)</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>TIMI minor bleed – n (%)</td>
<td>1 (3.4%)</td>
<td>2 (7.2%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Transfusion – n (%)</td>
<td>1 (3.4%)</td>
<td>2 (7.2%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Author’s Conclusions

- Study did not demonstrate differences in platelet inhibition at 72h when receiving clopidogrel 600 mg bolus
- There is significant improvement in platelet inhibition at 48h and a major reduction in incidence of HPR
- Larger confirmation studies will be required to definitely determine associations to clinical outcomes
- Data suggests to individualize strategy at time of switching balancing risk of bleeding vs. ischemic complications

Thromb Haemost 2017; 117:303-310
Critique

**Strengths**
- Randomized treatment strategy
- Utilized a validated measurement of platelet reactivity previously associated with ischemic complications at high levels (HPR) and bleeding complications at low levels (LPR)
- Utilized clopidogrel loading dose of 600 mg vs. 300 mg

**Limitations**
- Small, single center
- At the 24, 48, and 72-hr time points, blood samples for PRU were collected either before (trough) or after (peak) scheduled dose of clopidogrel
- Did not have a clopidogrel control arm
Impact on Clinical Practice

• Bolus unless reason switching for switching is active bleeding
• Balance risk of ischemic complications vs. bleeding risk
  • Consider
    • Observed incidence of HPR significantly lower in patients receiving a bolus
    • Lack of difference in PRU by 72h between strategies
  • Highest risk of ischemic complications: bolus
    • Ex) ACS, early post-PCI who require switch within 48-72h and not candidates for prasugrel
  • Highest risk of bleeding complications: consider no bolus
Acknowledgements

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  • Jeffrey Lalama, PharmD, BCPS

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  • Mike Dorsch, PharmD, MS, BCPS (AQ Cardiology), FAHA, FCCP
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  • Genevieve Hale, PharmD, BCPS
  • Zachary Noel, PharmD, BCPS
  • Ted Berei, PharmD, MBA
  • Thomas Szymanski, PharmD Candidate
Additional Slides
ADAPT-DES Trial
“Assessment of DAPT with DES”

- Prospective, multicenter registry (N=8665)
- Patients with coronary artery disease treated with aspirin and clopidogrel after DES
- Platelet reactivity measured with VerifyNow

Lancet 2013; 382:614-23
GRAVITAS Trial
“Gauging Responsiveness with a VerifyNow assay-Impact on Thrombosis And Safety”

• Randomized controlled trial (N=2214)
• Patients after PCI with PRU >235
• Randomized to standard dose clopidogrel or repeated loading with 150 mg maintenance dose
• Composite endpoint of death, MI, stent thrombosis
• Platelet reactivity measured with VerifyNow

JAMA 2011; 305:1097-105
TRIGGER-PCI Trial

“Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel”

• Randomized controlled trial (N=423)
• Patients with stable CAD, elective PCI with DES, PRU >208
• Randomized to prasugrel or clopidogrel
• Primary endpoint of cardiac death or MI at 6 months
• Platelet reactivity measured with VerifyNow

J Am Coll Cardiol 2012; 59:2159-64
TRIGGER-PCI Trial
“Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel”

CV death, MI, stroke, or rehospitalization for cardiac ischemic event

Bleeding Risk
ARMYDA-BLEEDS Trial
“Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-Bleeding Study”

• Prospective study of 310 patients receiving clopidogrel before PCI

• PRU ≤ 189 predicts 30-day bleeding (sensitivity 87%; specificity 70%)

Am J Cardiol 2011; 107:995-1000