Interventional Pharmacology: *Now And The Future*

Matthew J. Price MD, FACC  
Director, Cardiac Catheterization Laboratory, Scripps Clinic  
Assistant Professor, Scripps Translational Science Institute  
La Jolla, CA
## Currently Available Oral Antiplatelet Agents

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DRUG CLASS</th>
<th>CLINICAL CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>COX-1 inhibitor</td>
<td>PO, Irreversible binding</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; (ADP) receptor antagonist</td>
<td>PO, Irreversible binding</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; (ADP) receptor antagonist</td>
<td>PO, Irreversible binding</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>P2Y&lt;sub&gt;12&lt;/sub&gt; (ADP) receptor antagonist</td>
<td>PO, Irreversible binding</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>PDE inhibitor; Increase cAMP</td>
<td>PO, Reversible inhibition</td>
</tr>
</tbody>
</table>

**COX** = cyclooxygenase; **ADP** = adenosine diphosphate; **PDE** = phosphodiesterase
TRITON-TIMI 38: Prasugrel vs Clopidogrel in ACS Treated With PCI

- **CV Death/MI/Stroke**
  - Clopidogrel: 12.1%
  - Prasugrel: 9.9%
  - HR 0.81 (95% CI, 0.73–0.90) \( P<0.001 \)
  - NNT=46

- **TIMI Major Non-CABG Bleeds**
  - Clopidogrel: 1.8%
  - Prasugrel: 2.4%
  - HR 1.32 (95% CI, 1.03–1.68) \( P=0.03 \)
  - NNH=167

The RECOVERY Trial: Duration Needed To Return To Baseline Function With The Thienopyridines

Return to baseline is defined as the return to within 60 P2Y₁₂ reaction units (PRUs) of baseline PRU value determined prior to thienopyridine therapy.

- The day on which the proportion of subjects returning to baseline PRU in the prasugrel group is closest to that attained by the clopidogrel group on Washout Period Day 5.
- The day on which the proportion of subjects returning to baseline PRU in the prasugrel group is closest to that attained by the clopidogrel group on Washout Period Day 7.

Price MJ, Angiolillo DJ et al, ACC/i2 2011
Ticagrelor: Pharmacology

- **Class:** Cyclopentyl-triazolo-pyrimidine (CPTP)

- **Mechanism:** Direct inhibition of the P2Y12 receptor (no metabolic activation required).

- **Onset of action:** Rapid, max reached at < 2 hrs

- **Administration:** Oral

- **Plasma** $t_{1/2}$ ≈ 10-12 hours (bid drug)

- **“Off-target” effects:** Blocks adenosine reuptake by RBC’s

---

PLATO: Time to first primary efficacy event (CV death, MI or stroke) – Ticagrelor vs Clopidogrel

HR 0.84 (95% CI 0.77–0.92), p=0.0003

PLATO: Non-CABG and CABG-related major bleeding

- Ticagrelor
- Clopidogrel

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CABG PLATO major bleeding</td>
<td>4.5%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Non-CABG TIMI major bleeding</td>
<td>2.8%</td>
<td>2.2%</td>
</tr>
<tr>
<td>CABG PLATO major bleeding</td>
<td>7.4%</td>
<td>7.9%</td>
</tr>
<tr>
<td>CABG TIMI major bleeding</td>
<td>5.3%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

p-values: p=0.026 for Non-CABG PLATO major bleeding, p=0.025 for Non-CABG TIMI major bleeding, NS for CABG PLATO major bleeding and CABG TIMI major bleeding.
ONSET/OFFSET: Duration Until Complete Recovery After Ticagrelor MD Is Similar To Clopidogrel MD

“ticagrelor should be discontinued 7 days prior to surgery if a patient is to undergo elective surgery and antiplatelet effect is not desired” – EMEA for ticagrelor

Gurbel P et al, Circulation 2009
CHAMPION-PCI: Cangrelor versus Standard Tx to Achieve Optimal Management of Platelet Inhibition

Patients with UA, MI, or ACS requiring urgent or elective PCI  
N=8716

Randomize

Clopidogrel  
600 mg

Cangrelor 30 µg/kg IV bolus,  
4 µg/kg/min infusion

Primary Objective: Superiority of cangrelor versus clopidogrel for PCI

1º end point: all-cause mortality, MI, or IDR at 48 hours
2º end points: all-cause mortality and MI at 48 hours

IDR, ischemia-driven revascularization.

## CHAMPION PCI: Efficacy End Points at 48 Hr

<table>
<thead>
<tr>
<th>Efficacy mITT</th>
<th>Cangrelor (n=3897)</th>
<th>Clopidogrel (n=3871)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI/IDR (primary end point)</td>
<td>7.5%</td>
<td>7.1%</td>
<td>1.05 (0.88–2.24)</td>
<td>.59</td>
</tr>
<tr>
<td>MI</td>
<td>7.1%</td>
<td>6.6%</td>
<td>1.09 (0.91–1.29)</td>
<td>.36</td>
</tr>
<tr>
<td>IDR</td>
<td>0.3%</td>
<td>0.6%</td>
<td>0.56 (0.28–1.11)</td>
<td>.10</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.2%</td>
<td>0.1%</td>
<td>1.59 (0.52–4.87)</td>
<td>.42</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.63 (0.25–1.63)</td>
<td>.34</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.2%</td>
<td>0.2%</td>
<td>0.85 (0.29–2.54)</td>
<td>.77</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>0.1%</td>
<td>0.3%</td>
<td>0.40 (0.12–1.27)</td>
<td>.12</td>
</tr>
<tr>
<td>Death/Q-wave MI/IDR</td>
<td>0.6%</td>
<td>0.9%</td>
<td>0.67 (0.39–1.14)</td>
<td>.14</td>
</tr>
<tr>
<td>Death/Q-wave MI/Stent thrombosis</td>
<td>0.5%</td>
<td>0.6%</td>
<td>0.78 (0.42–1.44)</td>
<td>.42</td>
</tr>
</tbody>
</table>

---

PHOENIX – Trial schematic

- Randomized, double blind, double dummy, superiority
- Cangrelor (bolus + infusion for 2 hr) compared to usual care clopidogrel
- Primary efficacy endpoint: Death/MI/IDR/ST at 48 hr

**CHAMPION PHOENIX**
N = 10900
SA/UA/ACS/STEMI
No clopidogrel allowed

- Cangrelor bolus then infusion
- Clopidogrel 300 or 600 mg oral
- PCI ~30’
- Clopidogrel 600 mg oral

**SCRIPPS CLINIC**
The Promise of the Platelet Thrombin Receptor Antagonists (PAR inhibitors)

From Price and Angiolillo, Topol’s Interventional Cardiology, 7th Edition
**Vorapaxar: Thrombin Receptor Antagonism**

**Vorapaxar Program (29,500 pts)**

- NSTE ACS 10,000 pts
- 2º Prevention 19,500 pts

**TRA-CER**

- TRA
- Placebo

**TRAP TIMI 50**

- TRA
- Placebo

**Primary Endpoint:** CV death, MI, stroke, urgent revascularization and recurrent ischemia w/ rehospitalization

---

ClinicalTrials.gov
Identifier: NCT00526474.

ClinicalTrials.gov
Identifier: NCT00527943.
In the TRACER study, patients will discontinue study drug and investigators are to begin now to close out the study in a timely and orderly fashion.

In the TRA-2P study, study drug…will be immediately discontinued in patients who experienced a stroke prior to entry into the study or during the course of the study.
Subjects with ACS (Unstable angina or NSTEMI)

$n = 603$

Randomization within 72 hours of symptom onset

Double-blind

Placebo QD

Atopaxar 400mg LD, 50mg QD

Atopaxar 400mg LD, 100mg QD

Atopaxar 400mg LD, 200mg QD

Randomize 1:1:1:1

12 Weeks Active Treatment, 4 Weeks Follow-Up

Primary Endpoint: Major bleeding (CURE) at 12 weeks
Incidence of any CURE Bleeding

Placebo  n=138
Active combined atopaxar  n=455
50mg QD  n=153
100mg QD  n=156
200mg QD  n=146

Relative Risk (95% CI) vs. placebo
RR 1.42 (0.44-4.8)  P = 0.63
RR 0.60 (0.11-3.00)  P = 0.62
RR 2.65 (0.78-10.3)  P = 0.13
RR 0.95 (0.18-5.04)  P = 0.99

Relative Risk (RR) for placebo vs. active treatments:
- Placebo vs. Active combined atopaxar: RR 1.42 (P = 0.63)
- Placebo vs. 50mg QD: RR 0.60 (P = 0.62)
- Placebo vs. 100mg QD: RR 2.65 (P = 0.13)
- Placebo vs. 200mg QD: RR 0.95 (P = 0.99)

P trend = 0.81
Incidence of CV death, MI, Stroke, or Recurrent ischemia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RR (95% CI) vs. placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo n=142</td>
<td>RR 1.04 (0.55-1.97)</td>
<td>0.93</td>
</tr>
<tr>
<td>Active combined atopaxar n=461</td>
<td>RR 0.50 (0.16-1.27)</td>
<td>0.18</td>
</tr>
<tr>
<td>50mg QD n=156</td>
<td>RR 1.40 (0.68-2.86)</td>
<td>0.37</td>
</tr>
<tr>
<td>100mg QD n=157</td>
<td>RR 1.22 (0.58-2.57)</td>
<td>0.63</td>
</tr>
<tr>
<td>200mg QD n=148</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Pipeline: New Targets For Platelet Adhesion and Activation

Revacept:
- a dimeric GPVI/Fc fusion protein and the extracellular domain of the human GPVI platelet receptor.
- binds to collagen and fibronectin in atherosclerotic stable or ruptured plaques

Ungerer M et al, Circulation 2011
Can We Do Better With our CURRENT Agents?
Meta-Analysis of OTR and Ischemic Events Post-PCI: Increasing Risk With Greater Residual Reactivity

N=3,041

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Event Rate</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4</td>
<td>15.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Q3</td>
<td>10.9%</td>
<td>0.02</td>
</tr>
<tr>
<td>Q2</td>
<td>6.9%</td>
<td>0.97</td>
</tr>
<tr>
<td>Q1</td>
<td>5.8%</td>
<td>-</td>
</tr>
</tbody>
</table>

P-values adjusted for multiple comparisons

Brar S, ACC 2011 (in press)
GRAVITAS: Standard- vs High-Dose Clopidogrel in Patients with High Reactivity after PCI (≥ 230 PRU)

2.3% vs. 2.3%
HR 1.01 (95% CI 0.58 - 1.76)
p=0.98

Observed event rates are listed; P value by log rank test.

GRAVITAS: Hazard of Primary Endpoint According To Achieved Reactivity (Baseline or 30 days)

CV Death, MI or ST at 60 Days

- PRU < 230
- PRU < 230, adjusted
- PRU < 208
- PRU < 208, adjusted

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRU &lt; 230</td>
<td>0.62 (0.25, 1.51)</td>
<td>0.30</td>
</tr>
<tr>
<td>PRU &lt; 230, adjusted</td>
<td>0.75 (0.30, 1.87)</td>
<td>0.53</td>
</tr>
<tr>
<td>PRU &lt; 208</td>
<td>0.18 (0.04, 0.79)</td>
<td>0.020</td>
</tr>
<tr>
<td>PRU &lt; 208, adjusted</td>
<td>0.23 (0.05, 0.98)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

CV Death, MI or ST at 6 Months

- PRU < 230
- PRU < 230, adjusted
- PRU < 208
- PRU < 208, adjusted

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRU &lt; 230</td>
<td>0.71 (0.41, 1.23)</td>
<td>0.22</td>
</tr>
<tr>
<td>PRU &lt; 230, adjusted</td>
<td>0.88 (0.50, 1.56)</td>
<td>0.67</td>
</tr>
<tr>
<td>PRU &lt; 208</td>
<td>0.43 (0.23, 0.83)</td>
<td>0.01</td>
</tr>
<tr>
<td>PRU &lt; 208, adjusted</td>
<td>0.54 (0.28, 1.04)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Cox regression using OTR as a time-varying covariate
Price MJ et al, in submission
CYP2C19 and Stent Thrombosis In Clopidogrel-Treated Patients: A Collaborative Meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carriers vs Non-Carriers</td>
<td>2.76 (1.77-4.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heterozygotes vs Wildtype</td>
<td>2.51 (1.59-3.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Homozygotes vs Wildtype</td>
<td>4.78 (2.01-11.39)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

N=5,772

Risk Lower with CYP2C19 Variant
Risk Higher with CYP2C19 Variant

Bedside Genotyping Has (Almost) Arrived!
Sample to result turn-around times < 4 hrs

- Nanosphere (3 - 4 hrs), Spartan (1 hr), Quest (1 hr)
- Whole Blood/Buccal Swab
- Includes nucleic acid purification step
- Can run single samples (no need to batch)
- Minimal pipetting – run in cath lab, holding area, or clinical lab
Now And The Future: The Challenge

- Ischemic events are frequent after PCI for ACS.
- Novel antiplatelet agents in the pipeline do not appear to overcome all the limitations with the current agents.
- Individualized antiplatelet therapy may allow us to use our current drugs more smartly.
  - *Rapid* genotyping platforms will help.
  - Adequately powered RCT’s using more potent agents in elective PCI will require very large sample sizes, need special attention to net clinical benefit.
  - The absence of data is not the same as the data of absence!