Catheterization Laboratory Pharmacology

Ankur Kalra, MD

Interventional Cardiologist, Cleveland Clinic
Associate Professor of Medicine, Cleveland Clinic Lerner College of Medicine
Section Head, Cardiovascular Research, Cleveland Clinic Akron General
Deepak L. Bhatt, MD, MPH

Executive Director of Interventional Cardiovascular Programs, BWH Heart and Vascular Center
Professor of Medicine, Harvard Medical School
Platelet Thrombus

Enteric Coated Aspirin

1-Year Mortality by Diabetic Status

<table>
<thead>
<tr>
<th>Diabetic Status</th>
<th>Days from Randomization</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes/ABX (n=888)</td>
<td>0-360</td>
<td>4.5%</td>
</tr>
<tr>
<td>Diabetes/PL (n=574)</td>
<td>0-360</td>
<td>2.6%</td>
</tr>
<tr>
<td>No Diabetes/ABX (n=3222)</td>
<td>0-360</td>
<td>2.5%</td>
</tr>
<tr>
<td>No Diabetes/PL (n=1850)</td>
<td>0-360</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

p=0.031

GP IIb/IIIa Blockade and Diabetes

**EPISTENT Trial***

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Glycoprotein IIb/IIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>4.1</td>
<td>1.9</td>
</tr>
<tr>
<td>No diabetes</td>
<td>1.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**ESPRIT Trial**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Glycoprotein IIb/IIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>3.5</td>
<td>1.3</td>
</tr>
<tr>
<td>No diabetes</td>
<td>1.5</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Stent arms only

Meta-Analysis of GP IIb/IIIa Inhibitors: Diabetic Patients With Non-ST-Segment Elevation ACS

OR with 95% CIs and corresponding P values for treatment effect on 30-day mortality among diabetic patients with ACS (n=6548)

In diabetic patients (n=1279) undergoing PCI during index hospitalization, the GPI use was associated with a mortality reduction at 30 days from 4.0% to 1.2% (OR 0.30; 95% CI 0.14 to 0.69; P=0.002; NNT=36).

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo (%)</th>
<th>GPI (%)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARAGON A</td>
<td>412</td>
<td></td>
<td>6.1 (4.2)</td>
<td>0.33</td>
</tr>
<tr>
<td>PARAGON B</td>
<td>1157</td>
<td></td>
<td>6.7 (7.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Pooled</td>
<td>6458</td>
<td></td>
<td>6.2 (5.1)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Breslow-Day: P=0.50

ADP Receptors

CLASSICS: Superior Safety Profile of Clopidogrel at 28 Days

**Primary Endpoint**

- **Ticlopidine**
  - (n = 340)
  - 9.12%

- **Clopidogrel**
  - (n = 680)
  - 4.56%

*p = 0.005

*Major bleeding complications, neutropenia, thrombocytopenia or early discontinuation of the study drug for non-cardiac adverse events (%)
†Combined groups

### MACE

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Odds Ratios &amp; 95% CI</th>
<th>Clop.</th>
<th>Ticl.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASSICS</td>
<td>1,020</td>
<td>1.3%</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>TOPPS</td>
<td>941</td>
<td>2.6%</td>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td>Müller</td>
<td>700</td>
<td>3.1%</td>
<td>2.0%</td>
<td></td>
</tr>
<tr>
<td>CCF</td>
<td>2,369</td>
<td>5.7%</td>
<td>8.9%</td>
<td></td>
</tr>
<tr>
<td>Lenox Hill</td>
<td>2,565</td>
<td>2.4%</td>
<td>3.8%</td>
<td></td>
</tr>
<tr>
<td>Mayo</td>
<td>2,827</td>
<td>0.6%</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>N. Memorial</td>
<td>1,378</td>
<td>0.8%</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>S. Illinois</td>
<td>875</td>
<td>2.1%</td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td>Wash. Hosp.</td>
<td>844</td>
<td>2.0%</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>Wessex</td>
<td>361</td>
<td>2.3%</td>
<td>5.3%</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>13,880</td>
<td>2.0%</td>
<td>4.0%</td>
<td></td>
</tr>
</tbody>
</table>

PCI-CURE Study: CV Death or MI From Randomization

CREDO: Long-Term (1 Year) Benefits of Clopidogrel in PCI Patients

MI, stroke, or death – ITT population

<table>
<thead>
<tr>
<th>Months from randomization</th>
<th>Placebo*</th>
<th>Clopidogrel*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 11.5% Placebo
- 8.5% Clopidogrel

27% RRR
P=0.02

Combined endpoint occurrence (%)

* Plus ASA and other standard therapies.

Mechanism of Action of Prasugrel

# TRITON TIMI-38: Net Clinical Benefit

## Bleeding Risk Subgroups

### Post hoc analysis

<table>
<thead>
<tr>
<th>Prior Stroke / TIA</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk (%)</td>
<td>P int</td>
</tr>
<tr>
<td>Prior Stroke / TIA</td>
<td>+54</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>-16</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>&gt;= 75</th>
<th>&lt; 75</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk (%)</td>
<td>P int</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wgt</th>
<th>&lt; 60 kg</th>
<th>&gt;= 60 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk (%)</td>
<td>P int</td>
</tr>
<tr>
<td></td>
<td>+3</td>
<td>0.36</td>
</tr>
</tbody>
</table>

### Overall

<table>
<thead>
<tr>
<th>HR</th>
<th>Prasugrel Better</th>
<th>Clopidogrel Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Intensifying Platelet Inhibition — Navigating between Scylla and Charybdis
Deepak L. Bhatt, M.D.
Mechanism of Action of Ticagrelor

PLATO: CV Death, MI, or Stroke

Cumulative incidence (%)

No. at risk
Ticagrelor  9,333  8,628  8,460  8,219  6,743  5,161  4,147
Clopidogrel  9,291  8,521  8,362  8,124  6,743  5,096  4,047

Days after randomisation

HR 0.84 (95% CI 0.77–0.92), p=0.0003

PLATO: Secondary Endpoints

Myocardial infarction

- Clopidogrel: 6.9%
- Ticagrelor: 5.8%

HR 0.84 (95% CI 0.75–0.95), p=0.005

Cardiovascular death

- Clopidogrel: 5.1%
- Ticagrelor: 4.0%

HR 0.79 (95% CI 0.69–0.91), p=0.001

Major Bleeding: Non-CABG vs CABG

Onset and Duration of Ticagrelor Reversal - LTA

Volunteers in Cohorts 7-10 were given fixed 18-g doses of PB2452 for 8, 12, and 16 hours in Cohorts 7, 8, and 9/10, respectively.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>5min</th>
<th>0.25h</th>
<th>0.5h</th>
<th>1h</th>
<th>2h</th>
<th>3h</th>
<th>6h</th>
<th>8h</th>
<th>10h</th>
<th>12h</th>
<th>16h</th>
<th>20h</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>0.040</td>
<td>0.131</td>
<td>0.037</td>
<td>0.040</td>
<td>0.019</td>
<td>0.019</td>
<td>0.019</td>
<td>0.019</td>
<td>0.152</td>
<td>0.019</td>
<td>0.019</td>
<td>0.224</td>
</tr>
<tr>
<td>8</td>
<td>0.019</td>
<td>0.019</td>
<td>0.019</td>
<td>0.019</td>
<td>0.019</td>
<td>0.019</td>
<td>0.152</td>
<td>0.019</td>
<td>0.019</td>
<td>0.019</td>
<td>0.019</td>
<td>0.019</td>
</tr>
<tr>
<td>10</td>
<td>0.043</td>
<td>0.020</td>
<td>0.020</td>
<td>0.020</td>
<td>0.020</td>
<td>0.020</td>
<td>0.020</td>
<td>N/A</td>
<td>0.020</td>
<td>0.020</td>
<td>0.020</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Due to the small sample size for cohort 9 (n=3), statistical testing was not performed. For Cohorts 9 and 10, no 10-hour timepoint was collected.
P-values for time point 24 hours or above are not significant.

1. Immediate and sustained ticagrelor reversal with bolus + prolonged infusion of 18 g PB2452.
2. Significant reversal was observed 5 minutes after initiation of PB2452 infusion.
3. Duration of reversal was infusion-time dependent, lasting 20-24 hours with a 16-hour infusion.

LTA = light transmittance aggregometry; ADP is the agonist.

Algorithm to Assess GI Risk With Antiplatelet Therapy

1. Need for antiplatelet therapy
   - Yes
   - Assess GI risk factors

2. Test for *H. pylori*; treat if infected
   - Yes

3. History of ulcer complication
   - Yes
   - History of ulcer disease (nonbleeding)
   - GI bleeding
   - Dual antiplatelet therapy
   - Concomitant anticoagulant

4. More than one risk factor:
   - Yes
   - Aged 60 years or more
   - Corticosteroid use
   - Dyspepsia or GERD symptoms
   - PPI

COGENT Trial – Effect of PPI on Composite GI Events

HR=0.34, 95% CI=0.18-0.63

P<0.001 by the log-rank test

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Omeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1885</td>
<td>1455</td>
</tr>
<tr>
<td></td>
<td>1455</td>
<td>951</td>
</tr>
<tr>
<td></td>
<td>951</td>
<td>523</td>
</tr>
<tr>
<td></td>
<td>523</td>
<td>260</td>
</tr>
<tr>
<td></td>
<td>260</td>
<td>231</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>1876</td>
<td>1500</td>
</tr>
<tr>
<td></td>
<td>1500</td>
<td>987</td>
</tr>
<tr>
<td></td>
<td>987</td>
<td>553</td>
</tr>
<tr>
<td></td>
<td>553</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>215</td>
</tr>
</tbody>
</table>

Bleeding Reduction Strategies

- Use lowest effective dose of aspirin
- Radial access
- Minimize DAPT duration
- Preferential use of clopidogrel over prasugrel or ticagrelor for P2Y$_{12}$ inhibition
- In patients treated with a VKA: target INR to the lower therapeutic range
- In patients treated with a NOAC: use the lowest effective dose for stroke prevention
- Routine addition of a PPI and avoid use of NSAID

EXAMINATION:
EES vs BMS in Acute MI

Can 2nd Generation DES Reduce Death?

First generation drug eluting stents $\rightarrow$ Second generation drug eluting stents

$\downarrow$ Stent restenosis $\uparrow$ Stent thrombosis $\downarrow$ Stent restenosis $\downarrow$ Stent thrombosis

$\downarrow$ Death, MI $\uparrow$ Death, MI $\downarrow$ Death, MI $\downarrow$ Death, MI

$\uparrow\downarrow$ Death, MI

Any Stent Thrombosis: Probability Best

% Probability of Lowest Any ST Rate

ZES-R 12.59
ZES 0.98
BMS 0.01
SES 0.12
EES 86.32

PRECISE DAPT score: weight of the single predictors

- Hb: 100 pts
- Prior Bleed: 0 pts
- CrCl: 25 pts
- WBC: 0 pts
- Age: 19 pt
- PRECISE DAPT score: 0 pts
Effect of *Long (12-24 mo.)* vs. short (3-6 mo.) DAPT

ACS subgroup

**NET BENEFIT OF LONG DAPT**

- **Ischemia:** $-4.13\%$ $p<0.001$ NNT=24
- **Bleeding:** $+0.14\%$ $p=0.80$

**NET HARM LONG DAPT**

- **Ischemia:** $+1.54\%$ $p=0.61$
- **Bleeding:** $+2.61\%$ $p=0.032$ NNT=38

**Benefit**

- Ischemia (MI, Def. ST, Stroke, TVR)
- Bleeding (TIMI major or minor)

**Harm**

- Very Low
- Low
- Moderate
- High

**PRECISE DAPT**

- <25
- $\geq25$
In the context of a comprehensive clinical evaluation process, the PRECISE-DAPT score can support clinical decision making for treatment duration.

Non – high PRECISE DAPT Score (<25)
Ischemic benefit long DAPT (12-24m)
No increase in TIMI bleeding

High PRECISE DAPT Score ≥ 25
No ischemic benefit long DAPT
Increase in TIMI bleeding

PRECISE DAPT <25
Non-High

LONG DAPT (12-24 months) BETTER

PRECISE DAPT ≥25
High

SHORT DAPT (3-6 months) BETTER

www.precisedaptscore.com
Bivalirudin: 20 amino acid peptide

Gly-Pro-Arg-Pro
(active site binding region)

(Gly)_4

C-terminal dodecapeptide
(exosite 1-binding region)
Specific, reversible binding

Gly-Pro-Arg-Pro (active-site-binding portion)

(Gly)_4

C-terminal dodecapeptide (Exosite 1-binding portion)

Thrombin

Bivalirudin
Trial design

**Trial design**

**1:1 randomization**

- **6002 PCI Patients**
  - Urgent or elective PCI

- **Aspirin Clopid. Stent**

- **Bivalirudin**
  - 0.75 mg/kg bolus
  - 1.75 mg/kg/h procedure
  - Provisional abciximab or eptifibatide

- **Heparin**
  - 65 U/kg

- **Abciximab or Eptifibatide**

**Endpoints**

- 30-day
  - Death
  - MI
  - Revasc
  - Hemorrhage

**Economics**

- 6-month
  - Death, MI, revasc

- 1-year
  - Death
Primary endpoint – 30 days

Lincoff AM et al JAMA 2003; 289: 853-863
1-year mortality – overall result

Death rate was lower on bivalirudin at twelve months

Event is defined as the first time occurrence within the period. P-values are based on the Log-rank test.
ISAR-REACT: Trial Design

2159 low- to intermediate-risk patients undergoing elective PCI with stent placement

- Clopidogrel (600-mg loading dose)
- 325-500 mg Aspirin

Randomized

- Abciximab + 70 U/kg heparin (n = 1079)
  - Clopidogrel 150 mg/d until discharge, then 75 mg/d for 4 wk*

- Placebo + 140 U/kg heparin (n = 1080)
  - Clopidogrel 150 mg/d until discharge, then 75 mg/d for 4 wk*

End Points:
- **Primary**
  - 30-day death/MI/urgent target-vessel revascularization
- **Secondary**
  - 30-day bleeding complications

Results of the Efficacy Analysis

Incidence of primary endpoint, %

Abciximab vs. Placebo

RR = 1.05 [95% CI, 0.67-1.59]
Safety Analysis

- Major bleeding: P=0.37
- Minor bleeding: P=0.38, Abciximab 2.5, Placebo 1.9
- Thrombocytopenia: P=0.002, Abciximab 0.9, Placebo 0
- Transfusion: P=0.007, Abciximab 2.4, Placebo 0.9
Potential Relationship Between Bleeding and Mortality

- Major Bleeding
  - Hypotension
  - Cessation of ASA/Clop
  - Transfusion

- Ischemia
- Stent Thrombosis
- Inflammation

Mortality

Bhatt DL. In Braunwald: Harrison’s Online 2005.
**ACUITY Study Design**

Moderate and high risk unstable angina or NSTEMI undergoing an invasive strategy (N = 13,819)

- Moderate and high risk ACS (n=13,819)
  - Aspirin in all
  - Clopidogrel dosing and timing per local practice

- UFH/Enox + GP IIb/IIIa (n=4,603)
- Bivalirudin + GP IIb/IIIa (n=4,604)
- Bivalirudin Alone (n=4,612)

*Stratified by pre-angiography thienopyridine use or administration*

Stone GW et al. NEJM 2006;355:2203-16
Primary Endpoint Measures (ITT) – 30 Days

UFH/Enoxaparin + GPI vs. Bivalirudin + GPI

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Risk ratio ±95% CI</th>
<th>Bival + IIb/IIIa</th>
<th>UFH/Enox + IIb/IIIa</th>
<th>RR (95% CI)</th>
<th>p value (non inferior) (superior)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net clinical outcome</td>
<td>11.8%</td>
<td>11.7% (0.90-1.12)</td>
<td>&lt;0.001</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Ischemic composite</td>
<td>7.7%</td>
<td>7.3% (0.92-1.23)</td>
<td>0.015</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5.3%</td>
<td>5.0% (0.78-1.10)</td>
<td>&lt;0.001</td>
<td>0.38</td>
<td></td>
</tr>
</tbody>
</table>

Bivalirudin + IIb/IIIa better

UFH/Enox + IIb/IIIa better

Stone GW et al. NEJM 2006;355:2203-16
## Primary Endpoint Measures (ITT) – 30 Days

### UFH/Enoxaparin + GPI vs. Bivalirudin Alone

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Risk ratio ±95% CI</th>
<th>Bival</th>
<th>UFH/Enox + Ilb/IIIa</th>
<th>RR (95% CI)</th>
<th>p value (non inferior) (superior)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net clinical outcome</td>
<td>10.1%</td>
<td>11.7%</td>
<td>(0.77-0.97)</td>
<td>(&lt;0.001) (0.015)</td>
<td></td>
</tr>
<tr>
<td>Ischemic composite</td>
<td>7.8%</td>
<td>7.3%</td>
<td>(0.93-1.24)</td>
<td>(0.01) (0.32)</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.0%</td>
<td>5.0%</td>
<td>(0.43-0.65)</td>
<td>(&lt;0.001) (&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

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Stone GW et al. NEJM 2006;355:2203-16
Death at 1-year
UFH/Enoxaparin + GPIIb/IIIa vs. Bivalirudin alone

Bivalirudin alone better

UFH/Enox + IIb/IIIa better

Hazard ratio ± 95% CI

Biomarkers (CK/Trop)
Elevated (n=5072)
Normal (n=3402)

Pre Thienopyridine
Yes (n=5751)
No (n=3305)

Actual Treatment
PCI (n=5179)
CABG (n=1040)
Medical (n=2994)

1 yr KM estimate

HR (95% CI) P_{int}

Bivalirudin alone
4.8%
2.4%
3.5%
4.0%
3.2%

UFH/Enox + IIb/IIIa
5.094 (0.80-1.34)
3.684 (0.55-1.28)
0.90 (0.68-1.18)
1.05 (0.74-1.48)
0.95 (0.70-1.29)

Influence of Major Bleeding and MI in the First 30 Days on Risk of Death Over 1 Year

Cox model adjusted for baseline predictors, with non-CABG major bleeding and MI as time-updated covariates

<table>
<thead>
<tr>
<th>Event</th>
<th>HR ± 95% CI</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td></td>
<td>2.89 (2.24-3.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td></td>
<td>2.47 (1.87-3.27)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HORIZONS AMI Trial Design

- Open-label, randomized, prospective, multicenter trial

3,602 pts with STEMI with symptom onset ≤12 hours

Aspirin, thienopyridine

UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide)

Bivalirudin monotherapy (± provisional GP IIb/IIIa)

Primary PCI Strategy

3,000 pts eligible for stent randomization

Bare metal stent

TAXUS® paclitaxel-eluting stent

Clinical FU at 30 days, 1 year, and then yearly through 5 years

Bivalirudin significantly reduced both primary end points.

- **NACE**: Bivalirudin monotherapy (n=1,800) vs. Heparin + GP IIb/IIIa inhibitor (n=1,802)
  - **Bivalirudin**: 9.2%
  - **Heparin + GP IIb/IIIa**: 41%
  - **P-value**: P=0.006

- **Major bleeding**: Bivalirudin monotherapy (n=1,800) vs. Heparin + GP IIb/IIIa inhibitor (n=1,802)
  - **Bivalirudin**: 4.9%
  - **Heparin + GP IIb/IIIa**: 8.3%
  - **P-value**: P<0.001

- **MACE**: Bivalirudin monotherapy (n=1,800) vs. Heparin + GP IIb/IIIa inhibitor (n=1,802)
  - **Bivalirudin**: 5.4%
  - **Heparin + GP IIb/IIIa**: 5.5%
  - **P-value**: P=1.00

1-Year All-Cause Mortality

Number at risk
Bivalirudin alone  1800  1705  1684  1669  1520
Heparin+GPIIb/IIIa  1802  1678  1663  1646  1486

Balancing Ischemia and Bleeding

Gutierrez A and Bhatt DL. EHJ 2014.
Time from hospital admission or first medical contact to coronary angiography in studies of ACS & STEMI

PCI-CURE
6 days

RITA-3
3 days

CRUSADE
23 hours

ACUITY
20 hours

CURRENT OASIS 7 NSTE-ACS
3 hours

ACCOAST
4 hours


Current OASIS 7 STEMI
7 hours

TRACER
4 hours

ASSENT-4 PCI
2 hours

PLATO STEMI
1 hour

ATOLL
42 minutes

EUROMAX
50 minutes

HORIZONS AMI
2 hours

CURRENT OASIS 7 STEMI
30 minutes

ATLANTIC
48 minutes

PCI-CLARITY
3 days

Capodanno D & Angiolillo DJ. Circ Cardiovasc Interv 2015
Early P2Y12 inhibition in ST-segment elevation myocardial infarction:

Bridging the gap.
Cangrelor

- Direct platelet P2Y\textsubscript{12} receptor antagonist
- ATP analogue MW=800 Daltons
- Parenteral administration
- T1/2 = 3 to 6 minutes
- Offset = 60 minutes

CHAMPION PHOENIX Study Design

CHAMPION PHOENIX
N = 10,900 MITT
SA/ NSTE-ACS/ STEMI
Patients requiring PCI
P2Y\textsubscript{12} inhibitor naïve

1 Randomization occurred once suitability for PCI was confirmed either by angiography or STEMI diagnosis. Double blind study medication was administered as soon as possible following randomization.

2 Study drug Infusion (cangrelor or matching placebo) was continued for 2-4 hours at the discretion of the treating physician. At the end of the infusion patients received a loading dose of clopidogrel or matching placebo and were transitioned to maintenance clopidogrel therapy.

3 Clopidogrel loading dose (or matching placebo) was administered as directed by the investigator. At the time of patient randomization, a clopidogrel loading dose of 600 mg or 300 mg was specified by the investigator.

MITT=modified intent-to-treat; NSTE-ACS=non-ST-elevation acute coronary syndrome; PCI=percutaneous coronary intervention; SA=stable angina; STEMI=ST-elevation MI.
Death/ MI/ IDR/ Stent Thrombosis within 48 Hours

Patient at Risk
- Cangrelor: 5472, 5233, 5229, 5225, 5223, 5221, 5220, 5217, 5213
- Clopidogrel: 5470, 5162, 5159, 5155, 5152, 5151, 5151, 5147, 5147

Event Rate (%)
- Cangrelor: 4.7%
- Clopidogrel: 5.9%

Log Rank P Value = 0.006

Stent Thrombosis within 48 Hours

Log Rank P Value = 0.01

Patient at Risk
- Cangrelor: 5472 5426 5421 5419 5419 5418 5417 5416 5414
- Clopidogrel: 5470 5392 5389 5388 5386 5385 5385 5383 5383

Event Rate (%)
- Cangrelor: 0.8%
- Clopidogrel: 1.4%

## Non-CABG Bleeding at 48 Hours, Safety

<table>
<thead>
<tr>
<th>Bleeding Scale</th>
<th>Cangrelor (N=5529)</th>
<th>Clopidogrel (N=5527)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO Severe</td>
<td>9 (0.16%)</td>
<td>6 (0.11%)</td>
<td>1.50 (0.53,4.22)</td>
<td>0.44</td>
</tr>
<tr>
<td>GUSTO Moderate</td>
<td>22 (0.4%)</td>
<td>13 (0.2%)</td>
<td>1.69 (0.85,3.37)</td>
<td>0.13</td>
</tr>
<tr>
<td>GUSTO Severe + Moderate</td>
<td>31 (0.6%)</td>
<td>19 (0.3%)</td>
<td>1.63 (0.92,2.90)</td>
<td>0.09</td>
</tr>
<tr>
<td>TIMI Major</td>
<td>5 (0.1%)</td>
<td>5 (0.1%)</td>
<td>1.00 (0.29,3.45)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>TIMI Minor</td>
<td>9 (0.2%)</td>
<td>3 (0.1%)</td>
<td>3.00 (0.81,11.10)</td>
<td>0.08</td>
</tr>
<tr>
<td>TIMI Major + Minor</td>
<td>14 (0.3%)</td>
<td>8 (0.1%)</td>
<td>1.75 (0.73,4.18)</td>
<td>0.2</td>
</tr>
<tr>
<td>Any Blood Transfusion</td>
<td>25 (0.5%)</td>
<td>16 (0.3%)</td>
<td>1.56 (0.83,2.93)</td>
<td>0.16</td>
</tr>
<tr>
<td>ACUITY Major</td>
<td>235 (4.3%)</td>
<td>139 (2.5%)</td>
<td>1.72 (1.39,2.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACUITY w/out hematoma</td>
<td>42 (0.8%)</td>
<td>26 (0.5%)</td>
<td>1.62 (0.99,2.64)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

48-Hour Stent Thrombosis
According to the # of HRF per Patient, and Randomization and Presentation

The Platelet Inhibition with CANgrelor and Crushed TICagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention (CANTIC) study

Francesco Franchi, MD, Fabiana Rollini, MD, Andrea Rivas, MD, Mustafa Wali, MD, Maryuri Briceno, MD, Malhar Agarwal, MD, Zubair Shaikh, MD, Ahmed Nawaz, MD, Gabriel Silva, MD, Latonya Been, AAS, Ramez Smairat, MD, Marc Kaufman, MD, Andres Pineda, MD, Siva Suryadevara, MD, Daniel Soffer, MD, Martin M Zenni, MD, Theodore A Bass, MD, Dominick J Angiolillo, MD, PhD

Circulation 2019
https://doi.org/10.1161/CIRCULATIONAHA.118.038317

Clinicaltrials.gov identifier: NCT03247738
Prospective, randomized, double-blind, placebo-controlled, parallel design study aimed to assess the PD effects of cangrelor vs placebo in patients undergoing P-PCI (n=50) concomitantly treated with crushed ticagrelor.

**PD testing**
- Baseline
- 5 min
- 30 min
- 1 h
- End of PCI
- 2 h
- 1 h post infusion
- 2 h post infusion

**Randomization**
1:1

**Crushed Ticagrelor 180mg**
- plus PLACEBO IV
- plus CANGRELOR IV

www.clinicaltrials.gov Unique Identifier: NCT03247738

PRU levels at 30 minutes (primary end point) were significantly lower with cangrelor compared with placebo [63 (32-93) vs. 214 (183-245); mean difference: 152; 95% CI: 108-195; p<0.001].

All patients concomitantly treated with 180mg LD of crushed ticagrelor at time of randomization (time 0)

End of PCI: 41 (21-54) minutes

Bridging with Cangrelor
Single-Center, Tertiary Care Experience (n=31)

- Cardiac surgery: 42%
- Gl surgery: 16%
- Spine/Orthopaedic surgery: 7%
- Thoracic surgery: 3%
- Limited enteral access/absorption: 16%
- High perceived bleed risk: 16%
Primary Efficacy Endpoint: MACE

To prevent one primary endpoint event would require 49 (95% CI 28 to 164) patients to be treated for 4 years.

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

Steg PG, ACC 2018, Orlando, FL.
# REDUCE-IT Tertiary Endpoints: Revascularization

<table>
<thead>
<tr>
<th>Revascularization Endpoint</th>
<th>Icosapent Ethyl n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary</td>
<td>376/4089 (9.2%)</td>
<td>544/4090 (13.3%)</td>
<td>0.66 (0.58, 0.76)</td>
</tr>
<tr>
<td>Emergent</td>
<td>41/4089 (1.0%)</td>
<td>65/4090 (1.6%)</td>
<td>0.62 (0.42, 0.92)</td>
</tr>
<tr>
<td>Urgent</td>
<td>181/4089 (4.4%)</td>
<td>268/4090 (6.6%)</td>
<td>0.66 (0.54, 0.79)</td>
</tr>
<tr>
<td>Elective</td>
<td>194/4089 (4.7%)</td>
<td>278/4090 (6.8%)</td>
<td>0.68 (0.57, 0.82)</td>
</tr>
<tr>
<td>Carotid Revascularization</td>
<td>31/4089 (0.8%)</td>
<td>26/4090 (0.6%)</td>
<td>1.18 (0.70, 1.98)</td>
</tr>
<tr>
<td>Salvage Revascularization</td>
<td>0/4089 (0.0%)</td>
<td>2/4090 (0.0%)</td>
<td>0.00 (0.00, -)</td>
</tr>
</tbody>
</table>

25 Years of Pharmacotherapy in PCI

- GPIIb/IIIa inhibitors a major advance in the aspirin/heparin era
- Advent of DAPT revolutionized PCI/stenting
- Clopidogrel really transformed the field
- Prasugrel, ticagrelor better in low bleeding risk patients
- Data for bivalirudin replacing heparin+GPIIb/IIIa inhibitors
- Cangrelor a newer option for intravenous antiplatelet blockade
- Impact of radial access, second generation DES, shorter times to PCI
- Other ongoing developments; this field just keeps evolving!
Thank You!

Ankur Kalra, MD
Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic,
225 West Exchange St, Suite 225, Akron, Ohio 44302
kalraa@ccf.org