The Role of New Anti-Platelet Agents: Will Prasugrel and Ticagrelor Change the DES Landscape?

Roxana Mehran, MD
Associate Professor of Medicine
Columbia University Medical Center
The Cardiovascular Research Foundation
Disclosures: Roxana Mehran

Clinical Research Support to Columbia: Sanofi/Aventis, BMS, Bracco

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Targets for antiplatelet therapies

- Ticlopidine
- Clopidogrel
- Prasugrel
- AZD6140
- Cangrelor
- PRT060128

- SCH 530348
- Ticlopidine
- Clopidogrel
- Prasugrel
- AZD6140
- Cangrelor
- PRT060128

- Dipyridamole
- PDE

- ASA
- Dipyridamole

- TXA₂
- ADP

- PAR-1
- Activation
- cAMP

- Thrombin
- Abciximab
- Eptifibatide
- Tirofiban

- GP IIb/IIIa (Fibrinogen receptor)

- Collagen
- TXA₂

- cAMP = cyclic adenosine monophosphate, COX = cyclooxygenase, PAR = protease-activated receptor, PDE = phosphodiesterase

## Combination Antiplatelet Therapy Reduces Coronary Events after Stenting

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Events</th>
<th>Cumulative Event Rate (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall (1996)</td>
<td>1996</td>
<td>226</td>
<td>0.8, 3.9</td>
<td>0.1</td>
</tr>
<tr>
<td>ISAR (1997)</td>
<td>1997</td>
<td>517</td>
<td>1.6, 6.2</td>
<td>0.01</td>
</tr>
<tr>
<td>STARS (1998)</td>
<td>1998</td>
<td>1653</td>
<td>0.5, 3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MATTIS (1998)</td>
<td>1998</td>
<td>350</td>
<td>2.7, 5.6</td>
<td>0.07</td>
</tr>
<tr>
<td>FANTASTIC (1998)</td>
<td>1998</td>
<td>485</td>
<td>5.7, 8.3</td>
<td>0.37</td>
</tr>
</tbody>
</table>

- **ASA + Ticlopidine**: Red
- **ASA only**: Blue
- **ASA + Warfarin**: Yellow

### Notes

Clopidogrel Trials – ACS/CAD

- Acute STEMI
- UA/NSTEMI
- PCI
- Long-term 2° 1° prevention

- COMMIT (CCS-2)
- CLARITY TIMI 28
- CURE
- CREDO
- CAPRIE Lancet 1996
- CHARISMA

STEMI
UA/ NSTEMI PCI

- 30 Days + Benefit
- 1 Year + Benefit
- 1 Year + Benefit
- 1-3 Years + Benefit

MI / stroke PAD
2.5 years Benefit selected 2° Prev
ARMYDA-2 Study: Design and Primary End Point

255 patients with stable CAD or NSTEMI prior to PCI
13% received GP IIb/IIIa inhibitors
20% received drug-eluting stents

Randomized 4-8 Hours Pre-PCI

High Loading Dose of Clopidogrel
600 mg
Pre-PCI

Standard Loading Dose of Clopidogrel
300 mg
Pre-PCI

Primary composite of death, MI, or target vessel revasc. at 30 days

P = .041

12%

4%

600 mg
300 mg

ARMYDA-2, Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty.
25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)
✓ Planned Early (<24 h) Invasive Management with intended PCI
✓ Ischemic ECG Δ (80.8%) or ↑cardiac biomarker (42%)

Randomized to receive (2 X 2 factorial):
CLOPIDOGREL: Double-dose (600 mg then 150 mg/d x 7d then 75 mg/d) vs Standard dose (300 mg then 75 mg/d)

ASA: High Dose (300-325 mg/d) vs Low dose (75-100 mg/d)

PCI 17,232 (70%)

Angio 24,769 (99%)

No PCI 7,855 (30%)

No Sig. CAD 3,616
CABG 1,809
CAD 2,430

Clop in 1st 7d (median) 7d 7d 2d

Complete Followup 99.8%

Efficacy Outcomes:
CV Death, MI or stroke at day 30
Stent Thrombosis at day 30

Safety Outcomes:
Bleeding (CURRENT defined Major/Severe and TIMI Major)

Key Subgroup:
PCI v No PCI
Clopidogrel: Double vs Standard Dose
Definite Stent Thrombosis (Angio confirmed)

- Clopidogrel Standard Dose
- Clopidogrel Double Dose

HR 0.58
95% CI 0.42-0.79
P=0.001

42% RRR
Clopidogrel: Double vs Standard Dose
Primary Outcome: PCI Patients

CV Death, MI or Stroke

Cumulative Hazard

Days

Clopidogrel Standard

Clopidogrel Double

15% RRR

HR 0.85
95% CI 0.74-0.99
P=0.036
Definite Stent Thrombosis in 4 Groups (Angiographically Proven)

|                  | Standard Clop | Double Clop | HR  | P    | P Int
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High ASA</td>
<td>1.2</td>
<td>0.6</td>
<td>0.49</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Low ASA</td>
<td>1.2</td>
<td>0.8</td>
<td>0.6</td>
<td>0.058</td>
<td>0.35</td>
</tr>
</tbody>
</table>
Primary Endpoint CV
Death, MI, Stroke

- **Clopidogrel**
  - HR 0.80
  - \( P = 0.0003 \)
  - ITT = 13,608
  - LTFU = 14 (0.1%)
  - 12.1 (%)
  - (781)
  - 9.9 (%)
  - (643)
  - NNT = 46

- **Prasugrel**
  - HR 0.77
  - \( P = 0.0001 \)
  - ITT = 13,608
  - LTFU = 14 (0.1%)
  - HR 0.81
  - (0.73-0.90)
  - \( P = 0.0004 \)
  - NNT = 46
Stent Thrombosis (ARC Definite + Probable)

Endpoint (%)

- Any Stent at Index PCI
  N= 12,844

Days

0 30 60 90 180 270 360 450

Clopidogrel

- HR 0.48
- $P < 0.0001$
- NNT = 77

Prasugrel

- 1.1 (142)
- N= 12,844
- $P < 0.0001$
- NNT = 77

NNT = 77
Mortality During Follow up (%) Post-Stent Thrombosis

HR 13.1 (9.8 – 17.5)  
P<0.0001

25.9

2.6

% of Subjects

Stent Thrombosis  
N=210

No Stent Thrombosis  
N=12634
Balance of Efficacy and Safety

- CV Death / MI / Stroke
  - Prasugrel: 12.1 events
  - Clopidogrel: 9.9 events
  - HR 0.81 (0.73-0.90)
  - P=0.0004

- TIMI Major NonCABG Bleeds
  - Prasugrel: 2.4 events
  - Clopidogrel: 1.8 events
  - HR 1.32 (1.03-1.68)
  - P=0.03

NNT = 46
NNH = 167
Ticagrelor (AZD 6140): an oral reversible P2Y$_{12}$ antagonist

Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- **Direct acting**
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the P2Y$_{12}$ receptor
  - Greater inhibition of platelet aggregation than clopidogrel

- **Reversibly bound**
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of all circulating platelets
PLATO study design

Primary endpoint:
CV death + MI + Stroke

Primary safety endpoint:
Total major bleeding

PLATO = percutaneous coronary intervention; ASA = acetylsalicylic acid; CV = cardiovascular; TIA = transient ischaemic attack
K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days after randomisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9,291</td>
<td>9,333</td>
</tr>
<tr>
<td>60</td>
<td>8,628</td>
<td>8,460</td>
</tr>
<tr>
<td>120</td>
<td>8,460</td>
<td>8,219</td>
</tr>
<tr>
<td>180</td>
<td>8,219</td>
<td>6,743</td>
</tr>
<tr>
<td>240</td>
<td>6,743</td>
<td>5,161</td>
</tr>
<tr>
<td>300</td>
<td>5,161</td>
<td>4,147</td>
</tr>
<tr>
<td>360</td>
<td>4,147</td>
<td></td>
</tr>
</tbody>
</table>

HR 0.84 (95% CI 0.77–0.92), p=0.0003

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

Duke Clinical Research Institute
Secondary efficacy endpoints over time

**Myocardial infarction**

- Clopidogrel
- Ticagrelor

Cumulative incidence (%) over days after randomisation with HR 0.84 (95% CI 0.75–0.95), p=0.005

**Cardiovascular death**

- Clopidogrel
- Ticagrelor

Cumulative incidence (%) over days after randomisation with HR 0.79 (95% CI 0.69–0.91), p=0.001

---

**No. at risk**

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days after randomisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9,333</td>
<td>9,291</td>
</tr>
<tr>
<td>60</td>
<td>8,678</td>
<td>8,560</td>
</tr>
<tr>
<td>120</td>
<td>8,520</td>
<td>8,405</td>
</tr>
<tr>
<td>180</td>
<td>8,279</td>
<td>8,177</td>
</tr>
<tr>
<td>240</td>
<td>6,796</td>
<td>6,703</td>
</tr>
<tr>
<td>300</td>
<td>5,210</td>
<td>5,136</td>
</tr>
<tr>
<td>360</td>
<td>4,191</td>
<td>4,109</td>
</tr>
</tbody>
</table>
## Stent thrombosis

*(evaluated in patients with any stent during the study)*

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (n=5,640)</th>
<th>Clopidogrel (n=5,649)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stent thrombosis, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>71 (1.3)</td>
<td>106 (1.9)</td>
<td>0.67 (0.50–0.91)</td>
<td>0.009</td>
</tr>
<tr>
<td>Probable or definite</td>
<td>118 (2.1)</td>
<td>158 (2.8)</td>
<td>0.75 (0.59–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Possible, probable, definite</td>
<td>155 (2.8)</td>
<td>202 (3.6)</td>
<td>0.77 (0.62–0.95)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Time-at-risk is calculated from first stent insertion in the study or date of randomisation*
Time to major bleeding – primary safety event

**PLATO**

<table>
<thead>
<tr>
<th>Days from first IP dose</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>11.58</td>
<td>11.20</td>
</tr>
<tr>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>360</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR 1.04 (95% CI 0.95–1.13), p=0.434

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9,235</td>
<td>9,186</td>
</tr>
<tr>
<td>60</td>
<td>7,246</td>
<td>7,305</td>
</tr>
<tr>
<td>120</td>
<td>6,826</td>
<td>6,930</td>
</tr>
<tr>
<td>180</td>
<td>6,545</td>
<td>6,670</td>
</tr>
<tr>
<td>240</td>
<td>5,129</td>
<td>5,209</td>
</tr>
<tr>
<td>300</td>
<td>3,783</td>
<td>3,841</td>
</tr>
<tr>
<td>360</td>
<td>3,433</td>
<td>3,479</td>
</tr>
</tbody>
</table>
Safety of New DAPT Regimens
3 Active Controlled Trials (vs Standard Clop)

**Significant bleeding (%)**

- **ASA + Clopidogrel**
  - CURRENT: 2.0%
  - TRITON: 3.8%
  - PLATO: 3.8%

- **New Regimen**
  - CURRENT: 2.5%
  - TRITON: 5.0%
  - PLATO: 4.5%

**Non-CABG related bleeding**

- **CURRENT**
  - Major bleed: 2.0%
  - TIMI major+minor bleed: 3.8%

- **TRITON**
  - Major bleed: 5.0%
  - TIMI major+minor bleed: 4.5%

- **PLATO**
  - Major bleed: 3.2%
  - TIMI major+minor bleed: 3.2%

**CABG related bleeding**

- **CURRENT**
  - Major bleed: 2.0%
  - TIMI major+minor bleed: 3.8%

- **TRITON**
  - Major bleed: 3.2%
  - TIMI major+minor bleed: 3.2%

- **PLATO**
  - Major bleed: 7.9%
  - TIMI major+minor bleed: 7.4%

Efficacy of New DAPT Rx in ACS
3 Active Controlled Trials (vs Standard Clop)

<table>
<thead>
<tr>
<th></th>
<th>CURRENT</th>
<th>Triton</th>
<th>Plato</th>
<th>Current ST</th>
<th>Triton ST</th>
<th>Plato ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant Events (%)</td>
<td>4.4%</td>
<td>12.1%</td>
<td>11.7%</td>
<td>2.3%</td>
<td>2.4%</td>
<td>2.8%</td>
</tr>
<tr>
<td>P</td>
<td>P=0.37</td>
<td>P&lt;0.001</td>
<td>P=0.0003</td>
<td>P=0.02</td>
<td>P&lt;0.001</td>
<td>P=0.02</td>
</tr>
<tr>
<td>N</td>
<td>25,087</td>
<td>13,608</td>
<td>18,864</td>
<td>15,087</td>
<td>13,608</td>
<td>18,864</td>
</tr>
<tr>
<td>15-month FU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Year FU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASA + Clopidogrel
New Regimen
How will these results change the landscape?
Stent thrombosis: Past and present trial results

30 day results
BMS Trials 1991-1997

16%
Coumadin

High-pressure balloons and Ticlid®

0.6%

4 year results definite and probable ARC
Pooled DES vs BMS Trials 2002-2006

Non Target Lesion Events outnumber stent specific outcomes in long term follow up

HCRI database N=6186 with complete 5y follow up

Stent thrombosis accounts for a minority of clinical events

<table>
<thead>
<tr>
<th></th>
<th>SES</th>
<th>BMS</th>
<th>PES</th>
<th>BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>57 (6.7%)</td>
<td>45 (5.3%)</td>
<td>86 (6.1%)</td>
<td>92 (6.6%)</td>
</tr>
<tr>
<td>ST Death</td>
<td>4 (0.5%)</td>
<td>5 (0.6%)</td>
<td>7 (0.5%)</td>
<td>5 (0.4%)</td>
</tr>
<tr>
<td>ST death/total death</td>
<td>7%</td>
<td>11%</td>
<td>8%</td>
<td>6%</td>
</tr>
</tbody>
</table>

ST represents less about 10% of mortality, and a smaller proportion of death/MI composite. Clinical endpoints may not distinguish differences in ST

Bleeding and Mortality

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

- Ischemia
- Stent Thrombosis

- Mortality

Bhatt DL. In Braunwald EB, Harrison’s Online. 2005.
### Time-updated covariate adjusted Cox model relating 30-day events to 30-day mortality

- **Complete model** in 3,124 pts with successfully implanted stents

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>HR [95% CI]</th>
<th>P-value</th>
<th>Attributable Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis (definite)</td>
<td>10.62</td>
<td>&lt;0.001</td>
<td>4.5* [3.7, 4.8]</td>
</tr>
<tr>
<td>Incidence 57 (1.8%) 5 deaths with event</td>
<td>[3.96, 28.48]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding (non CABG)</td>
<td>6.22</td>
<td>&lt;0.001</td>
<td>15.1** [12.6, 16.4]</td>
</tr>
<tr>
<td>Incidence 195 (6.2%) 18 deaths with event</td>
<td>[3.33, 11.60]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard Ratio [95% CI]

- 0.01
- 0.1
- 1
- 10
- 100

- **C-statistic = 0.87.**
- Attributable deaths = N deaths among pts with the time updated event (attribute) X (adj. HR – 1)/adj. HR
- *8.3% of 54 total deaths
- **28.0% of 54 total deaths

Stent thrombosis: Incidence 57 (1.8%) 5 deaths with event

Major bleeding (non CABG): Incidence 195 (6.2%) 18 deaths with event
## Definitions of Major/Severe Bleeding in Randomized Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Type of bleeding</th>
<th>GUSTO</th>
<th>TIMI phase I</th>
<th>TIMI phase II</th>
<th>REPLACE-2</th>
<th>OASIS-5 ESSENCE</th>
<th>CURE</th>
<th>STEEPLE</th>
<th>ACUITY HORIZONS</th>
<th>PLATO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial/intracerebral</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Intraocular</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Bleeding causing hemodynamic compromise</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Bleeding requiring surgical intervention</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hematoma &gt;5cm at the puncture site</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Transfusion, units</td>
<td>≥1</td>
<td>≥1</td>
<td>≥1</td>
<td>≥2</td>
<td>≥2</td>
<td>≥2</td>
<td>≥1</td>
<td>≥1</td>
<td>≥4</td>
</tr>
<tr>
<td>Decrease in Hgb with overt bleeding, g/dL</td>
<td>-</td>
<td>≥5.0*</td>
<td>≥3.0</td>
<td>≥3.0</td>
<td>-</td>
<td>≥3.0</td>
<td>≥3.0</td>
<td>≥5.0</td>
<td>≥5.0</td>
</tr>
<tr>
<td>Decrease in Hgb without overt bleeding, g/dL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>≥4.0</td>
<td>-</td>
<td>≥5.0</td>
<td>-</td>
<td>≥4.0</td>
<td>-</td>
</tr>
</tbody>
</table>

*Or decrease in Hct ≥15%
## Influence of Bleeding Severity within 30 Days After PCI on the Risk of Death Over 1 Year

Baseline covariate-adjusted time-updated Cox multivariable model

<table>
<thead>
<tr>
<th>Type of Bleed</th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>Attributable deaths within 1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI major bleed</td>
<td>4.85 (3.56-6.60)</td>
<td>&lt;0.001</td>
<td>53</td>
</tr>
<tr>
<td>ACUITY major (non TIMI major) bleed with transfusion*</td>
<td>2.98 (2.10-4.24)</td>
<td>&lt;0.001</td>
<td>40</td>
</tr>
<tr>
<td>ACUITY major (non TIMI major) bleed without transfusion*</td>
<td>1.79 (1.09-2.93)</td>
<td>0.02</td>
<td>17</td>
</tr>
<tr>
<td>Hematoma ≥5 cm only</td>
<td>1.30 (0.58-2.92)</td>
<td>0.53</td>
<td>6</td>
</tr>
</tbody>
</table>

* Excluding hematomas if the only criteria
Each patient is represented only once according to their most severe bleed
Change in Platelet Aggregation between Pre- and Post-Clopidogrel Time Points: Distribution

From Serebruany, et al. JACC 2005;45:246-251
Impact of clopidogrel hyporesponsiveness after stents: 683 pts with ACS after BMS or DES were tested by the VerifyNow P2Y12 assay within 24 hrs after 600 mg clopidogrel load. By ROC, pts with PRU ≥240 defined as nonresponders.


- CV death or MI: P=0.01
- CV death: P=0.03
- MI: P=0.006
- TLR: P=0.23

Responders (n=699) Non Responders (PRU ≥240; n=219, 32%)
Impact of clopidogrel hyporesponsiveness after DES: 804 pts after PES or SES were tested by LTA 12-18 hrs after 600 mg clopidogrel load. Pts with platelet aggregation by 10 umol ADP ≥90th percentile of controls (70%) were defined as non responders.

Impact of clopidogrel hyporesponsiveness after DES

Clopidogrel responsiveness in loaded pts was assessed in 380 pts receiving SES by the Accumetrics VerifyNow P2Y12 assay. Hyporesponsiveness was defined as post-treatment reactivity PRU ≥235 (~ the upper tertile) by ROC analysis to optimize prediction of 6 month MACE.

![Bar graph showing 6-month out-of-hospital events (CV death, Nonfatal MI, Stent thrombosis, Death, MI or ST) for PRU <235 and PRU ≥235 groups.]

Price MJ et al. EHJ 2008;29:992–1000
ADAPT-DES
Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents

11,000 – 15,000 pts
10-15 sites in US, Germany, Italy

Aspirin: ≥300 mg oral ≥6 hrs or 324 mg chewed or 250 mg IV ≥30 mins prior to PCI
Clopidogrel: Assess ≥6’ after 600 mg or ≥12’ after 300 mg or ≥5d after 75 mg qd
GP IIb/IIIa inhibitor: Optional per standard of care, but washout required

PCI with non investigational DES
(IVUS/VH substudy; n=3000)

Assessment of platelet function: Accumetrics VerifyNow Aspirin, VerifyNow P2Y12, and VerifyNow IIb/IIIa assays (results blinded to investigators)

Clinical FU ≥2 yrs (5 yrs max)
Angio core lab assessment all STs w/1:3 matching controls
In patients in whom subacute thrombosis may be catastrophic or lethal (unprotected left main, bifurcating left main, or last patent coronary vessel), platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg per day if less than 50% inhibition of platelet aggregation is demonstrated.

Successful PCI with DES without major complication or GPIIb/IIIa use

Post-PCI VerifyNow P2Y12 Assay (PRU) 12-24 hours post-PCI

N ~ 6600

Yes

PRU ≥ 230?

Non-Responder

No

Responder

Random Selection

A N = 1100

“Tailored Therapy” clopidogrel 150-mg/day

B N = 1100

“Standard Therapy” clopidogrel 75mg +placebo/day

C N = 583

“Standard Therapy” clopidogrel 75mg +placebo/day

Clinical Follow-up And VerifyNow Assessment at 30 days, 6 months

Primary Endpt: 6 month CV Death, Non-Fatal MI, ARC Def/Prob Stent Thrombosis

Study PI: Matthew J. Price, MD

Coordinating Center: Scripps Advanced Clinical Trials
In patients who have undergone PCI, clopidogrel 75 mg daily should be given for at least 1 month after bare-metal stent implantation (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks), 3 months after sirolimus stent implantation, and 6 months after paclitaxel stent implantation, and ideally up to 12 months in patients who are not at high risk of bleeding.

Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy


Although the safety profiles of coronary stents eluting sirolimus or paclitaxel do not seem to differ from those of bare metal stents in the short-to-medium term, concern has arisen about the potential for late stent thromboses related to delayed endothelialisation of the stent struts. We report four cases of angiographically-confirmed stent thrombosis that occurred late after elective implantation of polymer-based paclitaxel-eluting (343 and 442 days) or sirolimus-eluting (335 and 375 days) stents, and resulted in myocardial infarction. All cases arose soon after antiplatelet therapy was interrupted. If confirmed in systematic long-term follow-up studies, our findings have potentially serious clinical implications.

Clopidogrel for >1-year?
50% of patients continue on Dual Antiplatelet Therapy

50% of patients receive aspirin + placebo

All patients on aspirin + open-label thienopyridine therapy for 12 months

1:1 Randomization at month 12

Total 33 month patient evaluation including additional 3-month follow-up

DES n = 15,245
BMS n = 5,400

12 mos.

18 mos.
MI, Bleeding and All-Cause Mortality

Large RCTs with significant reductions in death

<table>
<thead>
<tr>
<th>Trial</th>
<th>MI</th>
<th>Major bleed*</th>
<th>Death (time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OASIS-5 (n=20,078)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Enoxaparin</td>
<td>4.1%</td>
<td>5.0%</td>
<td>↓ 6.5%</td>
</tr>
<tr>
<td>- Fondaparinux</td>
<td>3.9%</td>
<td>3.1%</td>
<td>↓ 5.8%</td>
</tr>
<tr>
<td>HORIZONS (n=3,602)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- UFH/GPI</td>
<td>1.8%</td>
<td>10.8%</td>
<td>↓↓ 4.8%</td>
</tr>
<tr>
<td>- Bivalirudin</td>
<td>1.8%</td>
<td>6.8%</td>
<td>↓ 3.5%</td>
</tr>
<tr>
<td>PLATO (n=18,624)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Clopidogrel</td>
<td>6.9%</td>
<td>11.2%</td>
<td>↓ 5.9%</td>
</tr>
<tr>
<td>- Ticagrelor</td>
<td>5.8%</td>
<td>11.6%</td>
<td>↓ 4.5%</td>
</tr>
</tbody>
</table>

*TIMI major + minor or protocol major

Stone, GW NEJM 2010
## MI, Bleeding and All-Cause Mortality

Large RCTs without significant reductions in death

<table>
<thead>
<tr>
<th>Trial</th>
<th>MI</th>
<th>Major bleed*</th>
<th>Death (time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA (n=15,603)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Placebo</td>
<td>2.0%</td>
<td>1.3%</td>
<td>4.8%</td>
</tr>
<tr>
<td>- Clopidogrel</td>
<td>1.9%</td>
<td>-</td>
<td>4.8%</td>
</tr>
<tr>
<td>CURRENT (n=25,807)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- LD Clopidogrel</td>
<td>2.2%</td>
<td>2.0%</td>
<td>2.2%</td>
</tr>
<tr>
<td>- HD Clopidogrel</td>
<td>1.9%</td>
<td>2.5%</td>
<td>2.1%</td>
</tr>
<tr>
<td>SYNERGY (n=10,027)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- UFH</td>
<td>12.7%</td>
<td>7.6%</td>
<td>7.3%</td>
</tr>
<tr>
<td>- Enoxaparin</td>
<td>11.7%</td>
<td>9.1%</td>
<td>7.7%</td>
</tr>
<tr>
<td>REPLACE-2 (n=6,010)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- UFH/GPI</td>
<td>6.2%</td>
<td>4.1%</td>
<td>1.4%</td>
</tr>
<tr>
<td>- Bivalirudin</td>
<td>7.0%</td>
<td>2.4%</td>
<td>1.0%</td>
</tr>
<tr>
<td>ACUITY (n=9,215)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- UFH/GPI</td>
<td>4.9%</td>
<td>11.8%</td>
<td>3.9%</td>
</tr>
<tr>
<td>- Bivalirudin</td>
<td>5.4%</td>
<td>9.1%</td>
<td>3.8%</td>
</tr>
<tr>
<td>CURE (N=12,562)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Placebo</td>
<td>6.7%</td>
<td>2.7%</td>
<td>6.2%</td>
</tr>
<tr>
<td>- Clopidogrel</td>
<td>5.2%</td>
<td>3.7%</td>
<td>5.8%</td>
</tr>
<tr>
<td>TRITON (n=13,608)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Clopidogrel</td>
<td>9.5%</td>
<td>3.8%</td>
<td>3.2%</td>
</tr>
<tr>
<td>- Prasugrel</td>
<td>7.3%</td>
<td>5.0%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

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Stone, GW NEJM 2010
Conclusions

- Pharmacologic treatment of patients undergoing PCI has improved over the years to decrease ischemic and bleeding complications.

- As most drugs which ↓ ischemia also ↑ bleeding, the offsetting impact of adverse ischemic and hemorrhagic events must be carefully examined.

- The net balance of ischemia and bleeding should be strongly considered when choosing APT for individual pts in an attempt to minimize complications.