Does The Efficacy of Bivalirudin During PCI Depend on Clopidogrel Pre-treatment?

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IIa Recommendation

For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to omit upstream administration of an intravenous GP IIb/IIIa antagonist before diagnostic angiography if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 h earlier than planned catheterization or PCI. (Level of Evidence: B)
Randomized, double-blind, active-controlled trial

**Aspirin clopidogrel stent**

- **6,002** Urgent or elective PCI patients

- **2,994** Aspirin

- **3,008** Clopidogrel

**Bivalirudin**
- 0.75 mg/kg bolus
- 1.75 mg/kg/h procedure with provisional GP IIb/IIIa

**Heparin**
- 65 units/kg

**Planned abciximab or eptifibatide**

**Primary Endpoints**
- 30-Day: Death
- MI
- Revascularization
- Major bleeding

**Economics**
- 6-Month ischemia
- 1-Year mortality

Secondary composite end point=death, MI, or urgent revascularization.

Clopidogrel 300-mg encouraged 2 to 12 hrs before PCI

REPLACE 2: Results Stratified By Clopidogrel Tx
No Differential Benefit Between Heparin/GPI and Bival

~85% of patients in each arm received clopidogrel pre-PCI.
~20% were pretreated > 6 hours prior to PCI.

REPLACE 2: Results Stratified By Clopidogrel Tx
No Differential Benefit On Net Clinical Events

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

ACUITY Study Design
First Randomization

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)

Angiography within 72h

Medical management

PCI
CABG

Randomization Stratified by pre-angiography thienopyridine use or administration
### ACUITY: Influence of Thienopyridine Exposure

#### 30 Day Primary Endpoint Adverse Events

<table>
<thead>
<tr>
<th>Thienopyridine Exposed</th>
<th>UFH/Enoxaparin + IIb/IIIa (N=1722)</th>
<th>Bivalirudin Alone (N=1789)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR [95%CI]</td>
<td>RR [95%CI]</td>
<td>RR [95%CI]</td>
</tr>
<tr>
<td>0.81 (0.68-0.96)</td>
<td>0.96 (0.77-1.20)</td>
<td>0.50 (0.37-0.67)</td>
</tr>
</tbody>
</table>

| Interaction P values     | 0.17, 0.19 and 0.65 respectively    |

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*Thienopyridine at any time, any dose, up to time of PCI*
Underwent PCI and received clopidogrel at some time prior to or during hospitalization N= 7517

No clopidogrel N= 129

Clopidogrel pre-hospital N=1820 (24%)

Clopidogrel at hospital but pre-randomization N= 2383 (32%)

Clopidogrel after randomization N= 3314 (44%)

Known dose and duration

Clopidogrel Pre-angiography N = 928
Clopidogrel Peri- PCI N =1572
Clopidogrel Post-PCI N = 814

Steinhubl, TCT 2007
ACUITY and Clopidogrel Preloading
Method of Analysis of Timing of Clopidogrel

• Timing for the initiation of clopidogrel was *a priori* designated as:
  – **Pre-PCI** if it was initiated at any time prior to the angiogram.
  – **Peri-PCI** if it was initiated after angiography and within 30 minutes of the end of PCI.
  – **Post-PCI** if it was initiated > 30 minutes after PCI

Steinhubl, TCT 2007
### Timing of Clopidogrel Exposure

<table>
<thead>
<tr>
<th>Timing of Clopidogrel Exposure</th>
<th>Composite Ischemia %</th>
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<tbody>
<tr>
<td>Pre-PCI N=5131</td>
<td>8.8 8.1</td>
</tr>
<tr>
<td>Peri-PCI N=1572</td>
<td>8.2 8.6</td>
</tr>
<tr>
<td>Post-PCI N=814</td>
<td>9.7 12.6</td>
</tr>
<tr>
<td>None N=129</td>
<td>14.0 23.3</td>
</tr>
</tbody>
</table>

- **GPIIb/IIIa antagonist + any anticoagulant**
- **Bivalirudin alone**

30-Day Ischemic Outcomes Based on Antiplatelet Therapy

P-values:
- Pre-PCI: P=0.36
- Peri-PCI: P=0.77
- Post-PCI: P=0.22
- None: P=0.18

Steinhubl, TCT 2007
30-Day Ischemic Outcomes in Troponin Positive Patients Only

Composite Ischemia %

- **Pre-PCI**: N=2824
  - GPIIb/IIa antagonist + any anticoagulant: 9.0 (%), P=0.60
  - Bivalirudin alone: 8.4%

- **Peri-PCI**: N=950
  - GPIIb/IIa antagonist + any anticoagulant: 8.2 (%), P=0.97
  - Bivalirudin alone: 8.3%

- **Post-PCI**: N=471
  - GPIIb/IIa antagonist + any anticoagulant: 9.1 (%), P=0.13
  - Bivalirudin alone: 13.7%

- **None**: N=77
  - Bivalirudin alone: 23.1%, P=0.72

Steinhubl, TCT 2007
ACUITY PCI: Impact of Timing of Clopidogrel Administration on 1 Yr Mortality (Tn + patients)

PCI troponin+ patients

1-year Mortality Hazard Ratio ± 95% CI

HR (95% CI)

Clopidogrel at any time prior to hospitalization, randomization or end of angiography (n=1,891) 1.07 (0.66-1.73)

Clopidogrel after end of angiography to 30’ post PCI (n=649) 1.09 (0.46-2.58)

Clopidogrel after 30’ post PCI (n=307) 0.56 (0.17-1.93)

No clopidogrel (n=51) 3.07 (0.32-29.49)

White et al, JACC 2008
What dose and duration is an adequate preload?

Analysis of the CREDO trial

Log Odds of Death, MI or UTVR at 28 Days

Placebo

Clopidogrel

P = 0.020 for treatment / timing interaction

Steinhubl et al, Am. Coll. Cardiol. 2006;47;939-943
What dose and duration is an adequate preload?

Time to inhibition for different clopidogrel loading doses

* p < 0.01 (600- or 900-mg vs. 300-mg)

Price MJ, Am J Cardiol 2006;98(5):681-4
1-Year Stent Thrombosis: Impact of Clopidogrel Loading Dose (all pts)

HR [95%CI] = 1.30 [0.86-1.95]  
P = 0.10
Stent Thrombosis 1-Day Landmark Analysis: Impact of Clopidogrel Loading (Bivalirudin)

HR [95%CI] = 1.30 [0.54-3.16]  
P = 0.56

HR [95%CI] = 2.11 [1.07,4.17]  
P = 0.03

Def/Prob Stent Thrombosis (%)  
0 1 2 3 4 5

0 1 30 90 180 270 365  
Time in Days

Def/Prob Stent Thrombosis (%)  
1.2% 1.5% 2.1% 3.4%

600 mg Clopidogrel  
300 mg Clopidogrel

Number at risk  
600 mg: 1013 1009 990 969 957 943 863  
300 mg: 519 514 497 486 480 474 430
Efficacy of Clopidogrel Pre-treatment in Patients Receiving GpIs: Combined Analysis PCI-CURE, CREDO and PCI-CLARITY
CV Death, MI, or Stroke Following PCI

### Without GPI

<table>
<thead>
<tr>
<th>Trial</th>
<th>Clop PreRx</th>
<th>No PreRx</th>
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<tr>
<td>PCI-CURE</td>
<td>27/1039 (2.6)</td>
<td>39/988 (3.9)</td>
</tr>
<tr>
<td>CREDO</td>
<td>26/473 (5.5)</td>
<td>34/519 (6.6)</td>
</tr>
<tr>
<td>PCI-CLARITY</td>
<td>22/639 (3.4)</td>
<td>30/615 (4.9)</td>
</tr>
<tr>
<td>OVERALL</td>
<td>75/2151 (3.5)</td>
<td>103/2122 (4.9)</td>
</tr>
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<tr>
<td>PCI-CURE</td>
<td>14/274 (5.1)</td>
<td>23/357 (6.4)</td>
</tr>
<tr>
<td>CREDO</td>
<td>29/427 (6.8)</td>
<td>32/396 (8.1)</td>
</tr>
<tr>
<td>PCI-CLARITY</td>
<td>12/288 (4.2)</td>
<td>28/310 (9.0)</td>
</tr>
<tr>
<td>OVERALL</td>
<td>55/989 (5.6)</td>
<td>83/1063 (7.8)</td>
</tr>
</tbody>
</table>

**OR (95% CI)**

Without GPI:
- **OR 0.72 (0.53-0.98)**, *P*=0.03, Favors PreRx
- **OR 0.69 (0.47-1.00)**, *P*=0.05, Favors No PreRx

With GPI:
- *P*=0.85 for heterogeneity by GPI use

The Response To A Uniform Dose Of Clopidogrel Is Not Uniform

Maximal Aggregation

5 μmol/L ADP (%)

Time from Loading Dose to Catheterization (hr)

n = 1001, clopidogrel 600-mg

PRINCIPLE TIMI 44: Time and Magnitude of Onset of Inhibition of Prasugrel Compared with 600-mg Clopidogrel

IPA (20 mM ADP)  N = 201

P<0.0001 for each

 IPA = inhibition of platelet aggregation.

TRITON-TIMI 38: Primary Endpoint

Conclusions

• In REPLACE 2, clopidogrel pretreatment did not influence the relative efficacy of bivalirudin versus heparin plus a GPI. However, pretreatment was associated with a trend towards lower clinical events overall.

• In ACUITY, patients who received clopidogrel either prior to, or at the time of, PCI achieved similar ischemic event rates and significantly less bleeding when randomized to bivalirudin alone versus a GPI, irrespective of troponin status.

• There was a trend in ACUITY towards worse ischemic outcomes among patients receiving clopidogrel > 30 min after PCI or no clopidogrel at all.
Conclusions (2)

- Clopidogrel pre-treatment is beneficial whether or not a GPI is used at the time of PCI.

- The desire or ability to pre-treat an ACS patient with clopidogrel prior to PCI should not influence the choice of antithrombotic therapy.

- In the case of ACS, the availability of prasugrel, which provides greater, more consistent, and quicker onset of inhibition than clopidogrel, may make the question of clopidogrel pretreatment moot.