Pushing the envelope for bivalirudin monotherapy:
Design, rationale and status of
ISAR-REACT 4 and HORIZONS

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Periprocedural Antithrombotic Therapy

- Aspirin
- Clopidogrel
- Heparins (UFH or LMWH)
- IIb/IIIa Inhibitors
  - Bivalirudin
- Stable/Unstable Angina
- NSTE Acute Coronary Syndromes
- STEMI
Rationale for New a Trial of Bivalirudin in ACS

- Value of early invasive strategy
- Need for upstream use of IIb/IIIa inhibitors
- Role of pre-treatment with 600 mg of clopidogrel
- Recent evidence on adjunct antithrombotic therapy
ISAR-COOL Trial

410 patients with ACS

207 Pts
Cooling-off antithrombotic pretreatment for 72 - 120 h

203 Pts
Early PCI antithrombotic pretreatment for < 6 h

Neumann et al. JAMA 2003
ISAR-COOL: Primary Endpoint

Combined incidence of death and MI (%)

- cooling-off, 11.6%
- early PCI, 5.9%

p=0.04

Neumann et al. JAMA 2003
Primary Endpoint Before and After Catheterization

# of events (death or MI)

before  after

cooling-off  early PCI

p=0.002  p=0.96
Need for Upstream Use of IIb/IIIa Inhibitors - ACUITY Timing Trial -

Routine Upstream IIb/IIIa vs. Deferred PCI IIb/IIIa

<table>
<thead>
<tr>
<th>Event</th>
<th>Routine Upstream IIb/IIIa (N=4605)</th>
<th>Deferred PCI IIb/IIIa (n=4602)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day events (%)</td>
<td>11.7%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Net clinical outcome</td>
<td>P_NI &lt; 0.0001, P_Sup = 0.93</td>
<td></td>
</tr>
<tr>
<td>Ischemic composite</td>
<td>P_NI = 0.044, P_Sup = 0.13</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>P_NI &lt; 0.0001, P_Sup = 0.009</td>
<td></td>
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</tbody>
</table>

ACUITY Timing ACC 2006
In ACS patients, data support early invasive treatment without the need for upstream use of IIb/IIIa inhibitors.

Does pre-treatment with 600 mg of clopidogrel obviate the need for IIb/IIIa inhibitors in ACS patients undergoing PCI such as it did for elective PCI patients?
ISAR–REACT 2 Trial

2022 patients with high-risk ACS
Pre-treated with 600 mg clopidogrel

Abciximab

Placebo

Double-blind

1010 Pts

1012 Pts

PCI

30-day outcome

ISAR-REACT 2, JAMA 2006
ISAR–REACT 2: Primary End Point

Death/MI/UTVR, %

Abciximab vs. Placebo

RR = 0.75 [95% CI, 0.58-0.97]

ISAR-REACT 2, JAMA 2006
Troponin Level and Benefit With Abciximab

Death/MI/UTVR, %

Troponin-Positive: RR=0.71 [0.54-0.95]

Abciximab vs. Placebo

Troponin-Negative: RR=0.99 [0.56-1.76]
One-Year Survival Free of MACE

RR: 0.80 [0.67-0.95], *P*=0.012
One-Year Survival Free of MI

RR: 0.74 [0.59-0.94], \( P=0.015 \)
Bivalirudin in ACS
- ACUITY -

13,819 Pts

ACUITY, ACC 2006
**ACUITY**
- Primary End Point -

UFH/Enoxaparin + GPI vs. Bivalirudin Alone

<table>
<thead>
<tr>
<th>30 day events (%)</th>
<th>UFH/Enoxaparin+GPI (N=4603)</th>
<th>Bivalirudin alone (N=4612)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Net clinical outcome</strong></td>
<td>11.7%</td>
<td>10.1%</td>
</tr>
<tr>
<td><strong>Ischemic composite</strong></td>
<td>7.3%</td>
<td>7.8%</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td>5.7%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

- **P_{NI} <0.0001**
- **P_{Sup} = 0.015**
- **P_{NI} = 0.011**
- **P_{Sup} = 0.32**
- **P_{NI} <0.0001**
- **P_{Sup} <0.0001**

ACUITY ACC 2006
Issues With ACUITY
- Design -

- Open-label trial
- ACUITY did not address specifically Trop+ pts
- Major bleeding definition

  ▪ Non CABG related bleeding
    - Intracranial bleeding or intraocular bleeding
      - Retroperitoneal bleeding
    - Access site bleed requiring intervention/surgery
      - Hematoma ≥5 cm
    - Hgb ↓≥3g/dL with an overt source or ↓≥4g/dL w/o overt source
    - Blood product transfusion
    ▪ Reoperation for bleeding
## Issues With ACUITY
### - Invasive Strategy -

<table>
<thead>
<tr>
<th></th>
<th>UFH/Enoxaparin + GP IIb/IIIa (N=4,603)</th>
<th>Bivalirudin + GP IIb/IIIa (N=4,604)</th>
<th>Bivalirudin alone (N=4,612)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiography</strong></td>
<td>99.2%</td>
<td>98.8%</td>
<td>98.9%</td>
</tr>
<tr>
<td><strong>Adm. to angio (h)</strong></td>
<td>19.7 (7.0-29.3)</td>
<td>19.5 (7.0-28.2)</td>
<td>19.8 (7.3-29.0)</td>
</tr>
<tr>
<td><strong>Drug to angio/interv (h)</strong></td>
<td>5.6 (1.6-22.5)</td>
<td>5.0 (1.4-21.4)</td>
<td>5.2 (1.5-22.5)</td>
</tr>
<tr>
<td><strong>Actual procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>55.6%</td>
<td>56.7%</td>
<td>56.8%</td>
</tr>
<tr>
<td><strong>CABG</strong></td>
<td>11.9%</td>
<td>10.8%</td>
<td>10.6%</td>
</tr>
<tr>
<td><strong>Medical therapy</strong></td>
<td>32.4%</td>
<td>32.5%</td>
<td>32.6%</td>
</tr>
</tbody>
</table>
Issues With ACUITY
- Control Group Therapy -

Control group:
A mixture of UFH and Enoxaparin

- Eptifibatide: 64
- Tirofiban: 27
- Abciximab: 9
Is bivalirudin inferior to abciximab+UFH in patients with NSTEMI undergoing PCI?
ISAR–REACT 4 Trial

1700 patients with NSTEMI
Pre-treated with 300-600 mg of clopidogrel

Double-blind

Bivalirudin  Abciximab+UFH

PCI

30-day Outcome
• Patients with rest angina between 18 and 80 years
• Positive cardiac biomarkers (troponin or CK-MB)
ISAR-REACT 4
Major Exclusion Criteria

- Acute STEMI
- Hemodynamic instability
- Suspected aortic dissection, pericarditis
- Increased risk of bleeding, malignancies
- Relevant hematologic deviations
- Known allergic reaction to the study medication
Primary Quadruple End Point

A composite of death, MI (Q-wave or 5xCK-MB elevation), urgent target vessel revascularization within the first 30 days after PCI or in-hospital major bleeding (intracranial, intraocular or retroperitoneal hemorrhage or any decrease in hemoglobin of more than 40 g/L associated with either overt source of bleeding or need for transfusion of 2 or more units).

Study Hypothesis:

30% reduction of the primary end point with abcicimab from 15.3% to 10.7%
ISAR-REACT 4: Status

~250 Patients Included to Date
Rationale for a new trial of bivalirudin and DES in patients with acute STEMI undergoing PCI
IIb/IIIa Inhibitors
During PCI in AMI

De Luca et al, Metaanalysis, JAMA 2005
IIb/IIIa Inhibitors During PCI in AMI

Mortality reduction by abciximab (%)

Mortality in the control group (%)
IIb/IIIa Inhibitors are currently strongly recommended during primary PCI. Data on the value of bivalirudin during primary PCI are lacking.
DES in AMI and Risk of MACE

<table>
<thead>
<tr>
<th>Trial</th>
<th>DES group</th>
<th>BMS group</th>
<th>Favors DES</th>
<th>Favors BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASKET-AMI</td>
<td>20/142</td>
<td>15/74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Lorenzo</td>
<td>20/180</td>
<td>24/90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAAMU-STENT</td>
<td>15/82</td>
<td>14/82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MISSION</td>
<td>22/158</td>
<td>40/152</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASSION</td>
<td>29/310</td>
<td>40/309</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SESAMI</td>
<td>11/160</td>
<td>26/160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STRATEGY</td>
<td>17/87</td>
<td>31/88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYPHOON</td>
<td>24/355</td>
<td>62/357</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>158/1474</td>
<td>252/1312</td>
<td>0.53</td>
<td></td>
</tr>
</tbody>
</table>

$P_{(Heterogeneity)} = 0.22$

$I^2 = 26\%$

$P_{(Overall\,Effect)} < 0.001$
Experience with DES in AMI is still limited, especially in the case of the Taxus stent. It is not known whether it safely reduces the need for reintervention.
HORIZONS AMI Trial

- 3400 randomized patients undergoing primary PCI -

**Hypothesis:** Use of the polymer-based slow-release paclitaxel-eluting TAXUS stent will safely reduce the 1-year rate of ischemia-driven TLR. 1° clinical endpoint at 12 mo; 2° angio endpoint at 13 mo.

**Hypothesis:** Bivalirudin compared to UFH + routine IIb/IIIa will reduce the composite rate of death, reinfarction, TVR, stroke and major bleeding at 30-days.

**Anti-thrombotic therapy**
- Randomize 1:1
  - UFH + IIb/IIIa inhibitor
  - Bivalirudin + bail-out IIb/IIIa

**Target vessel stenting**
- Randomize 3:1
  - TAXUS stent
  - Bare metal Express stent

Sponsor: The Cardiovascular Research Foundation (PI: Gregg W. Stone), with unrestricted grant support from: Boston Scientific & The Medicine’s Co.
New Enrollment Target / Timeline

- Assumption: stent eligible subjects
  (estimate ~88% = 3000)
- Current enrollment: stent eligible subjects
  (Actual ~83%)

Therefore, **3600** total patients randomized to the drug arm are needed to enroll 3000 subjects randomized to the drug and stent arm.
US HORIZONS Sites
- 50 sites currently active/enrolling-

Courtesy of Gregg Stone
OUS HORIZONS Sites - 71 sites currently active/enrolling-

Courtesy of Gregg Stone
Total Number of Subjects Enrolled: 3520
(793 US and 2727 OUS)
Top 10 Enrolling Sites in HORIZONS

Number of Subjects Enrolled in These Centers: 1423 (40% of Total)
Enrollment

114 Study Sites enrolled 3520 patients by April 24, ’07
On target for May, ’07 enrollment completion