Antithrombin Therapy During PCI: Bivalirudin is Better ????

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Northwell Health
Hofstra Northwell Health School of Medicine
# Faculty Disclosure

<table>
<thead>
<tr>
<th>Company</th>
<th>Nature of Affiliation</th>
<th>Unlabeled Product Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic, Edwards Lifesciences, Abiomed, Boston Scientific, Avinger</td>
<td>• Research Grants, • Advisory Board</td>
<td>• None</td>
</tr>
</tbody>
</table>
Real Disclosure ...

• Heparin is better ...
• I only use heparin ...
Pharmacotherapy Across the Spectrum of CAD/PCI

Risk (Mortality)

- Stable angina
- Unstable angina
- NSTEMI
- STEMI
Pharmacotherapy Across the Spectrum of CAD: Unfractionated heparin (all conservative care)

- Stable angina
- Unstable angina
- NSTEMI
- STEMI

Risk (Mortality)

N = 1,353 randomized patients

6 small studies
Unfractionated Heparin in ACS (N=1,353)

Summary Relative Risk
0.67 (0.44–0.1.02)

Heparin + ASA
55/698 = 7.9%

ASA Alone
68/655=10.4%

Oler et al. JAMA 1996;276:811–6
# Limitations of Heparins

<table>
<thead>
<tr>
<th>Attribute</th>
<th>UFH</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active moieties in substance</td>
<td>30–35%</td>
<td>Unpredictable</td>
</tr>
<tr>
<td>Action independent of AT</td>
<td>No</td>
<td>Unpredictable</td>
</tr>
<tr>
<td>Non-specific protease binding</td>
<td>Yes</td>
<td>Unpredictable</td>
</tr>
<tr>
<td>Variable PK-PD</td>
<td>Yes</td>
<td>Unpredictable</td>
</tr>
<tr>
<td>Inhibits fibrin-bound thrombin</td>
<td>No</td>
<td>Need ↑ dose</td>
</tr>
<tr>
<td>Activates/aggregates platelets</td>
<td>Yes</td>
<td>Need IIb/IIIa</td>
</tr>
<tr>
<td>$T_{0.5}$ in minutes</td>
<td>60–90’</td>
<td>↑ Bleeding</td>
</tr>
<tr>
<td>PF-4 complexing &amp; risk of HIT</td>
<td>Yes</td>
<td>Very bad</td>
</tr>
</tbody>
</table>
Antithrombin Choices for PCI, ACS and AMI

Unfractionated heparin

IdoA  GlcA

Trisulfated disaccharide  Disulfated disaccharide  Antithrombin Pentasaccharide Binding Site  Trisulfated disaccharide

Fondaparinux

Bivalirudin

LMW Heparin

Chemical β elimination  Oxidation  Deam degradation  Enzymatic β elimination

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Bivalirudin
Bivalent Synthetic Direct Thrombin Inhibitor

- Specifically inhibits
  - Fluid phase thrombin
  - Clot-bound thrombin
  - Collagen and thrombin-mediated platelet aggregation (blocks activation of PAR-1 and PAR-4 receptors)
- Reversible
- $T_{0.5}$ 25 minutes

Topol EJ: Textbook of Interventional Cardiology
## Overcoming Limitations of Heparins

<table>
<thead>
<tr>
<th>Attribute</th>
<th>UFH</th>
<th>Enox</th>
<th>Fonda</th>
<th>Bivalirudin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active moieties in substance</td>
<td>30–35%</td>
<td>40–60%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Action independent of AT</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Non-specific protease binding</td>
<td>Yes</td>
<td>Partial</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Variable PK-PD</td>
<td>Yes</td>
<td>Less</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Inhibits fibrin-bound thrombin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Activates/aggregates platelets</td>
<td>Yes</td>
<td>+/-</td>
<td>?</td>
<td>Inhibits</td>
</tr>
<tr>
<td>$T_{0.5}$ in minutes</td>
<td>60–90’</td>
<td>270’</td>
<td>15–18°</td>
<td>25’</td>
</tr>
<tr>
<td>PF-4 complexing &amp; risk of HIT</td>
<td>Yes</td>
<td>Reduced</td>
<td>Low</td>
<td>No</td>
</tr>
</tbody>
</table>
Bivalirudin Inhibits, Doesn’t Activate Platelets

Direct platelet activation by UFH but not bivalirudin¹

*Scanning electron micrographs were acquired at a magnification of 4,000x with the investigator blinded to treatment.

Bivalirudin inhibitors both thrombin-induced and collagen-induced platelet activation²

¹Anand SX et al. *Am J Cardiol.* 2007;100:417-424
²Kimmelstiel C et al. *Circ CV Interv.* 2011;4:
Pharmacotherapy Across the Spectrum of CAD: Bivalirudin

N = 27,593 randomized patients
Bivalirudin vs Heparin + GPIIb/IIIa Inhibitor During PCI
6,012 Patients Undergoing Urgent or Elective PCI

Randomization – double blind, triple dummy

Heparin
65 U/kg initial bolus
Planned GP IIb/IIIa
(abciximab or eptifibatide)

Target ACT ≥ 225 sec

Bivalirudin
0.75 mg/kg initial bolus,
1.75 mg/kg-hr during PCI
Provisional GP IIb/IIIa
(abciximab or eptifibatide)

abciximab: 0.25 mg/kg bolus, 0.125 µg/kg-min (max 10 µg/min) x 12 hrs

eptifibatide: 180 µg/kg double bolus, 2.0 µg/kg-min x 18-24 hrs

Primary “Quadruple Endpoint” at 30 Days

Lincoff AM et al. JAMA 2003;289:853–63
30 Day Primary Endpoint
6,012 Patients Undergoing PCI

Lincoff AM et al. JAMA 2003;289:853–63
## Bleeding Complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Bivalirudin N = 2994</th>
<th>Heparin + GP IIb/IIIa N = 3008</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>2.4</td>
<td>4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>13.4</td>
<td>25.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large hematoma</td>
<td>0.8</td>
<td>2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retroperitoneal hemorrhage</td>
<td>0.2</td>
<td>0.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Major organ bleeding</td>
<td>0.5</td>
<td>1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0</td>
<td>0.1</td>
<td>1.00</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;100K)</td>
<td>0.7</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transfusion</td>
<td>1.7</td>
<td>2.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Lincoff AM et al. JAMA 2003;289:853–63
1-year Mortality
All 6,012 Patients (ITT)

Cumulative Deaths

Days

Heparin+GPIIb/IIIa N=3008
Bivalirudin N=2994

P value = 0.16

2.5%
1.9%

Lincoff AM et al. JAMA 2004;292:696–703
ISAR-REACT 3: 4570 troponin negative pts were loaded with clopidogrel 600 mg and randomized to UFH (140 U/kg) vs. bivalirudin.

Primary endpoints = MACE, major bleeding (R2 scale), and MACE or major bleeding

<table>
<thead>
<tr>
<th>30 Day Outcomes</th>
<th>Bivalirudin</th>
<th>UFH</th>
<th>RR [95%CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, or urgent TVR</td>
<td>5.9%</td>
<td>5.0%</td>
<td>1.16 [0.91,1.49]</td>
<td>0.23</td>
</tr>
<tr>
<td>- Death</td>
<td>0.1%</td>
<td>0.2%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- MI</td>
<td>5.6%</td>
<td>4.8%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Urgent TVR</td>
<td>0.8%</td>
<td>0.7%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Major bleed (R2 defn.)</td>
<td>3.1%</td>
<td>4.6%</td>
<td>0.66 [0.49,0.90]</td>
<td>0.008</td>
</tr>
<tr>
<td>TIMI major or minor bleed</td>
<td>1.8%</td>
<td>3.3%</td>
<td>0.57 [0.32,0.78]</td>
<td>0.001</td>
</tr>
<tr>
<td>- major bleed</td>
<td>0.5%</td>
<td>1.1%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- minor bleed</td>
<td>1.3%</td>
<td>2.2%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>D, MI, uTVR, or major bleed</td>
<td>8.3%</td>
<td>8.7%</td>
<td>0.94 [0.77,1.15]</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Katrati A et al. NEJM 2008;359:688-96
ACUITY: First Randomization

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)

Angiography 19.6° median

- Medical management
  - PCI 56%
  - CABG 11%

*Stratified by pre-angiography thienopyridine use or administration

Stone GW et al. NEJM 2006;355:2203-16
Ischemic Composite Endpoint

Cumulative Events (%)

Days from Randomization

UFH/Enoxaparin + IIb/IIIa (N=4603)
Estimate 7.4% (log rank)

Bivalirudin + IIb/IIIa (N=4604)
7.9% 0.37

Bivalirudin alone (N=4612)
8.0% 0.30

Stone GW et al. NEJM 2006;355:2203-16
Major Bleeding Endpoint

- UFH/Enoxaparin + IIb/IIIa (N=4603) Estimate 5.7% (log rank) P <0.0001
- Bivalirudin + IIb/IIIa (N=4604) Estimate 5.3% P 0.41
- Bivalirudin alone (N=4612) Estimate 3.1% P <0.0001

Stone GW et al. NEJM 2006;355:2203-16
## Bleeding Endpoints

<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>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACUITY Scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Major Bleed, all</td>
<td>11.8%</td>
<td>11.1%</td>
<td>9.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Major, non-CABG</td>
<td>5.7%</td>
<td>5.3%</td>
<td>3.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Minor, non-CABG</td>
<td>21.6%</td>
<td>21.7%</td>
<td>12.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>TIMI Scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Any</td>
<td>6.6%</td>
<td>6.5%</td>
<td>4.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Major</td>
<td>1.9%</td>
<td>1.7%</td>
<td>0.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Minor</td>
<td>6.4%</td>
<td>6.1%</td>
<td>3.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Blood transfusion</strong></td>
<td>2.7%</td>
<td>2.6%</td>
<td>1.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>11.1%</td>
<td>10.8%</td>
<td>9.9%</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

*P value for Bivalirudin alone vs. GP IIb/IIIa inhibitor based regimen
ISAR-REACT-4

1,721 Pts with NSTEMI (CK-MB or troponin+) undergoing PCI
Pre-treated with aspirin and 600 mg of clopidogrel

Double-blind (double-dummy drug)

UFH + Abciximab
- Bolus UFH 70 U/kg
- Bolus Abcx 0.25 mg/kg + infusion 0.125 μg/kg/min x12h
N=861

Bivalirudin
- Bolus 0.75 mg/kg + infusion 1.75 mg/kg/hr for duration of PCI
N=860

Primary endpoint = death, large MI, urgent TVR, or major bleeding at 30d
Powered for superiority of UFH/Abcix over bivalirudin
ISAR-REACT-4: Composite ischemia

Days

Death, MI, or urgent TVR (%)

- UFH + Abciximab (n=861)
- Bivalirudin (n=860)

RR (95%CI) = 1.04 (0.80–1.35)

P=0.76

ISAR-REACT-4: Major bleeding

**RR (95%CI) = 0.54 (0.33 – 0.91)**

P=0.02

*Intracranial, intraocular, or RP hemorrhage; Δhgb >4 g/dL with overt bleeding or ≥2U RBC Rx

Days

Major bleeding* (%)

0 5 10 15 20 25 30

UFH + Abciximab (n=861)

Bivalirudin (n=860)

4.6%

2.6%
Harmonizing Outcomes with Revascularization and Stents in AMI

3602 pts with STEMI with symptom onset ≤12 hours

Aspirin, thienopyridine

R 1:1

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

Bivalirudin monotherapy (± provisional GP IIb/IIIa)

Emergent angiography, followed by triage to...

CABG – Primary PCI – Medical Rx

3006 pts eligible for stent randomization

R 3:1

Paclitaxel-eluting TAXUS stent

Bare metal EXPRESS stent

Clinical FU at 30d, 6 mo, 1 yr, and then yearly through 3 yrs; angio FU at 13 mo

Stone GW et al
HORIZONS: 30 Day Adverse Events

- Reinfarction: 1.8%
- Major bleeding*: 4.9%
- Thrombocytopenia**: 1.8%

*Not related to CABG
** Plat cnt <100,000 cells/mm³

P = 0.90
P < 0.001
P = 0.002

Stone GW et al. NEJM 2008;358:2218-30
Three-Year All-Cause Mortality

- **Bivalirudin alone (n=1800)**
- **Heparin + GPIIb/IIIa (n=1802)**

30-day HR [95%CI] = 0.66 [0.44, 1.00]  
P = 0.048

3-yr HR [95%CI] = 0.75 [0.58, 0.97]  
P = 0.03

Number at risk:
- Bivalirudin alone: 1800
- Heparin + GPIIb/IIIa: 1802

Months:
- 0 3 6 9 12 15 18 21 24 27 30 33 36
- All-Cause Mortality (%)

0 1 2 3 4 5 6 7 8 9 10

Stone GW et al. NEJM 2008;358:2218-30
3-Year Mortality: Cardiac and Non Cardiac

Cardiac Mortality (%): 5.1% (3-yr HR [95%CI]= 0.56 [0.40, 0.80] P=0.001)
Non-Cardiac Mortality (%): 2.9% (3-yr HR [95%CI]= 1.11 [0.74, 1.65] P=0.62)

Number at risk:
- Bivalirudin alone (n=1800)
  - Bival: 1800
  - H + GPI: 1611
- Heparin + GPIIb/IIIa (n=1802)
  - Bival: 1802
  - H + GPI: 1689

### Bivalirudin vs. Heparin + GPI (n=18,819)

#### Mortality at 1-year by treatment and study

<table>
<thead>
<tr>
<th>Study</th>
<th>Bivalirudin (n=9406)</th>
<th>H+GPI (n=9413)</th>
<th>Adjusted HR [95%CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>REPLACE-2</td>
<td>1.9% (56/2994)</td>
<td>2.4% (72/3008)</td>
<td>0.78 (0.55 to 1.10)</td>
<td>0.16</td>
</tr>
<tr>
<td>ACUITY</td>
<td>3.7% (170/4612)</td>
<td>3.9% (178/4603)</td>
<td>0.96 (0.77 to 1.18)</td>
<td>0.67</td>
</tr>
<tr>
<td>HORIZONS-AMI</td>
<td>3.4% (61/1800)</td>
<td>4.8% (86/1802)</td>
<td>0.71 (0.51 to 0.98)</td>
<td>0.038</td>
</tr>
<tr>
<td>Pooled</td>
<td>3.1% (287/9406)</td>
<td>3.6% (336/9413)</td>
<td>0.84 (0.72 to 0.99)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Lincoff AM et al. JAMA 2004;292:696-703
Stone GW et al. JAMA 2007;298:2497-506
Bivalirudin vs. Heparin + GPIIb/IIIa

N = 127,185 pts undergoing PCI 2003-2006
(Premier Perspective Database, ~1/6th of all US hosps; bival in 26%)

In-hospital transfusion

<table>
<thead>
<tr>
<th>Study</th>
<th>Bivalirudin</th>
<th>H+GPI</th>
<th>Adjusted HR [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>REPLACE-2**</td>
<td>3.0%</td>
<td>4.6%</td>
<td>0.67 [0.61 - 0.73]</td>
</tr>
<tr>
<td>ACUITY**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HORIZONS-AMI**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISAR-REACT**</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**33% ↓ Transfusion**

Favors Bival 
Favors H+GPI

Rassen JA et al. EHJ 2010;31:561-72
Bivalirudin vs. Heparin + GPIIb/IIIa

N = 127,185 pts undergoing PCI 2003-2006
(Premier Perspective Database, ~1/6th of all US hosps; bival in 26%)

In-hospital death

Unadjusted (All)  Adjusted (All)  Adjusted (urgent subgroup)  Adjusted (elective subgroup)  REPLACE-2**  ACUITY**  HORIZONS-AMI**  ISAR-REACT*

Favors Bival  Favors H+GPI

Bivalirudin  H+GPI

0.8%  2.1%

Adjusted HR [95%CI]
0.51 [0.44 – 0.60]

49% ↓ Death

**30 days

Rassen JA et al. EHJ 2010;31:561-72
### Bivalirudin vs. Heparin + GPIIb/IIIa

#### Primary PCI in 59,917 STEMI pts 2004-2008

(Premier Perspective Database, ~1/6<sup>th</sup> of all US hosps)

#### 3:1 propensity adjusted matching

<table>
<thead>
<tr>
<th>In-hospital outcomes</th>
<th>Bivalirudin (N=5,329)</th>
<th>UFH + GPI (N=15,987)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>6.9%</td>
<td>10.5%</td>
<td>0.52 (0.41, 0.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Transfusion</td>
<td>5.9%</td>
<td>7.6%</td>
<td>0.75 (0.66–0.86)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bleeding + transf</td>
<td>1.6%</td>
<td>3.0%</td>
<td>0.63 (0.56–0.71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death</td>
<td>3.2%</td>
<td>4.0%</td>
<td>0.80 (0.67–0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>4.3 ± 4.5</td>
<td>4.5 ± 4.4</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cost (median)</td>
<td>$14,462</td>
<td>$15,772</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
# Anticoagulation Regimens During PCI

**N = 458,448 PCI pts 2004-2008 at 299 hosps**
(Premier Perspective Database, ~1/5th of all US hosp discharges; bival in 41%)

## In-hospital events, propensity adjusted

### Bleeding + Transfusion

<table>
<thead>
<tr>
<th>Comparator</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Comparator</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivalirudin monotherapy</td>
<td>0.51 (0.48, 0.55)</td>
<td>&lt;0.0001</td>
<td>Bivalirudin + GPI</td>
<td>0.59 (0.54, 0.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(n=156,064)</td>
<td></td>
<td></td>
<td>(n=182,948)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bivalirudin + GPI</td>
<td>0.96 (0.87, 1.06)</td>
<td>0.37</td>
<td>Bivalirudin + GPI</td>
<td>0.82 (0.72, 0.94)</td>
<td>0.004</td>
</tr>
<tr>
<td>(n=33,566)</td>
<td></td>
<td></td>
<td>(n=33,566)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin alone</td>
<td>0.71 (0.66, 0.76)</td>
<td>&lt;0.0001</td>
<td>Heparin alone</td>
<td>0.88 (0.82, 0.96)</td>
<td>0.003</td>
</tr>
<tr>
<td>(n=85,870)</td>
<td></td>
<td></td>
<td>(n=85,870)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Mortality

<table>
<thead>
<tr>
<th>Comparator</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Comparator</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivalirudin monotherapy</td>
<td>0.88 (0.82, 0.96)</td>
<td>0.003</td>
<td>Bivalirudin monotherapy</td>
<td>0.88 (0.82, 0.96)</td>
<td>0.003</td>
</tr>
<tr>
<td>(n=156,064)</td>
<td></td>
<td></td>
<td>(n=156,064)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bivalirudin + GPI</td>
<td>0.82 (0.72, 0.94)</td>
<td>0.004</td>
<td>Bivalirudin + GPI</td>
<td>0.82 (0.72, 0.94)</td>
<td>0.004</td>
</tr>
<tr>
<td>(n=33,566)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Heparin alone</td>
<td>0.88 (0.82, 0.96)</td>
<td>0.003</td>
<td>Heparin alone</td>
<td>0.88 (0.82, 0.96)</td>
<td>0.003</td>
</tr>
<tr>
<td>(n=85,870)</td>
<td></td>
<td></td>
<td>(n=85,870)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Bivalirudin vs UFH Monotherapy Meta-analysis

16 studies (3 rand, 13 reg), 32,492 pts undergoing PCI:

### Major Bleeding

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Bivalirudin</th>
<th>Heparin</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observational</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolfram 2003</td>
<td>4</td>
<td>335</td>
<td>35</td>
</tr>
<tr>
<td>Rha 2005</td>
<td>1</td>
<td>54</td>
<td>2</td>
</tr>
<tr>
<td>Chu 2006</td>
<td>2</td>
<td>216</td>
<td>14</td>
</tr>
<tr>
<td>Bonello 2009</td>
<td>23</td>
<td>566</td>
<td>14</td>
</tr>
<tr>
<td>Lemesle 2009</td>
<td>10</td>
<td>79</td>
<td>20</td>
</tr>
<tr>
<td>Lemesle 2009-b</td>
<td>26</td>
<td>1207</td>
<td>101</td>
</tr>
<tr>
<td>Delhaye 2010</td>
<td>5</td>
<td>267</td>
<td>2</td>
</tr>
<tr>
<td>Lindsey 2010</td>
<td>6</td>
<td>503</td>
<td>26</td>
</tr>
<tr>
<td>Lopes 2010</td>
<td>101</td>
<td>1771</td>
<td>89</td>
</tr>
<tr>
<td>Schultz 2010</td>
<td>12</td>
<td>2289</td>
<td>16</td>
</tr>
<tr>
<td>Bangalore 2011</td>
<td>38</td>
<td>1511</td>
<td>78</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>8798</td>
<td>10414</td>
<td></td>
</tr>
<tr>
<td><strong>Total Events</strong></td>
<td>228</td>
<td>397</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\text{Tau}^2=0.11$, $\text{Chi}^2=20.84$, df=10 ($P=0.02$), $I^2=52\%$
Test for overall effect: $Z=3.55$ ($P=0.0004$)

<table>
<thead>
<tr>
<th><strong>Randomized</strong></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Kastrati 2008</td>
<td>12</td>
<td>2289</td>
<td>24</td>
</tr>
<tr>
<td>Parodi 2010</td>
<td>3</td>
<td>363</td>
<td>8</td>
</tr>
<tr>
<td>Patti 2011</td>
<td>1</td>
<td>198</td>
<td>2</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>2850</td>
<td>2792</td>
<td></td>
</tr>
<tr>
<td><strong>Total Events</strong></td>
<td>16</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\text{Tau}^2=0.00$, $\text{Chi}^2=0.37$, df=2 ($P=0.83$), $I^2=0\%$
Test for overall effect: $Z=2.60$ ($P=0.009$)

**Total (95% CI)** | 11648       | 13206   | 0.55 [0.43, 0.72] |
**Total Events** | 244         | 431     | 45% ↓ |

Test for heterogeneity: $\text{Tau}^2=0.08$, $\text{Chi}^2=21.99$, df=13 ($P=0.06$), $I^2=41\%$
Test for overall effect: $Z=4.38$ ($P<0.0001$)
Test for subgroup differences: $\text{Chi}^2=0.47$, df=1 ($P=0.49$), $I^2=0\%$

# Bivalirudin vs UFH Monotherapy Meta-analysis

16 studies (3 rand, 13 reg), 32,492 pts undergoing PCI:

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Bivalirudin Events</th>
<th>Heparin Events</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observational</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolfram 2003</td>
<td>0</td>
<td>1</td>
<td>1.53 [0.06, 37.70]</td>
</tr>
<tr>
<td>Gurm 2005</td>
<td>3</td>
<td>4</td>
<td>0.69 [0.15, 3.11]</td>
</tr>
<tr>
<td>Rha 2005</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Chu 2006</td>
<td>7</td>
<td>9</td>
<td>1.66 [0.61, 4.53]</td>
</tr>
<tr>
<td>Gurm 2007</td>
<td>3</td>
<td>7</td>
<td>0.82 [0.21, 3.17]</td>
</tr>
<tr>
<td>Bonello 2009</td>
<td>6</td>
<td>3</td>
<td>1.18 [0.29, 4.74]</td>
</tr>
<tr>
<td>Lemesle 2009</td>
<td>3</td>
<td>4</td>
<td>0.87 [0.19, 4.00]</td>
</tr>
<tr>
<td>Lemesle 2009-b</td>
<td>48</td>
<td>124</td>
<td>0.48 [0.34, 0.67]</td>
</tr>
<tr>
<td>Delhaye 2010</td>
<td>5</td>
<td>1</td>
<td>2.44 [0.28, 21.13]</td>
</tr>
<tr>
<td>Lindsey 2010</td>
<td>0</td>
<td>4</td>
<td>0.19 [0.01, 3.52]</td>
</tr>
<tr>
<td>Lopes 2010</td>
<td>12</td>
<td>18</td>
<td>0.51 [0.25, 1.06]</td>
</tr>
<tr>
<td>Schultz 2010</td>
<td>3</td>
<td>5</td>
<td>0.66 [0.16, 2.75]</td>
</tr>
<tr>
<td>Bangalore 2011</td>
<td>1</td>
<td>8</td>
<td>0.12 [0.02, 1.00]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>11713</td>
<td>15137</td>
<td>0.62 [0.45, 0.85]</td>
</tr>
<tr>
<td>Total Events</td>
<td>91</td>
<td>188</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\tau^2=0.03$, Chi$^2=11.92$, df=11 ($P=0.37$), $I^2=8\%$

Test for overall effect: $Z=2.98$ ($P=0.003$)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Bivalirudin Events</th>
<th>Heparin Events</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kastrati 2008</td>
<td>3</td>
<td>4</td>
<td>0.75 [0.17, 3.34]</td>
</tr>
<tr>
<td>Parodi 2010</td>
<td>1</td>
<td>4</td>
<td>0.21 [0.02, 1.89]</td>
</tr>
<tr>
<td>Patti 2011</td>
<td>1</td>
<td>0</td>
<td>3.09 [0.13, 76.33]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>2850</td>
<td>2792</td>
<td>0.63 [0.20, 2.01]</td>
</tr>
<tr>
<td>Total Events</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\tau^2=0.00$, Chi$^2=1.96$, df=2 ($P=0.38$), $I^2=0\%$

Test for overall effect: $Z=0.78$ ($P=0.44$)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Bivalirudin Events</th>
<th>Heparin Events</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>14563</td>
<td>17929</td>
<td>0.58 [0.45, 0.75]</td>
</tr>
<tr>
<td>Total Events</td>
<td>96</td>
<td>196</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\tau^2=0.00$, Chi$^2=13.90$, df=14 ($P=0.46$), $I^2=0\%$

Test for overall effect: $Z=4.15$ ($P<0.0001$)

Test for subgroup differences: Chi$^2=0.00$, df=1 ($P=0.97$), $I^2=0\%$

**Mortality**

Health

Impact of Bleeding Avoidance Strategies

NCDR CathPCI Registry 2004-2008: **PCI in 1,522,935 pts**

Manual compression alone, closure devices, bivalirudin, or both were used in 35%, 24%, 23%, and 18% of pts, respectively.

**Propensity-adjusted bleeding**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Major bleeding (%)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual compression</td>
<td>2.7</td>
<td>0.77 (0.73 – 0.80)</td>
<td>508,455</td>
</tr>
<tr>
<td>Vascular closure devices</td>
<td>2.5</td>
<td>0.67 (0.63 – 0.70)</td>
<td>205,606</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>1.9</td>
<td>0.38 (0.35 – 0.42)</td>
<td>130,378</td>
</tr>
<tr>
<td>Bivalirudin + VCD</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Marso SP et al. JAMA. 2010;303:2156-64**
Impact of Access and Non-Access Site Bleeding after PCI

17,393 pts underwent PCI in REPLACE-2, ACUITY and HORIZONS
925 pts (5.3%) had TIMI major or minor bleeding within 30 days

568 (61.4%) non access site related

357 (38.6%) Access site only
145 (15.7%) Indeterminate
142 (15.4%) Non access site
281 (30.4%) Access + non access site

Source of bleeding (absolute rate)

Indeterminate – most likely intraprocedural (catheter exchanges) or baseline anemia with lower transfusion threshold

Verheugt FWA et al. JACC Int 2011;4;191-197
Impact of Access and Non-Access Site Bleeding after PCI

17,393 pts underwent PCI in REPLACE-2, ACUITY and HORIZONS
925 pts (5.3%) had TIMI major or minor bleeding within 30 days

Time-updated multivariable risk of death within 1-year

<table>
<thead>
<tr>
<th>TIMI Bleed</th>
<th>HR [95%CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI Bleed - All</td>
<td>3.17 [2.51, 4.00]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TIMI Bleed – Non Access Site</td>
<td>3.94 [3.07, 5.15]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TIMI Bleed – Access Site Only</td>
<td>1.82 [1.17, 2.83]</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Adjusted risk of 1-year mortality

Verheugt FWA et al. JACC Int 2011;4;191-197
Impact of Access and Non-Access Site Bleeding after PCI

17,393 pts underwent PCI in REPLACE-2, ACUITY and HORIZONS
925 pts (5.3%) with 30-day TIMI major or minor bleeding

Impact of bivalirudin on bleeding according to site

<table>
<thead>
<tr>
<th>Site</th>
<th>Relative Risk</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access site</td>
<td>0.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non Access Site</td>
<td>0.62</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>- Non Access + Access Site</td>
<td>0.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>- Non Access Site Only</td>
<td>0.70</td>
<td>0.08</td>
</tr>
<tr>
<td>- Indeterminate</td>
<td>0.75</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Bivalirudin better

NNT for bivalirudin to prevent 1 non-access site-related TIMI bleed = 71
NNT for bivalirudin to prevent 1 access site-related TIMI bleed = 74
Impact of Access and Non-Access Site Bleeding after PCI

17,393 pts underwent PCI in REPLACE-2, ACUITY and HORIZONS
925 pts (5.3%) with 30-day TIMI major or minor bleeding

Impact of bivalirudin on non-access site bleeding

<table>
<thead>
<tr>
<th>Region</th>
<th>Hep + GPI (%)</th>
<th>Bivalirudin (%)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>0.04</td>
<td>0.03</td>
<td>0.66</td>
</tr>
<tr>
<td>GI</td>
<td>0.6</td>
<td>0.28</td>
<td>0.44</td>
</tr>
<tr>
<td>GU</td>
<td>0.64</td>
<td>0.28</td>
<td>0.44</td>
</tr>
<tr>
<td>HEENT</td>
<td>0.33</td>
<td>0.22</td>
<td>0.66</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0.18</td>
<td>0.05</td>
<td>0.31</td>
</tr>
<tr>
<td>Other</td>
<td>0.30</td>
<td>0.15</td>
<td>0.49</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>1.87</td>
<td>1.40</td>
<td>0.75</td>
</tr>
<tr>
<td>All Non - Access Site</td>
<td>3.66</td>
<td>2.27</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Bivalirudin better
H + GPI better
HORIZONS-AMI: 3-year Cardiac Mortality in Pts with vs without Major Bleeding

- **Major bleeding**: P<0.0001
- **No major bleeding**: P=0.04

<table>
<thead>
<tr>
<th></th>
<th>Major bleeding</th>
<th>No major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>11.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Heparin + GPI</td>
<td>14.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>5.8</td>
<td>2.6</td>
</tr>
</tbody>
</table>

- % of cardiac deaths among pts who bled:
  - All pts: 24.6% (34/138)
  - Heparin + GPI: 30.7% (27/88)
  - Bivalirudin: 14.0% (7/50)
  - P=0.03
HORIZONS-AMI: 3-Year Cardiac Mortality in pts with and without Major Bleeding According to Treatment

- **Heparin + GPI (n=1802)**
  - 3-Year Cardiac Mortality: 14.6%
  - HR [95%CI] = 2.56 [1.12, 5.88]
  - P = 0.02

- **Bivalirudin (n=1800)**
  - 3-Year Cardiac Mortality: 5.8%
  - HR [95%CI] = 1.47 [1.00, 2.17]
  - P = 0.048

**Major bleeding**
- Δ = ↓20 deaths

**No major bleeding**
- Δ = ↓18 deaths

# fewer cardiac deaths with bivalirudin

\[ \text{P}_{\text{int}} = 0.34 \]
### HORIZONS-AMI: Multivariable Model for 3-Year Cardiac Mortality, Including Adverse Events

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5 years)</td>
<td>1.34 (1.23 to 1.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC (per 10^9 cells/L)</td>
<td>1.15 (1.09 to 1.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S. creatinine (per 0.1 mg/dl)</td>
<td>1.10 (1.05 to 1.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Killip class 2-4</td>
<td>2.17 (1.41 to 3.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAD PCI</td>
<td>1.68 (1.13 to 2.50)</td>
<td>0.007</td>
</tr>
<tr>
<td>Diabetes, medically treated</td>
<td>1.50 (1.01 to 2.23)</td>
<td>0.045</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.97 (1.88 to 4.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acquired thrombocytopenia</td>
<td>2.10 (1.36 to 3.24)</td>
<td>0.001</td>
</tr>
<tr>
<td>Bivalirudin (vs UFH+GPI)</td>
<td>0.54 (0.38 to 0.79)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Excludes 145 pts with thrombocytopenia at baseline. Other variables in model: current smoker, female gender, prior MI, # vessels treated, hemoglobin.
Procedural anticoagulant use during PCI
CathPCI Registry (~85% cath labs in the US)

941,248 PCIs between Jan 2010 and June 2011

Conclusions: Antithrombin options to support PCI in pts with SIHD and ACS

1. UFH and LMWH have substantial limitations as regards their indirect mechanism of action and non-linear PK/PD (unpredictable), lack of a point-of-care monitoring assay (LMWH), platelet activation (requiring GPIIb/IIIa), and immunogenicity (HITTS)

2. Whether LMWH has meaningful clinical advantages over UFH is uncertain

3. Fondaparinux may have advantages over UFH/LMWH for chronic use, but cannot be used as a stand-alone procedural anticoagulant (catheter thrombosis)
Conclusions: Antithrombin options to support PCI in pts with SIHD and ACS

4. Compared to UFH + GPI, bivalirudin reduces mortality across the spectrum of pts undergoing PCI

5. The mortality benefit of bivalirudin can be attributed to a complex interplay of reduced rates of major bleeding (especially non-access site related), thrombocytopenia, and other mechanisms that have not yet been elucidated

6. These benefits are realized in all PCI pts - including those undergoing radial intervention

7. By reducing major bleeding, bivalirudin is cost-saving
Thanks

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