Anticoagulants in the Cath Lab: The Ongoing Battle

Khiet Nguyen, Pharm.D.
PGY1 Pharmacy Resident
Valley Baptist Medical Center - Brownsville

Abbreviations

- PCI: percutaneous coronary intervention
- PTCA: percutaneous transluminal coronary angioplasty
- uTVR: urgent target-vessel revascularization
- GPI: glycoprotein IIb/IIIa inhibitor
- ACS: acute coronary syndrome
- MI: myocardial infarction
- STEMI: ST-segment elevation myocardial infarction
- UFH: unfractionated heparin
- CVA: cerebrovascular accident
- MACE: major adverse cardiovascular events
- NACE: net adverse clinical events
- DES: Drug-eluting stent
- CAD: coronary artery disease

Patient Case

- 26-year-old male presented to the ER with chest pain
- ECG: STEMI
- Labs: elevated troponin I
- Past medical history: CAD, MI (about 6 months ago)
- Medications: aspirin 325 mg, ticagrelor 180 mg

The cardiologist has requested that the patient go to the cath lab for further evaluation
Which anticoagulant is ideal for this patient undergoing PCI?

A. UFH  
B. UFH + GPI  
C. Bivalirudin  
D. Bivalirudin + GPI  
E. Enoxaparin  
F. Fondaparinux

Objectives

1. Describe the rationale for using anticoagulants during PCI
2. Summarize the early studies that support the use of bivalirudin
3. Discuss the major studies that generate the controversy between bivalirudin and UFH
4. Evaluate the current state and future direction for anticoagulation therapy during PCI

Percutaneous Coronary Intervention

- PCI is recommended for patient with ACS
- Stent can trigger thrombus formation
- Antithrombotic therapy needed to decrease risk of early thrombosis
- UFH was used in PTCA (before stent era)

http://www.acvcare.com/cardiac-catheterization.html
Chest. 1998;114(5 Suppl):728S
Bivalirudin vs. UFH

<table>
<thead>
<tr>
<th></th>
<th>UFH</th>
<th>Bivalirudin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting factor target</td>
<td>IIa and Xa</td>
<td>IIa</td>
</tr>
<tr>
<td>Clotting factor inhibition</td>
<td>Indirect (Antithrombin)</td>
<td>Direct</td>
</tr>
<tr>
<td>Anticoagulant activity</td>
<td>33%</td>
<td>100%</td>
</tr>
<tr>
<td>Onset of action</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td>Half-life</td>
<td>30-60 minutes</td>
<td>25 minutes</td>
</tr>
<tr>
<td>Monitoring in cath lab</td>
<td>ACT</td>
<td>None (or ACT)</td>
</tr>
<tr>
<td>Elimination</td>
<td>Reticulo-endothelial system</td>
<td>Enzymatic/Renal</td>
</tr>
<tr>
<td>Inhibits clot-bound thrombin</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Platelet binding</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Antibody</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Early Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CACHET 2002</td>
<td>Patients with elective or urgent PCI N = 268</td>
<td>Bivalirudin (3 dosing arms) ± GPI (2 arms) vs UFH (70 u/kg) + GPI</td>
<td>- No difference in 30 days death, MI, or uTVR - No difference in major bleeding</td>
</tr>
<tr>
<td>REPLACE-1 2004</td>
<td>Patients with elective or urgent PCI N = 1,056</td>
<td>Bivalirudin ± GPI vs UFH (60-70 u/kg) ± GPI</td>
<td>- No difference in death, MI, or uTVR by hospital discharge or within 48 hours or randomization - No difference in major bleeding</td>
</tr>
</tbody>
</table>

Early Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>REPLACE-2 2003</td>
<td>Patients with elective or urgent PCI N = 9,010</td>
<td>Bivalirudin ± GPI vs UFH (65 u/kg) + GPI</td>
<td>- No difference in 30 day death, MI, or uTVR - Major bleeding lower with bivalirudin (2.4% vs 4.1%; p &lt; 0.001, NNH = 77)</td>
</tr>
<tr>
<td>ACUITY-PCI 2006</td>
<td>Patients with moderate- or high-risk ACS N = 13,819</td>
<td>Bivalirudin vs UFH or GPI vs UFH (60 u/kg) or LMWH + GPI</td>
<td>Bivalirudin vs UFH + GPI - No difference in 30 day death, MI, uTVR, or stent thrombosis - Major bleeding lower with bivalirudin (3.0% vs 5.7%; p &lt; 0.001, NNH = 37)</td>
</tr>
</tbody>
</table>
And the Battle Started: HORIZONS-AMI

- Design: multinational, multicenter, open-label randomized controlled trial
- N = 3,602 patients with STEMI undergoing primary PCI
- Follow-up: 30-days, 6 months, 1 year, and yearly for 5 years
- Analysis: intention to treat

HORIZONS-AMI

Patients with STEMI and symptom onset ≤ 12 hours

300-600 mg clopidogrel or ticlopidine 500 mg before PCI

Bivalirudin* ± GPI

Primary endpoint at 30 days:
1. Major bleeding
2. Net Adverse Clinical Events (death, MI, TVR, stroke, major bleed)

* Bivalirudin was given bolus 0.75 mg/kg followed by 1.75 mg/kg/h infusion

HORIZONS-AMI

Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>80.2 years; male 76.6%</td>
</tr>
<tr>
<td>Past Medical History</td>
<td>Diabetes (15.6%), hypertension (51.8%), hyperlipidemia (43.4%), current smoker (47.2%), renal insufficiency (15.8%)</td>
</tr>
<tr>
<td>Cardiac History</td>
<td>Prior MI (10.4%), prior PCI (10.5%), prior CABG (3.3%)</td>
</tr>
<tr>
<td>Weight</td>
<td>80 kg</td>
</tr>
<tr>
<td>Interval from symptom onset to hospital</td>
<td>2.2 hours</td>
</tr>
<tr>
<td>LVEF</td>
<td>50%</td>
</tr>
</tbody>
</table>

HORIZONS-AMI


Follow-up: 30-days, 6 months, 1 year, and yearly for 5 years

Analysis: intention to treat
• 92.7% patients received PCI
• P2Y12 use:
  - 61% loaded with 600 mg clopidogrel
  - 34% loaded with 300 mg clopidogrel
  - No ticagrelor or prasugrel
• GPI use
  - UFH: 98% (planned)
  - Bivalirudin: 7.2% (provisional)
• Radial access: 7%
• 66% of patients in the bivalirudin group received heparin before cardiac catheterization

### HORIZONS-AMI

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>UFH + GPI N = 1802 (%)</th>
<th>Bivalirudin N = 1800 (%)</th>
<th>NNT/NNH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net adverse clinical events</td>
<td>12.1</td>
<td>9.2</td>
<td>35</td>
<td>0.005</td>
</tr>
<tr>
<td>Major bleeding, non-CABG related</td>
<td>8.3</td>
<td>4.9</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major adverse cardiovascular events</td>
<td>5.5</td>
<td>5.4</td>
<td>-</td>
<td>0.95</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3.1</td>
<td>2.1</td>
<td>100</td>
<td>0.047</td>
</tr>
<tr>
<td>Stent thrombosis, acute (≤ 24 hour)</td>
<td>0.3</td>
<td>1.3</td>
<td>100</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stent thrombosis, subacute (&gt; 24 hour – 30 days)</td>
<td>1.7</td>
<td>1.2</td>
<td>-</td>
<td>0.28</td>
</tr>
</tbody>
</table>

### HORIZONS-AMI

2013 ACCF/AHA STEMI Guidelines

- For patients with STEMI undergoing primary PCI, the following supportive anticoagulant regimens are recommended
  - UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP IIb/IIIa receptor antagonist has been administered (Class I, level C) or
  - Bivalirudin with or without prior treatment with UFH (Class I, level B)
- For patients with STEMI undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and GP IIb/IIIa receptor antagonist (Class IIa, level B)
### Other studies along with HORIZONS-AMI

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Interventions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-REACT 2008</td>
<td>Stable/unstable angina with PCI (N = 4,570)</td>
<td>Bivalirudin* vs UFH (140 units/kg)</td>
<td>No difference at 30 days death, MI, or uTVR (5.9% Bival vs 5.0% UFH); Major bleeding lower with bivalirudin (NNH = 67)</td>
</tr>
<tr>
<td>ISAR-REACT 3a 2010</td>
<td>Stable/unstable angina with PCI (N = 1,056)</td>
<td>UFH (100 units/kg) vs ISAR REACT UFH arm (140 units/kg)</td>
<td>UFH 100 units/kg non-inferior to bivalirudin NACE at 30 days; Major bleeding lower with 100 units/kg (NNH = 100; p = 0.013)</td>
</tr>
<tr>
<td>EuroMAX 2013</td>
<td>STEMI (N = 2,218)</td>
<td>Bivalirudin + GPI vs UFH (80-100 units/kg) ± GPI; drugs started on transport to hospital</td>
<td>No difference in 30 days MACE (6% Bivalirudin vs 6.2% UFH ± GPI); No difference in mortality at 30 days; Major bleeding lower with bivalirudin (NNH = 29, p &lt; 0.001)</td>
</tr>
</tbody>
</table>

*Bivalirudin bolus of 0.75 mg/kg, followed by 1.75 mg/kg infusion

### Battle Tide Turned: HEAT PCI

- Single-center, open-label, blocked, randomized controlled trial
- Inclusion: undergoing PCI for STEMI or suspected STEMI
- N = 1,812
- Enrollment: February 2012 to November 2013
- Mean follow-up: 28 days
- Analysis: intention to treat

### HEAT PCI

- Patients undergoing PCI for STEMI or suspected STEMI
- Ticagrelor, prasugrel, or clopidogrel before PCI
- UFH 70 units/kg ± GPI (repeat bolus by ACT)
- Bivalirudin ± GPI (repeat bolus by ACT)

- Primary endpoint: at 28 days
  - Efficacy: MACE (all-cause mortality, CVA, reinfarction, TVR, stroke)
  - Safety: Major bleeding (BARC 3-5)

- Bivalirudin given bolus 0.75 mg/kg followed by 1.75 mg/kg infusion

All patients received dual antiplatelet before PCI (ASA + clopidogrel, prasugrel, or ticagrelor)
HEAT PPCI

Baseline Characteristics

Demographics
Age 63.3 years; male 72%

Past Medical History
Diabetes (14%), hypertension (41%), hyperlipidemia (41%), current smoker (42%)

Cardiac History
Prior MI (12%), prior PCI (7%), prior CABG (2%)

Weight
80 kg

Interval from symptom onset to randomization
2.8 hours

HEAT PPCI

Methodology

- 82% patients received PCI
- P2Y12 use:
  - Ticagrelor ~ 62%
  - Prasugrel ~ 27%
  - Clopidogrel ~ 11%
- GPI use (bailout):
  - Bivalirudin: 13%
  - UFH: 15%
- Radial access: 81%

HEAT PPCI

Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>UFH N = 907 (%)</th>
<th>Bivalirudin N = 905 (%)</th>
<th>NNT/NNH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse cardiovascular events</td>
<td>5.7</td>
<td>8.7</td>
<td>33</td>
<td>0.01</td>
</tr>
<tr>
<td>Death</td>
<td>4.3</td>
<td>5.1</td>
<td>-</td>
<td>0.43</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1.2</td>
<td>1.6</td>
<td>-</td>
<td>0.43</td>
</tr>
<tr>
<td>New MI or reinfarction</td>
<td>0.9</td>
<td>2.7</td>
<td>56</td>
<td>0.04</td>
</tr>
<tr>
<td>Unplanned TVR</td>
<td>0.7</td>
<td>2.7</td>
<td>50</td>
<td>0.001</td>
</tr>
<tr>
<td>Major bleeding (BARC 3-5)</td>
<td>3.1</td>
<td>3.5</td>
<td>-</td>
<td>0.59</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>0.9</td>
<td>3.4</td>
<td>40</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Lancet 2014;384:1849-58
HEAT PPCI

• Provided strong evidence against the bleeding reduction benefit of bivalirudin
• Use of bivalirudin is decreased for primary PCI and only in patients intolerant to heparin
• 2013 ACCF/AHA guidelines have not been updated

BRIGHT

Patients undergoing emergent PCI for STEMI (88%) or NSTEMI (12%)
N = 2194

- Clopidogrel 300-600 mg
- Clopidogrel 300-600 mg
- Clopidogrel 300-600 mg
- UFH 100 units/kg (repeat bolus by ACT)
- UFH 60 units/kg + GPI (repeat bolus by ACT)
- Bivalirudin* (repeat bolus by ACT)

Primary endpoint: at 30 days
Net Adverse Clinical Events (death, MI, TVR, stroke, and bleeding (BARC 1-5))

*Bivalirudin was given bolus 0.75 mg/kg followed by 1.75 mg/kg/h infusion

BRIGHT

<table>
<thead>
<tr>
<th>Endpoint (at 30 days)</th>
<th>UFH N = 729 (%)</th>
<th>Bivalirudin N = 735 (%)</th>
<th>NNT/NNH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net adverse clinical events</td>
<td>13.2 6.8</td>
<td>8.8 22.7</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Major adverse cardiovascular events</td>
<td>5.8 5.0</td>
<td>4.0 125</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Major bleeding (BARC 1-5)</td>
<td>7.5 4.1</td>
<td>4.9 29.4</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.0 0.6</td>
<td>0.8 333.3</td>
<td>0.81</td>
<td></td>
</tr>
</tbody>
</table>

• Lower bleeding rate of bivalirudin was driven by BARC 1-2
• No difference in major bleeding (BARC 3-5)
• UFH dose (100 units/kg) is not commonly used
• Open-label study done in China
**MATRIX Antithrombin**

- **Design:** multicenter, open-label, nested randomized controlled trial
- **N = 7,213 patients with STEMI (56%) or NSTEMI (46%) requiring emergent PCI
- **Enrollment:** October 2011 to November 2014
- **Follow-up:** 30 days
- **Analysis:** intention to treat

**Interventions**

Patients undergoing emergent PCI for STEMI (56%) or NSTEMI (54%)

- Ticagrelor, prasugrel, or clopidogrel
- UFH* 70-100 unit/kg ± GPI
- Bivalirudin* ± GPI

**Primary endpoint:** at 30 days

1. Major Adverse Cardiovascular Events (death, MI, stroke)
2. Net Adverse Clinical Events (MACE + BARC 3 or 5 bleeding)

*For patient not receiving GPI, heparin was given at dose 70-100 units/kg
*For patient receiving GPI, heparin was given at dose 50-70 units/kg

**Included both NSTEMI and STEMI patients**
- 94.4% of patients underwent PCI
- P2Y12 use:
  - Clopidogrel (45.9%), ticagrelor (23.7%), prasugrel (12.8%)
- GPI use:
  - Heparin (25.9%), bivalirudin (4.6%)
- 50% had radial access
  - Author claimed radial or femoral access did not affect any of the major outcomes
### MATRIX Antithrombin

#### Endpoint (at 30 days)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>UFH N = 3603 (%)</th>
<th>Bivalirudin N = 3610 (%)</th>
<th>NNT/NNH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not adverse clinical events</td>
<td>12.4</td>
<td>11.2</td>
<td>-</td>
<td>0.12</td>
</tr>
<tr>
<td>Major adverse cardiovascular events</td>
<td>10.9</td>
<td>10.3</td>
<td>-</td>
<td>0.44</td>
</tr>
<tr>
<td>Major bleeding (BARC 3 or 5)</td>
<td>2.5</td>
<td>1.4</td>
<td>91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>2.3</td>
<td>1.7</td>
<td>167</td>
<td>0.04</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>0.6</td>
<td>1.0</td>
<td>250</td>
<td>0.048</td>
</tr>
</tbody>
</table>

*Net adverse clinical events*

*Major adverse cardiovascular events*

*Major bleeding (BARC 3 or 5)*

*Death from any cause*

*Stent thrombosis*

---

### MATRIX Antithrombin

- P2Y12 loading different from previous trials
- Asymmetry use of GPI
  - UFH: 25.9% (21.8% planned + 4.1% bailout)
  - Bivalirudin: 4.6%
- Much lower number of cases used radial access approach (50%) than HEAT PPCI
- Wide range of heparin dose (70-100 units/kg) when no GPI, otherwise 50-70 units/kg

---

### What does all this leave us?

<table>
<thead>
<tr>
<th></th>
<th>HORIZONS-AMI 2008</th>
<th>HEAT PPCI 2014</th>
<th>MATRIX 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients received PCI</td>
<td>92.7%</td>
<td>82%</td>
<td>94.4%</td>
</tr>
<tr>
<td>Ticagrelor or Prasugrel Use</td>
<td>0%</td>
<td>90%</td>
<td>36.5%</td>
</tr>
<tr>
<td>GPI Use</td>
<td>Bivalirudin: 7%</td>
<td>Bivalirudin: 13%</td>
<td>Bivalirudin: 4.6%</td>
</tr>
<tr>
<td></td>
<td>UFH: 93%</td>
<td>UFH: 95%</td>
<td>UFH: 25.9%</td>
</tr>
<tr>
<td>Radial access</td>
<td>7%</td>
<td>81%</td>
<td>50%</td>
</tr>
<tr>
<td>MACE</td>
<td>No difference</td>
<td>Lower with UFH</td>
<td>No difference</td>
</tr>
<tr>
<td>Major Bleeding (different definition)</td>
<td>Lower with bivalirudin</td>
<td>No difference</td>
<td>Lower with bivalirudin</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>Greater with bivalirudin (1.3%)</td>
<td>Greater with bivalirudin (3.4%)</td>
<td>Greater with bivalirudin (1.9%)</td>
</tr>
</tbody>
</table>
Current State of the Battle

- HEAT PPCI have different results from HORIZONS-AMI, BRIGHT, and MATRIX-Antithrombin
  - These studies had different methodologies
- Many hope the VALIDATE-SWEDEHEART trial will offer more insight
  - Hybrid registry-based randomized controlled trial
  - Will enroll 6,000 STEMI/NSTEMI patients getting PCI
  - Will use death, MI, and BARC 2, 3, or 5 as composite endpoints
  - Prasugrel, ticagrelor, or cangrelor as part of DAPT

Patient Revisit

Which anticoagulant is ideal for this patient undergoing PCI?
A. UFH
B. UFH + GPI
C. Bivalirudin
D. Bivalirudin + GPI
E. Enoxaparin
F. Fondaparinux

Key Takeaways

- Practice changes, such as radial access, limited GPI use, use of newer P2Y12 inhibitors, new generation of DES have changed the risk of ischemia, bleeding, and stent thrombosis in cath lab
- Recent bivalirudin vs UFH studies have shown conflicting results due to inconsistent methodology
- For patients undergoing PCI with radial access, UFH is preferred over bivalirudin.
- For patients undergoing PCI with high risk of bleeding, bivalirudin is preferred over UFH.
Thank You

• Evan J. Peterson, PharmD, BCPS
• Justin Gonzalez, PharmD
• Andy Orsa, PharmD
• Y-Nha Nguyen, PharmD, BCPS, BCCCP
• Eric Bou, PharmD, BCPS
• Ahmad Khalil, PharmD, BCPS, FCCP
• Mario Varela, PharmD, BCPS

Anticoagulants in the Cath Lab:
The Ongoing Battle