Μπιβαλιρουδίνη σε STEMI

Παύλος Στουγιάννος
Καρδιολόγος
ΓΝΑ «Η ΕΛΠΙΣ»
Conflict of interest: None
The coagulation cascade with bivalirudin and heparin inhibition targets
2018 ESC/EACTS Guidelines on myocardial revascularization

The Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS)

<table>
<thead>
<tr>
<th>DOWNGRADES</th>
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</thead>
<tbody>
<tr>
<td>Distal protection devices for PCI of SVG lesions</td>
</tr>
<tr>
<td>Bivalirudin for PCI in NSTE-ACS</td>
</tr>
<tr>
<td><strong>Bivalirudin for PCI in STEMI</strong></td>
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<tr>
<td>PCI for MVD with diabetes and SYNTAX score &lt;23</td>
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<tr>
<td>Platelet function testing to guide antiplatelet therapy interruption in</td>
</tr>
<tr>
<td>patients undergoing cardiac surgery</td>
</tr>
<tr>
<td>EuroSCORE II to assess in-hospital mortality after CABG</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Class I</th>
<th>Class IIa</th>
<th>Class IIb</th>
<th>Class III</th>
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</thead>
<tbody>
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</tbody>
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[Image: www.hcs.gr]
The Rise and Fall of Anticoagulation with Bivalirudin During Percutaneous Coronary Interventions: A Review Article

Constantinos Andreou · Christos Maniotis · Michael Koutouzis
# Bivalirudin trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial</th>
<th>Population</th>
<th>Primary end point</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>REPLACE-2</td>
<td>Patients without acute MI</td>
<td>Composite of death, MI, urgent repeat revascularization within 30 days of randomization or in-hospital major bleeding</td>
<td>9.2% bivalirudin vs. 10% heparin plus GPI, p = 0.32</td>
</tr>
<tr>
<td>2006</td>
<td>ACUITY</td>
<td>ACS patients</td>
<td>1st: 30-day composite ischemic end point (death, MI, unplanned revascularization for ischemia)</td>
<td>(a) 7.7% bivalirudin plus GPI vs. 7.3% heparin plus GPI, p = 0.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2nd: 30-day major bleeding</td>
<td>(b) 7.8% bivalirudin alone vs. 7.3% heparin plus GPI, p = 0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3rd: 30-day net clinical outcome (composite of ischemia or major bleeding)</td>
<td>(a) 5.3% bivalirudin plus GPI vs. 5.7% heparin plus GPI, p = 0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(b) 3.0% bivalirudin alone vs. 5.7% heparin plus GPI, p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(a) 11.8% bivalirudin plus GPI vs. 11.7% heparin plus GPI, p = 0.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(b) 10.1% for bivalirudin alone vs. 11.7% for heparin plus GPI, p = 0.02</td>
</tr>
<tr>
<td>2008</td>
<td>HORIZONS-AMI</td>
<td>STEMI patients</td>
<td>1st: 30-day major bleeding</td>
<td>4.9% bivalirudin vs. 8.3% heparin plus GPI, p &lt; 0.001</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>2nd: 30-day combined adverse clinical events (death, reinfarction, target vessel revascularization for ischemia, stroke, and major bleeding)</td>
<td>9.2% for bivalirudin vs. 12.1% for heparin plus GPI, p = 0.005</td>
</tr>
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</table>
There was a significant 1.0% increase of stent thrombosis during the first 24 h after PCI among patients treated with bivalirudin.

Patients treated with bivalirudin who received UFH before randomization had a more favorable prognosis.

Time-to-Event Curves through 30 Days

The HORIZONS-AMI Trial

HORIZONS-AMI: 30-Day Adverse Events

- Heparin + GPIIb/IIIa inhibitor (N=1802)
- Bivalirudin monotherapy (N=1800)

30 day event rates (%)

- Reinfarction: P=0.90
- Major bleeding*: P<0.001
- Thrombocytopenia**: P=0.002

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

Stone GW et al. NEJM 2008;358:2218-30

The HORIZONS-AMI Trial

3-Year Mortality: Cardiac and Non Cardiac

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

3-yr HR [95%CI] = 0.56 [0.40, 0.80]
P = 0.001
5.1%

2.9%

3-yr HR [95%CI] = 1.11 [0.74, 1.65]
P = 0.62
3.1%

2.8%

## Bivalirudin trials

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<td>Composite of all-cause mortality, cerebrovascular accident, reinfarction or unplanned target lesion revascularization at 28 days</td>
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<td>NAPLES III</td>
<td>Elective PCI in high risk bleeding patients</td>
<td>In-hospital major bleeding</td>
<td>3.3% bivalirudin vs. 2.6% UFH, ( p = 0.54 )</td>
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<td>2014</td>
<td>BRIGHT</td>
<td>MI patients</td>
<td>A composite of death from any cause, reinfarction, ischemia-driven target vessel revascularization, stroke, or any bleeding at 30 days</td>
<td>8.8% bivalirudin vs. 13.2% heparin, vs. 17% for heparin plus tirofiban, ( p &lt; 0.001 )</td>
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| 2015 | MATRIX      | STEMI and NSTEMI patients   | Whether bivalirudin with bailout GP IIb/IIIa inhibitor (GPI) use was superior to UFH with planned or bailout GPI use in reducing MACE | STEMI patients: 5.9% bivalirudin vs. 6.5% heparin, \( p = 0.43 \)  
NSTEMI patients: 15.9% bivalirudin vs. 16.4% heparin, \( p = 0.74 \) |
HEAT PPCI

How Effective are Antithrombotic Therapies in PPCI

Heparin versus Bivalirudin in PPCI

Dr Adeel Shahzad
Dr Rod Stables (PI)
Liverpool Heart and Chest Hospital
Liverpool, UK

Lancet 2014: on-line
HEAT PPCI: Timing of First MACE

Death, ReMI, CVA, TLR (%)

- Bivalirudin
- Heparin

<table>
<thead>
<tr>
<th>Days</th>
<th>Bivalirudin</th>
<th>Heparin</th>
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<tbody>
<tr>
<td>0</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3%</td>
<td>5%</td>
<td>0.01</td>
</tr>
<tr>
<td>15</td>
<td>6%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>9%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>10%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>10%</td>
<td>12%</td>
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</tbody>
</table>

No. at risk
- Heparin: 907, 871, 866, 862, 857, 856
- Bivalirudin: 905, 853, 844, 835, 830, 828

Shahzad A. ACC 2014
## Bivalirudin trials

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MATRIX Program

NSTEMI or STEMI with invasive management
Aspirin+P2Y12 blocker

ACCESS

1:1

Trans-Radial Access

1:1

Trans-Femoral Access

Bivalirudin
Bailout GPI

Unfractionated Heparin
with planned or bailout GPI

ANTITHROMBIN
The MACE end point (death, MI, or stroke), was not statistically different between the two treatment regimens independently of the presence or not of ST segment elevation.

Rate ratio, 0.94; 95% CI, 0.81 to 1.10; P = 0.45

Cumulative incidence (%) vs Days since randomisation

UFH vs Bivalirudin

RR: 0.94; 95% CI: 0.81-1.10; P=0.45
Mortality:
All-Cause, Cardiac, Vascular and non-CV mortality

All-cause mortality
Rate ratio, 0.71; 95% CI, 0.51 to 0.99; P=0.042

Cumulative incidence (%)

Days since randomisation

UFH
Bivalirudin

CV Death Cardiac Non-CV
BIV 1.6 1.5 0.1
UFH 2.3 2.2 0.1

RR: 0.70 (0.50-0.98) P=0.037
RR: 0.68 (0.48-0.97) P=0.032
Bleeding endpoints: BARC 3 or 5

Rate ratio, 0.55; 95% CI, 0.39 to 0.78; P=0.001

Cumulative incidence (%)

Days since index procedure

UFH
Bivalirudin

2.5%
1.4%
Bleeding endpoints:
BARC, TIMI, GUSTO, access vs non-access related

**Access Site**
- Non Access Site: 0.6, 0.9, 0.8
- BARC 3: 1.6
- BARC 5: 0.1
- TIMI: 1
- GUSTO: 0.9

**BARC 3 or 5**
- Bivalirudin: 0.53, 0.59
- UFH: 1.04, 1.04

**P-values and Relative Risks (RR)**

- BARC 3 or 5: P=0.008, RR: 0.61 (0.42-0.88)
- Access Site: P=0.005, RR: 0.53 (0.34-0.83)
- TIMI: P=0.002, RR: 0.50 (0.33-0.75)
- GUSTO: P=0.027, RR: 0.61 (0.39-0.95)

*NOTE: RR values and P-values are approximate.*
# Bivalirudin trials

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**VALIDATE-SWEDHEART trial**

Bivalirudin versus heparin monotherapy  

$N = 6006$

Composite of death from any cause, myocardial infarction, or major bleeding during 180 days of follow-up occurred in 12.3% in the bivalirudin arm versus 12.8% in the heparin arm ($P=0.54$).
The VALIDATE-SWEDEHEART study

Bivalirudin versus Heparin Monotherapy in Myocardial Infarction

The VALIDATE-SWEDEHEART study

A randomized trial of Bivalirudin versus Heparin Monotherapy
The STEMI cohort

Stefan James, MD, PhD
Professor Cardiology,
Uppsala University, Sweden

J Andersson, O Angerås, M Danielewicz, D Ioanes, T Kellerth, S Koul, B Lagerqvist, E Omerovic, T Råmunddal, S Völz, L Wallentin, O Östlund, D Erlinge
The VALIDATE-SWEDEHEART study

Aim and end points

- The aim was to investigate bivalirudin compared to heparin in patients with STEMI using a modern strategy with:
  - mandatory use of potent P2Y12 inhibitors prior to PCI
  - recommended low dose of heparin prior to randomization
  - no planned GPI use
  - predominantly radial-artery access for PCI
- The primary end point was the composite of death, myocardial infarction, or major bleeding events at 180 days.
Study design

STEMI (n=3005)
Treatment with Ticagrelor, Prasugrel or Cangrelor
Heparin 5000U pre-hospital or < 3000 U allowed pre angio
Angiography performed: PCI intended

1:1

Heparin only
(70-100U/kg)
(no planned GPI)

Bivalirudin

Primary Endpoint:
NACE: Death, Myocardial Infarction or Bleeding events (BARC 2, 3 or 5) at 180 days

Coordinating PI: David Erlinge, Lund University, Sweden
Chairman: Stefan James, Uppsala University, Sweden

Clinicaltrials.gov: NCT02311231  Trial design: Erlinge et al., Am Heart J 2014
The VALIDATE-SWEDEHEART study

In-lab procedures

<table>
<thead>
<tr>
<th></th>
<th>Heparin</th>
<th>Bivalirudin</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI flow prior to PCI, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 0</td>
<td>57.7</td>
<td>60.0</td>
</tr>
<tr>
<td>TIMI 1</td>
<td>8.7</td>
<td>9.1</td>
</tr>
<tr>
<td>TIMI 2</td>
<td>14.8</td>
<td>14.4</td>
</tr>
<tr>
<td>TIMI 3</td>
<td>18.7</td>
<td>16.4</td>
</tr>
<tr>
<td>Radial approach, (%)</td>
<td>91.2</td>
<td>89.6</td>
</tr>
<tr>
<td>P2Y12, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>93.7</td>
<td>94.4</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>4.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Time from administration of oral P2Y12 to PCI (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 h</td>
<td>56.6</td>
<td>60.2</td>
</tr>
<tr>
<td>1-2 h</td>
<td>34.9</td>
<td>33.6</td>
</tr>
<tr>
<td>&gt; 2 h</td>
<td>8.5</td>
<td>6.2</td>
</tr>
</tbody>
</table>
The VALIDATE-SWEDEHEART study

Primary Endpoint at 180 days

- H.R. 0.95
- 95% CI, (0.78-1.17)
- P = 0.64

30 days: H.R. 0.91 (0.71-1.17)
P = 0.47
The VALIDATE-SWEDEHEART study

Mortality at 180 days

HR 1.15
95% CI, 0.68 – 1.94
P = 0.98

30 days: H.R. 1.08 (0.70-1.66)
P = 0.73
The VALIDATE-SWEDEHEART study

Bleeding events 30 days

- **Heparin**
  - BARC 2: 3.3
  - BARC 3: 2.8
  - BARC 5: 1.7

- **Bivalirudin**
  - BARC 2,3: 5.1
  - BARC 5: 4.8

NS indicates non-significant difference.
The VALIDATE-SWEDEHEART study

Stent thrombosis (ST) 30 days including intraprocedural

![Graph showing the comparison between Heparin and Bivalirudin in terms of possible, probable, and definitive ST with corresponding hazard ratios.]
Conclusions

- In patients presenting with STEMI treated with high-intensity platelet inhibition, UFH pre treatment and radial approach there was no difference between the treatment arms on the primary endpoint or any individual endpoints including stent thrombosis and minor bleeding.
- The results were consistent across major subgroups.
Use and Effectiveness of Bivalirudin Versus Unfractionated Heparin for Percutaneous Coronary Intervention Among Patients With ST-Segment Elevation Myocardial Infarction in the United States

Eric A. Secemsky, MD, MSc, a,b,c Ajay Kirtane, MD, SM, d Sripal Bangalore, MD, MHA, g Ion S. Jovin, MD, f Rachit M. Shah, MBBS, f Enrico G. Ferro, BS, b Neil J. Wimmer, MD, MSc, g Matthew Roe, MD, MHS, h Dadi Dai, PhD, h Laura Mauri, MD, MSc, b,i Robert W. Yeh, MD, MSc, b,c
B

Absolute Risk Differences with Bivalirudin

**Transradial Access**

- In-hospital major bleeding (p=0.16)
- In-hospital mortality (p=0.37)
- Access site bleeding (p=0.92)
- Non-access site bleeding (p=0.74)
- RBC transfusion (p=0.64)
- Repeat PCI for stent thrombosis (p=0.95)

Absolute Risk Differences with Bivalirudin

**Transradial Access, Adjusting for GPI Use**

- In-hospital major bleeding (p=0.84)
- In-hospital mortality (p=0.09)
- Access site bleeding (p=0.27)
- Non-access site bleeding (p=0.70)
- RBC transfusion (p=0.47)
- Repeat PCI for stent thrombosis (p=0.53)
C

Absolute Risk Differences with Bivalirudin

Transfemoral Access

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Bivalirudin -%</th>
<th>Difference -%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital major bleeding</td>
<td>-4.04</td>
<td>-4.04</td>
<td>(&lt;0.01</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>-1.69</td>
<td>-1.69</td>
<td>(p=0.25</td>
</tr>
<tr>
<td>Access site bleeding</td>
<td>-1.23</td>
<td>-1.23</td>
<td>(&lt;0.01</td>
</tr>
<tr>
<td>Non-access site bleeding</td>
<td>+0.48</td>
<td>+0.48</td>
<td>(&lt;0.01</td>
</tr>
<tr>
<td>RBC transfusion</td>
<td>+0.01</td>
<td>+0.01</td>
<td>(&lt;0.01</td>
</tr>
<tr>
<td>Repeat PCI for stent thrombosis</td>
<td>-0.96</td>
<td>-0.96</td>
<td>(&lt;0.01</td>
</tr>
</tbody>
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Absolute Risk Differences with Bivalirudin

Transfemoral Access, Adjusting for GPI Use

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<th>p-value</th>
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<td>In-hospital major bleeding</td>
<td>-0.78</td>
<td>-1.72</td>
<td>(&lt;0.01</td>
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<tr>
<td>In-hospital mortality</td>
<td>-0.65</td>
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<td>(&lt;0.01</td>
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Outcomes in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction Via Radial Access Anticoagulated With Bivalirudin Versus Heparin

A Report From the National Cardiovascular Data Registry

Ion S. Jovin, MD, ScD, Rachit M. Shah, MBBS, Dhavalkumar B. Patel, MBBS, MPH, Sunil V. Rao, MD, Dmitri V. Baklanov, MD, Issam Moussa, MD, Kevin F. Kennedy, MS, Eric A. Secemsky, MD, MSc, Robert W. Yeh, MD, MSc, Michael C. Kontos, MD, George W. Vetrovec, MD
Odds Ratios for Various Outcomes including the Main Endpoint

- **In-hospital Death/Stroke/MI**: 0.95 (0.87, 1.05)
- **In-hospital Death**: 0.91 (0.81, 1.03)
- **Acute Stent Thrombosis**: 2.11 (1.73, 2.57)
- **Subacute Stent Thrombosis**: 1.36 (1.09, 1.70)
- **In-hospital Major Bleeding**: 0.98 (0.91, 1.05)

<<< Outcome Better with Bivalirudin >>>

Outcome Worse with Bivalirudin >>>
Antithrombotic drugs in STEMI patients undergoing P-PCI
Take-home messages

✓ **Heparin** should be the preferred antithrombotic choice in STEMI.

✓ **Bivalirudin** should be considered as an alternative strategy only in patients **at high risk of bleeding**.

✓ Bivalirudin’s superiority regarding major bleeding is restricted only to **patients with femoral access** but not those undergoing PCI using the radial approach.
Ευχαριστώ για την προσοχή σας