Heparin induced thrombocytopenia and extracorporeal circulation:

WHAT SHOULD WE KNOW, WHAT CAN WE DO?

Co-assistent Alexander Dehouwer

Promotor: Prof. Dr. Arne Neyrinck
Outline

- Heparin
- Heparin Induced Thrombocytopenia
  - Mechanism of Action
  - Diagnosis
- Alternatives
  - Lepirudin
  - Bivalirudin
  - Heparin + Platelet inhibition
- Guidelines American College of Chest Physicians
Heparin: Mechanism of action

- **aPTT**
- **ACT**
- **Protamine**
## Heparin induced Thrombocytopenia

<table>
<thead>
<tr>
<th>HIT Type 1 “HAT”</th>
<th>HIT Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-immune mediated</td>
<td>Immune mediated</td>
</tr>
<tr>
<td>Between days 1 and 4 of treatment</td>
<td>Within 5 to 14 days of therapy (may occur within hours in case of recent exposure to heparin)</td>
</tr>
<tr>
<td>Platelet count seldom drops below 100,000/µL</td>
<td>Leads to extremely low platelet counts</td>
</tr>
<tr>
<td>Resolves without intervention or need to discontinue heparin</td>
<td>All heparin must be avoided in order for platelet count to recover</td>
</tr>
<tr>
<td>No thromboembolic events</td>
<td>Possibly devastating thromboembolic complications</td>
</tr>
</tbody>
</table>
HIT Type 2: Pathophysiology

The pathogenesis of heparin-induced thrombocytopenia

1. Immunoglobulin G (IgG) forms immune complexes with heparin and platelet factor 4 (PF4)

2. The immune complex binds to the platelet Fc receptor, resulting in strong platelet activation and release of more PF4

3. Additional immune complexes are formed, leading to a vicious cycle of platelet activation

4. These immune complexes also bind to the vascular endothelium, creating a cascade of events that accelerate platelet aggregation and thrombus formation
## 4T’s pretest probability for HIT

<table>
<thead>
<tr>
<th>4 T’s</th>
<th>2 points</th>
<th>1 point</th>
<th>0 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet count fall &gt; 50% and the lowest count (nadir) ≥ 20 x 10^9/liter</td>
<td>Platelet count fall 30-50% or platelet nadir 10-19 x 10^9/liter</td>
<td>Platelet count fall &lt;30% or platelet nadir &lt;10 x 10^9/liter</td>
</tr>
<tr>
<td>Timing of platelet count fall</td>
<td>Clear onset between days 5-10 or platelet fall ≤1 day (prior heparin exposure within 30 days)</td>
<td>Consistent with days 5-10 fall, but not clear (e.g. missing platelet counts); onset after day 10, or fall ≤1 day (prior heparin exposure 30-100 days ago)</td>
<td>Platelet count fall &lt;4 days without recent exposure</td>
</tr>
<tr>
<td>Thrombosis or other sequelae</td>
<td>New thrombosis (confirmed); skin necrosis; acute systemic reaction post intravenous UFH bolus</td>
<td>Progressive or recurrent thrombosis, Non necrotizing (erythematous) skin lesions, Suspected thrombosis (not proven)</td>
<td>None</td>
</tr>
<tr>
<td>Other causes for thrombocytopenia</td>
<td>None apparent</td>
<td>Possible (e.g. septicemia without proven microbiological cause)</td>
<td>Definite (e.g. proven bacteremia, within 72 hours of surgery, Posttransfusion purpura)</td>
</tr>
</tbody>
</table>

Problems with HIT during ECC

Activation of the clotting cascade by
1) Contact with foreign surfaces
2) Contact of blood with air
3) Contact of blood with Tissue Factor in the wound

Ideal anticoagulant for CPB
- Inexpensive
- Produces rapid anticoagulant effect
- Produces no drug-specific antibodies
- Rapid and simple method of reversing anticoagulant effect
- Rapid and simple method of monitoring anticoagulant effect

Solution: Heparin Coated circuit and Heparinisation of blood

COATING

Heparin coated

Not-coated

Carmeda coating: Covalent bound heparin coating
No activation of platelets

Fosforyl chlorine coating
Alternatives for UFH

- **Direct Thrombin Inhibitors**
  - Lepirudin (Refludan®)
  - Bivalirudin (Angiomax®/Angiox®)
  - Argatroban (Insufficient data) (Arganova®)

1: Catalytic site  
2: Substrate binding site

## Lepirudin (Refludan®) vs Bivalirudin (Angiox®)

<table>
<thead>
<tr>
<th></th>
<th>Lepirudin</th>
<th>Bivalirudin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elimination</strong></td>
<td>Primarily renal</td>
<td>80% proteolytic cleavage 20% renal excretion</td>
</tr>
<tr>
<td><strong>Plasma half-life</strong></td>
<td>80 minutes</td>
<td>25 minutes</td>
</tr>
<tr>
<td><strong>Anaphylaxis</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Monitoring:** Low doses: aPTT – High doses: Ecarin Clotting Time or ACTT

**Reversal:** No reversal agent known => Hemofiltration
Table 4. Treatment Protocol for Lepirudin Anticoagulation During CPB

<table>
<thead>
<tr>
<th>Lepirudin plasma level</th>
<th>Dosing modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4.5 μg/mL</td>
<td>Reduce infusion rate by 10 mL/h</td>
</tr>
<tr>
<td>3.5-4.5 μg/mL</td>
<td>No change in infusion rate</td>
</tr>
<tr>
<td>&lt;3.5 μg/mL</td>
<td>Increase infusion rate by 10 mL/h</td>
</tr>
</tbody>
</table>

Special steps toward end of CPB
Stop lepirudin infusion 15 minutes before anticipated end of CPB.
After disconnection of CPB, administer 5 mg of hirudin to the heart-lung machine to avoid clot formation.

Abbreviations: CPB, cardiopulmonary bypass; IV, intravenous.
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*Fifty milligrams of lepirudin are dissolved in 50 mL 0.9% sodium chloride.
†The target lepirudin level pre-CPB (>2.5 μg/mL) is lower than the ones sought during CPB (3.5-4.5 μg/mL) because of the addition of lepirudin to the pump circuit volume (0.2 mg/kg body weight).

Lepirudin: Treatment protocol

Lepirudin (Refludan®)

- Koster et al.: Retrospective data analysis on 57 patients with HIT undergoing cardiac surgical procedures with hirudin
  - 50 patients had uncomplicated surgery with low blood loss (170 mL over 24 hours)
  - 4 patients developed postoperative renal failure: all needed surgical reexploration
  - 3 patients died of complications unrelated to anticoagulation management

- Nuttall et al: Prospective study on 12 patients with a history of HIT
  - 6 pt were antibody negative, received UFH
    => Unsignificant transfusion requirements
  - 6 pt were antibody positive, received lepirudin
    => 5/6 pt received >40 U of blood products, 3/6 required surgical reexploration
Bivalirudin (Angiox®)

- **CHOOSE-ON trial by Koster et al.**
  - 49 patients with HIT and positive PF4/Heparin antibodies, treated with bivalirudin during cardiopulmonary bypass
  - After 7 days procedural succes in 46 patients (94%)
  - No differences in outcome between patients with moderately impaired renal function and others

- **EVOLUTION-ON trial by Dyke et al.**
  - 21 institutions randomized 101 non-HIT patients to bivalirudin and 49 patients to heparin treatment during CPB
  - No significant differences in mortality, 24-hour blood loss, overall incidence of transfusions, and duration of surgery between the two arms
# Bivalirudin: Treatment protocol

**Table 5. Treatment Protocol for Bivalirudin Anticoagulation During CPB**

<table>
<thead>
<tr>
<th>Initial bivalirudin dosing (pre-CPB)</th>
<th>1.5 mg/kg body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial IV bivalirudin bolus and initiate continuous IV infusion</td>
<td>2.5 mg/kg/h (42 µg/kg/min)</td>
</tr>
<tr>
<td>Bivalirudin added to pump circuit volume</td>
<td>50 mg</td>
</tr>
<tr>
<td>Target bivalirudin plasma level</td>
<td>&gt;10 µg/mL before start of CPB</td>
</tr>
<tr>
<td>If &lt;10 µg/mL, give additional bolus (0.25 mg/kg and increase infusion rate by 0.25 mg/kg/h)</td>
<td></td>
</tr>
</tbody>
</table>

**Bivalirudin dosing and monitoring while on CPB**

- Continue IV infusion (adjusted as below)
- Frequency of bivalirudin level monitoring: Every 30 minutes using ECT
- Intraoperative dose adjustments, based on ECT
  - Bivalirudin plasma level (ECT)*:
    - >15 µg/mL (>500 s)
    - 10-15 µg/mL (400-500 s)
    - <10 µg/mL (<400 s)
- Special steps at end of CPB
  - Stop bivalirudin infusion at end of CPB, then either:
    - (A) Within 10 minutes of stopping bivalirudin infusion: first reinfuse appropriate portion of pump volume to patient, and then give 50 mg bivalirudin bolus to the circuit to prevent clotting; start an infusion of 50 mg/h into the circuit only, and continue to recirculate; any subsequent reinfusion of remaining pump volume to patient should be processed through a cell saver (which removes >90% of bivalirudin) or
    - (B) Promptly empty remaining pump volume into cell-saving device (replacing the pump contents with crystalloid), thus avoiding need for postseparation bivalirudin boluses to circuit; process blood for reinfusion with cell saver to remove bivalirudin.

*The target bivalirudin concentration (10-15 µg/mL) corresponds to an ecarin clotting time (ECT) of 400-500 seconds using the RapidPoint Coag (Bayer, Pittsburgh, PA); with other ECT methods, the bivalirudin concentration should be determined using a calibration curve.

Bivalirudin (Angiox®) Protocol UZ Leuven

- **Initial Dosing**
  - 50mg in priming CPB
  - Bolus IV: 1.0 mg/kg
  - Continuous infusion 2.5mg/kg/h
  - Target ACT: 2.5 x Baseline ACT
  - If subtherapeutic ACT, then Additional bolus 0.2 mg/kg

- **During CPB**
  - Continuous infusion 2.5mg/kg/h
  - ACT monitoring every 15-30 minutes
  - If subtherapeutic ACT, then Additional bolus 0.1-0.5 mg/kg

- **End of CPB**
  - Stop Bivalirudin infusion 15 min before end CPB
  - Check ACT every 5 minutes
  - Empty CPB in Cellsaver and replace with crystalloids
  - Wash blood in Cellsaver to remove bivalirudin
Iloprost
- Analog of prostacyclin
- Antoniou et al.
  - 22 HIT patients
  - Good clinical outcomes

Epoprostenol (Flolan®)
- Freeze-dried preparation prostacyclin
- Aouifi et al.
  - 6 HIT patients
  - Better outcome then 4 controls treated with danaparoid

**Advantages**
1. Short Half-life (6 minutes)
2. ACT monitoring remains reliable
3. After complete inhibition, Heparin and Protamin can be used in standard dosis

**Disadvantages**
- Can cause vasodilatation
Epoprostenol (Flolan®) UZ Leuven Protocol

- Solve 1500 µg Flolan in 50 ml solvent
- Start infusion at 5 ng/kg/min
- Increase infusion every 5 minutes until a maximum of 30 ng/kg/min
- Treat hypotension with vasopression
- When the maximum dose of 30 ng/kg/min is reached heparin can be administered in standard dosing
- Monitor anticoagulation using ACT every 15-30 minutes
- If needed, protamine can be used for reversal at the end of the procedure. The Flolan infusion should not be stopped until 15 minutes after protamine reversal.
• In patients with acute HIT (thrombocytopenic, HIT antibody positive) or subacute HIT (platelets recovered, but still HIT antibody positive) who require urgent cardiac surgery, we suggest the use of bivalirudin over other non heparin anticoagulants and over heparin plus antiplatelet agents (Grade 2C).

• In patients with acute HIT who require nonurgent cardiac surgery, we recommend delaying the surgery (if possible) until HIT has resolved and HIT antibodies are negative (see section 6.1) (Grade 2C).
Thank you for your attention!