Interventional Pharmacology

Scott Smiley MSN, RN
Disclosure Statement of Financial Interest

I, (Scott Smiley) DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Mechanical vessel injury in PCI and spontaneous injury in ACS are thrombogenic.

**Acute coronary syndromes**

- **Stable angina**
  - Pain: Chest pain on exertion
  - Markers: Not elevated
  - ECG: ECG changes transient

- **UA / NSTE-ACS**
  - New onset of severe, accelerating, or rest pain
  - Troponin+
  - No ST elevation

- **STEMI**
  - Troponin+
  - CKMB++
  - ST elevation

---

**Mechanical processes**

- Atheroma
- Plaque rupture
- Clot
- Closure

Plaque rupture (caused by PCI)

---

**References**

Thrombus formation involves both platelet activation and blood coagulation
Current interventional drugs armamentarium for PCI

**Antithrombin drugs**
- Heparins (UFH, LMWH)
- Fondaparinux
- Bivalirudin

**Antiplatelet drugs**
- Aspirin
- Oral P2Y$_{12}$ antagonists (Clopidogrel, Prasugrel, Ticagrelor)
- Glycoprotein IIb/IIIa inhibitors (GPI)
Current interventional drugs armamentarium for PCI

**Antithrombin drugs**
- Heparins (UFH, LMWH)
- Fondaparinux
- Bivalirudin

**Antiplatelet drugs**
- Aspirin
- Oral P2Y<sub>12</sub> antagonists (Clopidogrel, Prasugrel, Ticagrelor)
- Glycoprotein IIb/IIIa inhibitors (GPI)
Heparins (UFH/LMWH): mechanism of action

- Heparin/antithrombin (AT) complex inhibits thrombin and Factor Xa
- Must have adequate AT present for anticoagulant effect

![Diagram showing the mechanism of action of heparins](image)

Adapted from Hirsh J et al. Chest 2001;119:64S–94S.
Pharmacological properties of current anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>UFH</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predictability in pharmacological profile</strong></td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td><strong>Cofactor required</strong></td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Renal clearance</strong></td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td><strong>Non-specific protein binding</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Platelet activation</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Rebound of thrombin generation after discontinuation</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Inhibition of bound thrombin</strong></td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><strong>Neutralization by platelet factor 4</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Inhibition of thrombin generation</strong></td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
### RCT comparing IV enoxaparin vs. UFH

<table>
<thead>
<tr>
<th>Study</th>
<th>Pts</th>
<th>Comparators</th>
<th>Setting</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEEPLE¹</td>
<td>3528</td>
<td>IV UFH Vs. IV enoxaparin 0.75 mg/kg Vs. IV enoxaparin 0.5 mg/kg</td>
<td>Elective PCI</td>
<td>▪ Significant reduction in 48h non-CABG-related bleeding* with Enoxaparin 0.5.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ Significant reduction in major bleeding with both enoxaparin groups.</td>
</tr>
<tr>
<td>SYNERGY²</td>
<td>10027</td>
<td>IV UFH Vs. Enoxaparin</td>
<td>NSTE-ACS with early invasive approach</td>
<td>▪ No differences in 30-day death/MI*.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ No differences in procedural events.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ Bleeding modestly higher with enoxaparin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ Relative advantage of enoxaparin when therapy crossovers were censored.</td>
</tr>
<tr>
<td>ATOLL³</td>
<td>910</td>
<td>IV UFH Vs. IV enoxaparin 0.5 mg/kg</td>
<td>STEMI</td>
<td>▪ Not significant reduction of 30-day ischaemic outcomes with enoxaparin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ No differences in bleeding.</td>
</tr>
</tbody>
</table>

*Primary endpoint

²Ferguson et al. JAMA. 2004;292:45-54.
Current interventional drugs armamentarium for PCI

Antithrombin drugs
- Heparins (UFH, LMWH)
- Fondaparinux
- Bivalirudin

Antiplatelet drugs
- Aspirin
- Oral P2Y<sub>12</sub> antagonists (Clopidogrel, Prasugrel, Ticagrelor)
- Glycoprotein IIb/IIIa inhibitors (GPI)
Fondaparinux

- Synthetic pentasaccharide
- **Indirect selective Factor Xa inhibitor**
- Inactive against thrombin already generated
- $T_{1/2} = 17-21 \text{ hrs}$
- Once-daily dosing
- No laboratory monitoring
Data on fondaparinux

- Fondaparinux Vs. enoxaparin In NSTE-ACS: lower bleeding, leading to lower 30-day mortality.
- Fondaparinux Vs. UFH in STEMI: reduced death/MI in pts treated with thrombolysis; increased ischemic events in primary PCI.
- Fondaparinux is not recommended for PCI because of higher catheter-related thrombosis; recommended adjunctive use of UFH at the time of PCI in NSTE-ACS.
- The addition of low or standard UFH dose at the time of PCI does not increase bleeding; low dose UFH was not superior to standard ACT-guided UFH dosing.
Current interventional drugs armamentarium for PCI

**Antithrombin drugs**
- Heparins (UFH, LMWH)
- Fondaparinux
- Bivalirudin

**Antiplatelet drugs**
- Aspirin
- Oral P2Y\textsubscript{12} antagonists (Clopidogrel, Prasugrel, Ticagrelor)
- Glycoprotein IIb/IIIa inhibitors (GPI)
Bivalirudin

- Bivalent reversible direct thrombin (free & clot-bound) inhibitor
- Lack of dependence on antithrombin-III
- Intravenous administration; 100% bioavailable
- T1/2 = 25 min
- Dose- and concentration-dependent anticoagulant activity
Pharmacological properties of current anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>UFH</th>
<th>LMWH</th>
<th>Bivalirudin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictability in pharmacological profile</td>
<td>−</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Cofactor required</td>
<td>+++</td>
<td>+++</td>
<td>−</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>−</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Non-specific protein binding</td>
<td>+++</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Platelet activation</td>
<td>+++</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Rebound of thrombin generation after discontinuation</td>
<td>+++</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Inhibition of bound thrombin</td>
<td>−</td>
<td>−</td>
<td>+++</td>
</tr>
<tr>
<td>Neutralization by platelet factor 4</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Inhibition of thrombin generation</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>
## RCT on bivalirudin

<table>
<thead>
<tr>
<th>Study</th>
<th>Pts</th>
<th>Comparators</th>
<th>Setting</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACUITY</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>13,819</td>
<td>Heparin + GPI Vs. Bivalirudin + GPI Vs. Bivalirudin</td>
<td>NSTE-ACS (PCI 56%)</td>
<td>Similar ischemic events.</td>
</tr>
<tr>
<td>(Multicenter)</td>
<td></td>
<td></td>
<td></td>
<td><strong>Bleed reduction</strong> with bivalirudin monotherapy</td>
</tr>
<tr>
<td><strong>ISAR-REACT 4</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1,721</td>
<td>UFH + GPI Vs. Bivalirudin</td>
<td>NSTE-ACS (PCI 100%)*</td>
<td>No differences in ischemic events/major bleed</td>
</tr>
<tr>
<td>(Multicenter)</td>
<td></td>
<td></td>
<td></td>
<td><strong>Bleed reduction</strong> with bivalirudin.</td>
</tr>
<tr>
<td><strong>HORIZONS-AMI</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3,602</td>
<td>UFH + GPI vs. Bivalirudin (infusion stopped at the end of PCI)</td>
<td>STEMI (P-PCI)</td>
<td><strong>Bleed and mortality reduction</strong> with bivalirudin.</td>
</tr>
<tr>
<td>(Multicenter)</td>
<td></td>
<td></td>
<td></td>
<td>Similar MACE; acute ST higher with bivalirudin.</td>
</tr>
<tr>
<td><strong>EUROMAX</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>2,218</td>
<td>Heparin + optional GPI Vs. Bivalirudin (infusion prolonged after PCI*)</td>
<td>STEMI (P-PCI)</td>
<td>• Death/major bleed reduction with bivalirudin.</td>
</tr>
<tr>
<td>(Multicenter)</td>
<td></td>
<td></td>
<td></td>
<td>• Similar death.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Acute ST higher with bivalirudin.</td>
</tr>
<tr>
<td><strong>BRIGHT</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2,194</td>
<td>UFH Vs. Bivalirudin Vs. UFH + Tirofiban</td>
<td>STEMI Non-STEMI</td>
<td><strong>Ischemic events/bleed reduction</strong> with bivalirudin compared to both groups.</td>
</tr>
<tr>
<td>(Multicenter)</td>
<td></td>
<td></td>
<td></td>
<td>**Bleed reduction with bivalirudin.</td>
</tr>
<tr>
<td><strong>HEAT-PPCI</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td>1,812</td>
<td>UFH Vs. Bivalirudin (infusion stopped at the end of PCI)</td>
<td>STEMI (P-PCI)</td>
<td>Reduction in ischemic events with UFH</td>
</tr>
<tr>
<td>(Sigle center)</td>
<td></td>
<td></td>
<td></td>
<td><strong>No difference in bleeding</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Acute ST higher</strong> with bivalirudin.</td>
</tr>
</tbody>
</table>

*Most patients received the prolonged infusion at 0.25 mg/kg/hr.
In a EUROMAX subanalysis, ST was not increased among patients continuing infusion at the PCI dosage 1.75 mg/kg/hr

---

## Antithrombin for PCI: guidelines

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>UFH</th>
<th>Bivalirudin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elective PCI (EU 2014)</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>IIa</td>
<td>I</td>
<td>IIa*</td>
</tr>
<tr>
<td><strong>Elective PCI (U.S. 2011)</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>IIb</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td><strong>NSTE-ACS (EU 2014)</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>IIa**</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td><strong>NSTE-ACS (U.S. 2011)</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>IIb</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td><strong>STEMI (EU 2014)</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>IIa</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td><strong>STEMI (U.S. 2013)</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>-</td>
<td>I</td>
<td>I</td>
</tr>
</tbody>
</table>

*In patients at high risk for bleeding*

**Enoxaparin should be considered for PCI in patients pre-treated with subcutaneous enoxaparin. Crossover of UFH and LMWH is not recommended.**

Current interventional drugs armamentarium for PCI

Antithrombin drugs
- Heparins (UFH, LMWH)
- Fondaparinux
- Bivalirudin

Antiplatelet drugs
- Aspirin
- Oral P2Y$_{12}$ antagonists (Clopidogrel, Prasugrel, Ticagrelor)
- Glycoprotein IIb/IIIa inhibitors (GPI)
Outcomes without pre-PCI aspirin
No ASA given w/i 24 hrs pre-PCI in 4,640 (7.1%) of 65,175 pts. Propensity-matched in-hospital outcomes in 4,008 pt pairs:

Current interventional drugs armamentarium for PCI

Antithrombin drugs
- Heparins (UFH, LMWH)
- Fondaparinux
- Bivalirudin

Antiplatelet drugs
- Aspirin
- Oral P2Y$_{12}$ antagonists (Clopidogrel, Prasugrel, Ticagrelor)
- Glycoprotein IIb/IIIa inhibitors (GPI)
Pharmacological properties of oral P2Y12 inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td>Thienopyridine</td>
<td>Thienopyridine</td>
<td>CPTP</td>
</tr>
<tr>
<td><strong>Receptor blockade</strong></td>
<td>irreversible</td>
<td>irreversible</td>
<td>reversible</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td>2-8 h</td>
<td>30 min-2 h</td>
<td>30 min – 2 h</td>
</tr>
<tr>
<td><strong>Offset of action</strong></td>
<td>7-10 days</td>
<td>7-10 days</td>
<td>3-5 days</td>
</tr>
<tr>
<td><strong>Need for metabolic activation</strong></td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>CYP drug interactions</strong></td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

PD data have shown that both Prasugrel and Ticagrelor provide faster and enhanced platelet inhibition than clopidogrel.
PCI CURE: PCI performed in 2658 pts (21%)

TRITON-TIMI 38 Study Design

All ACS Patients (N=13,608)

- UA/NSTEMI (n=10,074)
- STEMI (n=3534)

Randomization after angiography, except in STEMI <12h

CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

Median duration of therapy – 12 months

Net Clinical Benefit (CV Death/ MI/ CVA/TIMI Major Bleeding) Bleeding Risk Subgroups

Prior Stroke / TIA
- Yes: P_int = 0.006, Risk (%) +54
- No: Risk (%) -16

Age (years)
- >=75: P_int = 0.18, Risk (%) -1
- < 75: Risk (%) -16

Weight
- < 60 kg: P_int = 0.36, Risk (%) +3
- >= 60 kg: Risk (%) -14

OVERALL: Risk (%) -13

Prasugrel Better: 0.5 - 1 HR
Clopidogrel Better: 1 - 2 HR
Randomisation

Ticagrelor 180mg LD then 90 mg bd (n = 9,333)

Clopidogrel 300mg* LD then 75 mg od (n = 9,291)

*patients previously treated with clopidogrel will have placebo; Additional 300 mg of clopidogrel allowed pre PCI

All patients received aspirin (75-100mg od) + GP IIb/IIIa antagonist
Aspirin naive patients received a loading dose (160-500mg : 325mg preferred)

0       1 month  2 month   3 month  6-12months study length

PLATO: Efficacy Endpoints at 12 Months

**Primary Endpoint**
- HR 0.84; 95% CI 0.77-0.92; p<0.001

**Death**
- HR 0.78; 95% CI 0.69-0.89; p<0.001

**MI**
- HR 0.84; 95% CI 0.75-0.95; p=0.005

**Stroke**
- HR 1.17; 95% CI 0.91-1.52; p=0.22

**Definite/Probable ST**
- HR 0.75; 95% CI 0.59-0.95; p=0.02

*CV Death, Nonfatal MI, or Nonfatal Stroke

PLATO: Safety Endpoints at 12 Months

Current interventional drugs armamentarium for PCI

Antithrombin drugs
- Heparins (UFH, LMWH)
- Fondaparinux
- Bivalirudin

Antiplatelet drugs
- Aspirin
- Oral P2Y$_{12}$ antagonists (Clopidogrel, Prasugrel, Ticagrelor)
- Glycoprotein IIb/IIIa inhibitors (GPI)
GP IIb/IIIa inhibitors for PCI

- Recommended for **bail-out use**.
- Planned use can be considered in **selected high-risk patients** or in **ACS patients not pre-treated** with an oral P2Y$_{12}$ inhibitor.
- Implications of **routine bolus (IV, IC or IL)** during primary PCI for STEMI have to be better established.
Current issues on interventional antithrombotic therapy

1. **Pre-treatment with P2Y$_{12}$ inhibitors**: clinical benefit in STEMI; questionable benefit in low-risk NSTE-ACS; no benefit with prasugrel pre-treat in NSTE-ACS in the ACCOAST study.

2. **Optimal duration of DAPT**: evidence for no benefits of >12m DAPT, although current studies are not powered for low rate events. 6m DAPT seems safe as 12m for new gen DES.

3. **Optimal antiplatelet regimens after PCI**: ongoing studies on ticagrelor alone Vs DAPT after one month from stenting.

4. **Role of genetic and platelet function testing to guide therapy**: not yet established by RCTs, should be considered research tools.

5. **Management of PCI patients on anticoagulation**: recent EU consensus (Eur Heart J. 2014); more data are needed.
Closing remarks

▪ The **bivalirudin role vs. UFH (with provisional GPI use)** in primary PCI is currently unsettled. Multicenter studies are needed.

▪ Clopidogrel is the only drug indicated for PCI in stable CAD.

▪ **The choice of one P2Y12 inhibitor over another** should be based on clinical setting and risk-benefit ratio.

▪ Prasugrel contraindicated in pts with prior TIA/stroke and for pre-treatment

▪ **The best antithrombotic combination** therapy for PCI has to be established yet.

▪ New antithrombotic drugs are under evaluation for PCI.