Heparin-Induced Thrombocytopenia and New Anticoagulants

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How a Blood Clot Forms: Step One

**ENDOTHELIUM**

**PLATELETS ADHERE TO INJURED VESSEL WALL**

**Fibrinogen**

**PLATELETS AGGREGATE TO EACH OTHER**

**INJURED VESSEL WALL**

**GPIb**

**vWF**

**GPIIb/IIIa**
How a Blood Clot Forms: Step 2

- XII
- XI
- IX
- VIIIa
- VIIa/TF
- VII
- TF
- X
- Va
- IIa (thrombin)
- fibrinogen (factor I)
- Fibrin Clot

HMWK, PK (factor I)

PTT

PT
Natural Ways to Prevent a Blood Clot from Becoming too Large (a Thrombosis)

Activated Protein C with cofactor Protein S

Factor V Leiden

PTT

HMWK, PK

XII

XI

IX

VIIIa

X

IIa

V

II (prothrombin)

Plasminogen (factor I)

Fibrinogen

Fibrin Clot

Antithrombin III

Prothrombin Gene Mutation G20210A

Natural Ways to Prevent a Blood Clot from Becoming too Large (a Thrombosis)

Activated Protein C with cofactor Protein S

Factor V Leiden

PTT

HMWK, PK

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VIIIa

X

IIa

V

II (prothrombin)

Plasminogen (factor I)

Fibrinogen

Fibrin Clot

Antithrombin III

Prothrombin Gene Mutation G20210A
Doctor’s Ways to Prevent a Blood Clot from Becoming too Large (a Thrombosis)

- PTT
- PT
- Coumadin
- Heparin
- LMWH
- Fondaparinux
- Hirudin, Argatroban, or Bivalirudin

- Fibrinogen (factor I)
- Fibrin Clot
- IIa (thrombin)
HEPARIN

LOW-MOLECULAR WEIGHT HEPARIN

degrade

FONDAPARINUX
The Need for New Anticoagulants

- Heparin-induced thrombocytopenia
- Heparin prophylaxis for DVT is imperfect
- Heparin-associated osteoporosis
- Heparin does not inhibit clot-bound thrombin
- Warfarin requires several days to take effect
- Warfarin is suboptimal in certain common clinical situations, eg. Trousseau’s or antiphospholipid antibody syndrome
- Bleeding risk
## Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Anticoagulant:</th>
<th>Monitor by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coumadin</td>
<td>INR (calculate from PT)</td>
</tr>
<tr>
<td>Heparin</td>
<td>PTT</td>
</tr>
<tr>
<td></td>
<td>High dose (bypass): ACT</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>Monitor by</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Low-molecular weight heparin</td>
<td>Anti-factor Xa or no monitoring</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Anti-factor Xa or no monitoring</td>
</tr>
<tr>
<td>Hirudin</td>
<td>PTT</td>
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<tr>
<td>Argatroban</td>
<td>PTT</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>No monitoring or ACT</td>
</tr>
</tbody>
</table>
Heparin-Induced Thrombocytopenia

- Most significant adverse effect of heparin after bleeding
- Most common drug-induced thrombocytopenia
- Also called “white clot syndrome” because of the high risk for catastrophic thrombosis
- A large percentage of patients receive heparin: heparin flushes, heparin-coated catheters, deep vein thrombosis prophylaxis or treatment, myocardial infarction, vascular or cardiac procedures or surgery
The First 90 Consecutive HIT ELISA Positive Patients at the Massachusetts General Hospital

- 69% Thrombocytopenia without thrombosis
- 30% Thrombosis and thrombocytopenia
- 1% Thrombosis without thrombocytopenia
Effect of HIT on Length of Stay at MGH

Length of Stay (days)

\[ p < 0.05 \]
Consecutive HIT Patients with Thrombosis at MGH

- 31.1% (28/90) of all HIT patients
- **Mortality 25.0%** (7/28)
- Venous thrombosis 50.0% (14/28)
- Arterial thrombosis 46.4% (13/28)
- Severe skin necrosis 3.6% (1/28)
Thrombosis in HIT at MGH

- Pulmonary embolism (PE) 32.1% (9/28)
- Lower extremity arterial occlusion 25% (7/28)
- Stroke 21.4% (6/28)
- Deep vein thrombosis without PE 17.9% (5/28)
- Amputation 14.3% (4/28)
- Upper extremity venous thrombosis 14.3%
- Internal jugular vein thrombosis 10.7%

Many patients experienced more than one of the above
MGH SICU Study

2046 patients, 10% had HIT test; 19 HIT positive (4 had major thrombosis):

- Mortality 32% vs 7% (vs 19 matched controls)
- Length of Stay 20 vs 10 days
- Bacteremia 53% vs 16%
- Flushes induced HIT in 12/19 (63%)
- Five patients received platelet transfusions after HIT diagnosis; 4 died

*Crit Care Med 2003; 31:A60 (#286)*
**PI$^{A2}$ Enhances Thrombotic Risk in HIT**

<table>
<thead>
<tr>
<th>Type of Thrombus</th>
<th>Total Patients</th>
<th>PI$^{A2}$</th>
<th>PI$^{A1}$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous</td>
<td>13/66</td>
<td>3/16</td>
<td>10/50</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(19%)</td>
<td>(20%)</td>
<td></td>
</tr>
<tr>
<td>Arterial</td>
<td>10/66</td>
<td>6/16</td>
<td>4/50</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(38%)</td>
<td>(8%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4/66</td>
<td>2/16</td>
<td>2/50</td>
<td>NS</td>
</tr>
<tr>
<td>TOTAL</td>
<td>27/66</td>
<td>11/16</td>
<td>16/50</td>
<td>0.0088</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(69%)</td>
<td>(32%)</td>
<td></td>
</tr>
</tbody>
</table>
Is Repeat Testing Useful?

Among patients with an initially negative HIT result, what percent turned positive (mean = 3 days later)?:

- 43% (13/30) with a high-titer negative HIT result turned positive on average 3 days later
- 13% (4/32) with medium-titer negative
- 5% (1/20) with low-titer negative

Our lab now flags high-titer negatives with the comment “Negative but borderline; suggest repeat in 3 days”

*Am J Clin Pathol 2003; 119:61-65 at MGH*
HIT ELISA Assays

- Homebrew and commercial ELISAs vary in sensitivity and specificity

At MGH:
- Oct 1998 Stago 25/88 positive vs 10/88 GTI
- Jan 2000 Stago 18/45 positive vs GTI 28/45 positive (10 discrepant results)
- July 2000 Stago and GTI both 29/45 positive; 4 discrepant results
Treatment of Heparin-Induced Thrombocytopenia

- Discontinue all heparin (and LMWH)
  - No heparin flushes
  - No heparinized catheters
- Avoid platelet transfusions
  - Platelet transfusions can contribute to the formation or extension of a thrombus
Treatment of Heparin-Induced Thrombocytopenia

**FDA Indications:**

- **Hirudin** (Refludan/lepirudin): HIT patients with thrombosis
- **Argatroban**: HIT patients with or without thrombosis
- **Fondaparinux**: prevent venous thrombosis in knee or hip surgery
- **Bivalirudin**: angioplasty
Argatroban and Percutaneous Coronary Intervention (PCI) in HIT Patients

*FDA approved regimen:*

- 350 ug/kg bolus over 3-5 minutes then 25 ug/kg/min
- Check ACT in 5-10 minutes; goal 300-450 seconds
- If <300 seconds: bolus 150 ug/kg then 30 ug/kg/min
- If >450 seconds: 15 ug/kg/min
- Once ACT 300-450 is reached, use that dose throughout the procedure
- Check ACT 5-10 minutes after dosage change, and during prolonged procedures, every 20-30 minutes
- Additional 150 ug/kg boluses and 40 ug/kg/min may be used if needed to reach ACT goal
Orgaran (danaparoid)

- **Orgaran** is no longer available
- Was a good treatment option for HIT
- Follow platelet count when using **Orgaran** (danaparoid) and discontinue the drug if thrombocytopenia persists or worsens
Anticoagulants for the Treatment of Heparin-Induced Thrombocytopenia

- **Hirudin** (Refludan/lepirudin): Avoid if abnormal RENAL function; monitor with PTT

- **Argatroban**: Reduce dose if LIVER failure (can use with renal failure); monitor with PTT

- **Fondaparinux** (Arixtra):
  - Avoid if severe RENAL dysfunction
  - monitor with “heparin assay” (anti-factor Xa assay)
  - no published HIT trials yet with fondaparinux; case series of 20 patients at MGH with good outcome in press
Prophylactic Treatment of Heparin-Induced Thrombocytopenia

- HIT is a prothrombotic state- anticoagulation is recommended even if no thrombosis
- **Fondaparinux** 2.5 mg subcutaneously once daily
  - FDA-approved, but not specifically for HIT
- **Hirudin or Argatroban** same dose as for treatment of thrombosis
  - not yet FDA-approved for thrombosis prevention in non-HIT patients
Hirudin (lepirudin/Refludan) 0.4 mg/kg bolus then 0.15 mg/kg/hr to keep PTT 1.5-2.5x mean of normal

Argatroban 2 ug/kg/min (up to 10 ug/kg/min) to keep PTT 1.5-3x baseline

Fondaparinux 7.5 mg once daily (5 mg if <50 kg person, 10 mg if >100 kg (limited data- not FDA approved)
Renal and Liver Failure and the New Anticoagulants

- **Hirudin** avoid if RENAL failure
- **Argatroban** reduce dose to 0.5 ug/kg/min if LIVER failure (can use with renal failure)
  - MGH pharmacists data in press: decrease dose to 0.5-1 ug/kg/min with renal failure (Cardiology 2004; 38:25)
- **Fondaparinux** may need to reduce dose with RENAL failure
Hirudin

- Direct thrombin (factor IIa) inhibitor
- 65 amino acid protein from leech
- recombinant
- Prolongs PT, PTT, thrombin time, ACT, ecarin clotting time
- Monitor with PTT
  - thrombin time too sensitive
  - PT too insensitive
Hirudin Advantages

- No “heparin resistance”
- Dose-response more predictable than heparin
- Inhibits clot-bound thrombin
- Does not cause “HIT” and does not cross-react with HIT antibodies
- Short half-life of 1 hour (similar to heparin)
- Convenient laboratory monitoring with PTT
Hirudin Disadvantages

- Cleared by kidney
  - half-life prolonged to 52 hours or longer with end-stage renal failure
  - decrease dose when creatinine ≥ 1.6
- Anti-hirudin antibody formation
  - may prolong the anticoagulation half-life
- No reversal agent
  - may not be necessary due to short half-life
- Expensive
Emergency Reversal Options for Hirudin

- Plasmapheresis
- Hemofiltration; high-flux membranes with a cut-off point of 50,000 daltons
- Peritoneal Dialysis
Clinical Trials with Hirudin*

- Superior in **treatment of venous thrombosis** vs. heparin
- Superior in **prevention of venous thrombosis** vs. heparin, low-molecular weight heparin
- **Myocardial infarction** and **unstable angina** vs. heparin
- **HIT**, including case series reports of bypass surgery using hirudin

*similar bleeding rates as with heparin, LMWH*
Thrombin (factor IIa)

Hirudin

1 = Catalytic site
2 = Substrate-binding site

Bivalirudin

Argatroban

1 = Thrombin (factor IIa)

1 = Thrombin (factor IIa)

53-64
Bivalirudin (Angiomax)

- Amino acids 53-64 of hirudin, which binds to the substrate recognition site of thrombin
- PLUS D-phe-pro-arg-pro-(gly)₄ to the amino terminal end of the above, which binds to the active catalytic site of thrombin
- Transient effect because thrombin slowly cleaves the pro-arg bond
Bivalirudin

- FDA-approved for percutaneous transluminal coronary angioplasty (PTCA) in unstable angina patients, with aspirin
- 1 mg/kg IV bolus then 4 hours at 2.5 mg/kg/hr, then 0.2 mg/kg/hr for up to 20 hours, if needed
- Renal impairment: reduce dose and follow ACT (keep above 300 sec)
Bivalirudin Advantages

- No “heparin resistance” (independent of antithrombin III, does not bind proteins)
- Dose-response more predictable than heparin
- Inhibits clot-bound thrombin
- Does not cause “HIT” and does not cross-react with HIT antibodies
- Short half-life of 25 minutes
- No laboratory monitoring required for angioplasty unless renal failure (ACT), although studies did monitor ACT
Bivalirudin Disadvantages

- Cleared by kidney
  - Clearance reduced by 20% in moderate and severe renal dysfunction
  - Clearance reduced by 80% in hemodialysis patients
  - *(advantage: 25% is cleared by hemodialysis)*
- Anti-bivalirudin *antibody* developed in 2/494
- No *reversal agent*
  - may not be necessary due to short half-life
- Expensive
Argatroban

- Direct thrombin (factor IIa) inhibitor
- Synthetic, small, molecular structure
- Prolongs PT, PTT, thrombin time, ACT, ecarin clotting time
- Monitor with PTT
  - thrombin time too sensitive
  - PT too insensitive
Argatroban Advantages

- Same advantages as HIRUDIN
- Half-life less than one hour
- Can use with renal failure
- No anti-argatroban antibodies yet reported
Argatroban Disadvantages

- Half-life prolonged if **liver failure**
- No **reversal agent**
  - may not be necessary due to short half-life
- **Expensive**
Argatroban Clinical Trials

■ **HIT**: Arg 911 trial (304 HIT patients) found 44% (74% if HIT-thrombosis) improvement in new thrombosis, amputation, and death due to thrombosis

■ **MI**: MINT trial (125 patients) vs heparin, with tPA: enhanced reperfusion (significantly if patient presented after 3 hours)

*No increase in major bleeding vs historical controls*

*Bleeding less than with heparin for MI*
PT Therapeutic Range

- Argatroban < Bivalirudin < Hirudin
  - 1.15-2.0* 1.09-1.39* 1.06-1.2*

*PT ratio that corresponds to therapeutic PTT; use this instead of PTT if can’t use PTT (assumes normal baseline PT)

- Low ISI PT’s are less prolonged than High ISI PT’s

AJCP 2004; 121:593
HEPARIN

LOW-MOLECULAR WEIGHT HEPARIN

FONDAPARINUX

degrade
Fondaparinux (Arixtra)

- Factor Xa inhibitor
- Synthetic
- Pentasaccharide (the 5 saccharides of heparin that bind and enhance activity of antithrombin III)
- Long half-life (17-21 hr) good for outpatients
- No laboratory monitoring (yet)
Anti-Factor Xa Assay

1) Patient plasma + purified Xa +/- antithrombin III

2) residual Xa + artificial substrate

3) residual Xa cleaves substrate, releasing a yellow-colored compound

4) color is measured in a spectrophotometer
Fondaparinux (Arixtra)

- Peaks 3 hours after injection
- Anti-Xa peak 0.39-0.5 ug/mL after 2.5 mg
- Anti-Xa peak ~0.5-1.1 ug/mL after 7.5 mg (accumulates after repeated doses??)
- Use fondaparinux for the standard curve in the anti-Xa assay
- PT, PTT relatively insensitive
Fondaparinux (Arixtra) Advantages

- No “heparin resistance”
- Dose-response more predictable than heparin
- Does not cause HIT or cross-react with HIT antibodies (not proven?)
- Long half-life good for outpatients
- Easier to transition to Coumadin
Fondaparinux (Arixtra) Disadvantages

- Cleared by the kidney
- Long half-life and no reversal agent – problem if patient bleeds
- Expensive +/-
Fondaparinux Clinical Trials

- Fondaparinux better than enoxaparin for prevention of thrombosis with hip fracture surgery, or knee or hip replacement
- Equal or better than heparin for pulmonary embolism
- Bleeding not significantly different in most studies (but increased in at least one study)
Low Anti-Xa Level

- Confirm drug and dose
  - prophylactic dosing gives low anti-Xa level

- Did specimen take over an hour to arrive in the laboratory?
  - falsely low levels may result due to PF4

- If subcutaneous dosing, was the specimen drawn 4 hours after LMWH, 3 hours after fondaparinux, or 6 hours after Orgaran injection (peak level)?

- If indicated, offer a suggested higher dose
High Anti-Xa Level

- Confirm drug and dose
- Renal failure?
  - If yes, the drug half-life could be prolonged and a lower dose may be indicated
- Drawn from a heparinized line?
  - heparin contamination will increase the anti-Xa result
  - If HIT, there should not be heparin in the lines!
- If indicated, offer a suggested lower dose
Coumadin in Heparin-Induced Thrombocytopenia

- Coumadin alone has caused venous limb gangrene due to thrombosis from decreased protein C
- Therefore do not use coumadin alone
- Treat patients with hirudin, argatroban, Orgaran, or fondaparinux while initiating Coumadin until INR $> 2$
Monitoring Coumadin

- Can monitor coumadin with PT/INR while on fondaparinux or Orgaran
- Cannot monitor coumadin with PT/INR while on hirudin or argatroban because they prolong the PT/INR
  - **chromogenic factor X assays**: target factor X level approximately 20-40%
  - coumadin decreases factor X (and II, VII, IX)
  - chromogenic factor X assays do not involve thrombin (factor IIa) and therefore are not affected by hirudin or argatroban
Chromogenic Factor X
- substrate resembles factor X’s natural substrate (factor II)
- Factor X cleaves the artificial substrate, releasing a colored compound that is detected by the instrument

Routine Factor X (PT-based):
- PT clotting time is prolonged by hirudin or argatroban, causing falsely low factor X results by this method
Monitoring Coumadin while on Hirudin: Alternative Approaches

- **INR**: when INR reaches 2, decrease hirudin 50%; when INR reaches 2.5 stop hirudin OR

- **INR**: reduce hirudin to 1.5x PTT, stop hirudin when INR >2
Estimating Coumadin INR with Concomitant 2 ug/kg/min Argatroban

\[ ISI = 1.8 \]
INR Warfarin Alone

Reagents with higher ISI give higher INR on combined therapy of warfarin and argatroban.
Coumadin with Argatroban

- When you suspect the INR is in the therapeutic for Coumadin, discontinue argatroban and re-check INR in 4-6 hours.

- The graph is NOT reliable for doses above 2 ug/kg/min. Reduce dose to 2 ug/kg/min, and re-check INR in 4-6 hours.
Monitoring Coumadin with Chromogenic Factor X

- INR < 2 Subtherapeutic
- INR 2-3 Therapeutic
- INR > 3 Supratherapeutic
Chromogenic X versus INR: Establishing Therapeutic Range

- Patients stable on warfarin alone
- Chromogenic X 20-40% is approximately equivalent to INR 2-3 at MGH lab
- n = 22
Chromogenic X: Correlation is Approximate

- Fits with therapeutic range 20-40% = INR 2-3?:
  - Y = YES
  - X = NO
Bypass and Orgaran

53 patients

- Increased bleeding in 57% (severe in 23%); bleeding as expected in 43%
  - No anti-Xa monitoring
  - One-third had clots in the circuit or surgical field
  - 23% died by 6 weeks:
    - 3 within 48 hours (1 bleeding, 1 thrombosis, 1 heart failure) = 5.7%
    - 8 between 2-6 weeks post-op (4 thrombosis, 1 MOF, 1 liver failure, 1 Sweet’s syndrome, 1 unknown)

57 patients with hirudin and aprotinin

- ECT and chromogenic IIa monitoring q 15 minutes (3.5-4 ug/ml hirudin; ECT 300-400 sec)
- 7% required re-exploration for bleeding (all had renal dysfunction)
- 5.3% deaths (MI, ischemic bowel, septic MOF)
- 3.5% clots in CPB system
- Augmented hirudin elimination by lasix, mannitol, and ultrafiltration

Koster A…J Cardiothorac Vasc Anesth 2000; 14:243
Other Options for Bypass

- Delay surgery until HIT antibody disappears; use heparin during bypass only
- Prostaglandin E1 + heparin during bypass

*D’Ambra MN…Anesth Analg 2001; 92:SCA8*
Coagulation Tests Affected by Alternative Anticoagulants

Hirudin or Argatroban interfere with almost all coagulation testing!

- false positive lupus anticoagulant tests
- false positive mixing studies for inhibitors
- falsely low coagulation factor assays and fibrinogen
- falsely high antithrombin III levels
- falsely high/no result in protein S functional assays
- falsely high clot-based protein C functional assays
- unknown effect on activated protein C resistance assays
- prolonged ACT
Coagulation Tests Affected by Alternative Anticoagulants

- **Fondaparinux**: probably no interferences, but possible false positive lupus anticoagulant assays or mixing studies; thrombin time, PT, PTT, ACT prolongations possible?

- Unaffected assays:
  - **Immunoassays** including anticardiolipin antibody, protein C/S/ATIII antigen assays, HIT ELISA, homocysteine
  - **DNA-based** assays including PCR for factor V Leiden or prothrombin G20210A
  - **Reptilase time**
Summary:
Advantages of the New Anticoagulants

- Dose-response more predictable than heparin, making lab monitoring less important (especially for fondaparinux and Orgaran)
- Fondaparinux and Orgaran: easier to overlap with coumadin (compared with hirudin and argatroban)
- Hirudin and argatroban:
  - Short half-lives
  - Monitor with PTT
Summary: Disadvantages of the New Anticoagulants

- Expensive
- No reversal agents
- **Fondaparinux and Orgaran:**
  - long half-life
  - monitor with anti-factor Xa assays
- **Hirudin:** very sensitive to renal dysfunction
Laboratory Monitoring of Alternative Anticoagulants: Summary

- New anticoagulants are effective in preventing thrombosis and mortality in HIT
- **Hirudin** unless renal failure: PTT 1.5-2.5x
- **Argatroban** unless liver failure: PTT 1.5-3x
- **Fondaparinux** best for outpatients? (subcutaneous) Anti-Xa assays optional
- **Coumadin** with hirudin or argatroban: use chromogenic factor X assays to assess true INR