HIT or Miss: Direct Oral Anticoagulants For Heparin-Induced Thrombocytopenia

A presentation for HealthTrust members
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Disclosures

- The presenter has no financial relationships with any commercial interests pertinent to this presentation.

- This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand or drug.
Pharmacist Objectives

- Summarize the pathophysiology, clinical features and five phases of heparin-induced thrombocytopenia (HIT)
- Compare and contrast evidence-based guideline recommendations from the American College of Chest Physicians and the American Society of Hematology on the treatment of HIT
- Evaluate primary literature available for the use of direct oral anticoagulants (DOACs) in HIT
- Recall the mechanism of action and dosing of different DOACs used for HIT
Pharmacy Technician Objectives

- Recognize complications associated with the development of HIT
- Identify the five phases of HIT
- List the DOACs that have been used in the treatment of HIT
Heparin-Induced Thrombocytopenia

- Approximately one-third of hospitalized patients receive heparin each year in the United States

- Of these patients, 1–5% may experience heparin-induced thrombocytopenia (HIT)

- HIT is a life-threatening, prothrombotic state that results from an immune-mediated reaction to heparin exposure
  - May occur regardless of dose, route, frequency or type of heparin

- Paradoxically, HIT is strongly associated with thrombosis
  - “Heparin-induced thrombocytopenia with thrombosis” (HITT)
  - Requires prompt discontinuation of heparin and initiation of therapeutic non-heparin anticoagulation

Pathophysiology

1. Heparin forms immune complex with platelet factor 4 (PF4)
2. PF4-heparin complex results in IgG antibody production (HIT antibodies)
3. PF4-heparin-IgG immune complex binds to Fc receptors on platelets
4. Platelet activation occurs and prothrombotic platelet-derived microparticles are released
5. Generation of thrombin and formation of venous and arterial thrombosis

Risk Factors

- **Duration of therapy**
  - Prolonged exposure (>5 days)

- **Heparin type**
  - Unfractionated heparin > low molecular weight heparins

- **Dose**
  - Therapeutic dosing > prophylactic dosing

- **Route of administration**
  - Intravenous > subcutaneous > flushes

- **Biological source of heparin**
  - Bovine > porcine

- **Patient population**
  - Surgical > medical > obstetrical

- **Gender**
  - Females > males

Sources:
Clinical Features

■ Thrombocytopenia is the most common manifestation of HIT
  - Platelet count decline ≥50% from baseline or to <150 x 10⁹/L
  - Median platelet nadir is ~50-60 x 10⁹/L
  - Typical onset ~ 5–10 days after initial heparin exposure, but can occur within 24 hours if recent exposure in the past 30–90 days due to presence of circulating HIT antibodies

■ Thrombosis can occur in 50–89% of patients if HIT is left untreated
  - Venous thrombosis (deep vein thrombosis or pulmonary embolism)
  - Arterial thrombosis (peripheral arterial thrombosis, ischemic stroke or myocardial infarction)

■ Other complications include:
  - Limb gangrene → amputation
  - Necrotizing skin lesions at injection site
  - Anaphylactoid reactions
    - Fever/chills, tachycardia, hypertension, dyspnea, cardiopulmonary arrest

Sources:
Differential Diagnosis for Thrombocytopenia

- Immune thrombocytopenia
- Drug-induced thrombocytopenia
- Antiphospholipid syndrome
- Sepsis-associated disseminated intravascular coagulation
- Post-transfusion purpura

Agents Associated with Drug-Induced Thrombocytopenia

- Cytotoxic chemotherapeutic agents (carboplatin, alkylating agents, anthracycline antimetabolites)
- Ethanol
- Anti-inflammatory drugs (aspirin)
- Sedatives, anticonvulsants (diazepam, valproate, phenytoin, carbamazepine)
- Antibiotics (sulfonamides, penicillins, cephalosporins, trimethoprim, linezolid)
- Cardiovascular agents (thiazide diuretics, digoxin, quinidine, methylldopa)

## 4Ts Score

<table>
<thead>
<tr>
<th>Category</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 nadir ≥20 x 10^9/L</td>
<td>Platelet count fall 30–50% OR platelet nadir 10–19 x 10^9/L</td>
<td>Platelet count fall &lt;30% OR platelet nadir &lt;10 x 10^9/L</td>
</tr>
<tr>
<td>Timing of platelet count fall</td>
<td>Clear onset between days 5–10 or platelet fall ≤1 day if recent heparin exposure</td>
<td>Consistent with days 5–10, but not clear (e.g. missing counts)</td>
<td>≤ day 4 without recent heparin exposure</td>
</tr>
<tr>
<td>Thrombosis or other sequelae</td>
<td>New thrombosis or anaphylactoid reaction after heparin bolus</td>
<td>Progressive or recurrent thrombosis</td>
<td>None</td>
</tr>
<tr>
<td>Other causes for thrombocytopenia</td>
<td>None</td>
<td>Possible</td>
<td>Definite</td>
</tr>
</tbody>
</table>

### Probability of HIT:
Score: 0–3 = low, 4–5 = intermediate, 6–8 = high

Laboratory Testing

- Immunologic (antigenic) assay
  - Detects the presence of HIT antibodies
    - PF4-heparin IgG immunoassay

- Functional (platelet activation) assays
  - Detect evidence of platelet activation in the presence of heparin
    - Serotonin-release assay (SRA)
    - Heparin-induced platelet activation (HIPA) test

Approach to Suspected HIT

Suspicion for HIT

Calculate 4Ts score

Low probability (score ≤3)

Intermediate/high probability (score ≥4)

Discontinue heparin and start non-heparin anticoagulation

PF4-heparin IgG immunoassay

Negative

Positive

SRA or HIPA test

Negative

Positive

HIT unlikely

HIT likely

Therapeutic non-heparin anticoagulation warranted

HIT ruled out

Continue or restart heparin

# Phases of HIT

<table>
<thead>
<tr>
<th>Phase of HIT</th>
<th>Definition</th>
<th>Platelet count</th>
<th>Thrombotic risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected</td>
<td>Concern for HIT but results of confirmatory laboratory testing not yet available</td>
<td>Decreased</td>
<td>?</td>
</tr>
<tr>
<td>Acute</td>
<td>Diagnosis confirmed by laboratory testing</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Subacute HIT A</td>
<td>Platelet counts have recovered but washed platelet functional assay still remains positive</td>
<td>Normal</td>
<td>Increased?</td>
</tr>
<tr>
<td>Subacute HIT B</td>
<td>Washed platelet functional assay becomes negative but immunoassay still remains positive</td>
<td>Normal</td>
<td>Increased?</td>
</tr>
<tr>
<td>Remote</td>
<td>Anti-PF4/heparin antibodies are no longer detectable by immunoassay</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

In patients with HIT or isolated HIT (HIT without thrombosis), recommend non-heparin anticoagulants lepirudin, argatroban or danaparoid over further use of heparin or LMWH or initiation/continuation of a vitamin K antagonist (VKA) (Grade 1C)

In patients with HIT and renal insufficiency, suggest the use of argatroban over other non-heparin anticoagulants (Grade 2C)

Recommend against starting VKA until platelets have substantially recovered (≥150 x 10^9/L) over starting VKA at a lower platelet count and that the VKA be initially given in low doses (max. 5 mg of warfarin) over using higher doses (Grade 1C)

In patients with confirmed HIT, recommend that that the VKA be overlapped with a non-heparin anticoagulant for a minimum of 5 days and until the INR is within the target range (Grade 1C)

# Non-Heparin Parenteral Anticoagulants

<table>
<thead>
<tr>
<th>MOA</th>
<th>Argatroban</th>
<th>Bivalirudin</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing</td>
<td>Direct thrombin inhibitor</td>
<td>Direct thrombin inhibitor</td>
<td>Indirect factor Xa inhibitor</td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>Initial: 2 mcg/kg/min</td>
<td>Initial: 0.15–2 mg/kg/hr</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td></td>
<td>Lower starting rates used in critical illness, hepatic impairment, and multiorgan dysfunction</td>
<td>Lower starting rates used in renal or hepatic impairment, critical illness</td>
<td>&lt;50 kg: 5 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50–100 kg: 7.5 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;100 kg: 10 mg once daily</td>
</tr>
<tr>
<td>Laboratory monitoring</td>
<td>aPTT</td>
<td>aPTT</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Target aPTT 1.5–3 times baseline value; not to exceed 100 secs</td>
<td>Target aPTT 1.5–2.5 times baseline value</td>
<td></td>
</tr>
<tr>
<td>Place in therapy</td>
<td>FDA-approved use</td>
<td>Off-label use</td>
<td>Off-label use</td>
</tr>
<tr>
<td></td>
<td>Treatment of HIT</td>
<td>Treatment of HIT</td>
<td>Treatment of HIT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac surgery in patients with acute or subacute HIT</td>
<td></td>
</tr>
<tr>
<td>Considerations</td>
<td>• Falsely elevates PT/INR levels</td>
<td>• Requires renal dose adjustment</td>
<td>• Caution in renal impairment (contraindicated with CrCl &lt;30 mL/min)</td>
</tr>
</tbody>
</table>

Transitioning to Warfarin

**Argatroban**
- Stop infusion when INR >4 on combined warfarin + argatroban
- Repeat INR in 4–6 hours
- If INR subtherapeutic, restart argatroban
- Repeat daily until desired INR achieved on warfarin alone

**Bivalirudin**
- Stop infusion when INR >2.5 to 3 on combined warfarin + bivalirudin
- Repeat INR in 4 hours
- If INR subtherapeutic, restart bivalirudin
- Repeat daily until desired INR is achieved on warfarin alone

Requires platelet count recovery to $\geq 150 \times 10^9$ and minimum 5 days overlap of non-heparin parenteral agent and warfarin

Why Not Warfarin for Acute HIT?

■ Mechanism of action:
  - Inhibits the synthesis of vitamin K-dependent clotting factors II, VII, IX, X as well as proteins C and S

■ Rationale:
  - Decreases levels of protein C, leading to small vessel thrombotic occlusions
    ■ Contributes to hypercoagulable state associated with HIT

■ Consequences:
  - Venous limb gangrene
  - Warfarin-induced central skin necrosis

<table>
<thead>
<tr>
<th>Clotting factor</th>
<th>Half-life (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor II</td>
<td>60</td>
</tr>
<tr>
<td>Factor VII</td>
<td>4-6</td>
</tr>
<tr>
<td>Factor IX</td>
<td>24</td>
</tr>
<tr>
<td>Factor X</td>
<td>48–72</td>
</tr>
<tr>
<td>Protein C</td>
<td>8</td>
</tr>
<tr>
<td>Protein S</td>
<td>30</td>
</tr>
</tbody>
</table>

Limitations of Current Approach

- Agents used for acute HIT are only available as parenteral formulations
- Argatroban and bivalirudin require frequent monitoring of aPTTs and falsely elevates INR
- Transition to warfarin is time-consuming and challenging
  - Must wait until platelet counts have recovered
  - Requires minimum 5 days overlap of parenteral therapy until therapeutic INR is achieved
    - Longer hospitalization and increased costs
  - Frequent stopping/starting of parenteral direct thrombin inhibitors may lead to periods of time without therapeutic anticoagulation
- Warfarin has multiple drug and food interactions and needs close monitoring of INR
Should DOACs be Considered?

- No potentially deleterious immunologic interaction with HIT antibodies
- Rapid onset of action
- Oral administration
- Do not cause reductions in protein C natural anticoagulant activity
- Do not require therapeutic drug monitoring

American Society of Hematology 2018 Guidelines

- In patients with acute HITT or acute isolated HIT, suggest argatroban, bivalirudin, danaparoid, fondaparinux or a DOAC (conditional recommendation, very low certainty in the evidence about effects)
- In patients with critical illness, increased bleeding risk or increased potential need for urgent procedures, argatroban or bivalirudin may be preferred
- Fondaparinux and the DOACs are reasonable options in clinically stable patients
- In patients with HIT complicated by life- or limb-threatening thromboembolism, a parenteral non-heparin anticoagulant may be preferred

American Society of Hematology 2018 Guidelines

- In patients with subacute HIT A, suggest treatment with a DOAC (e.g., dabigatran, rivaroxaban or apixaban) rather than a VKA (conditional recommendation, moderate certainty in the evidence about effects)

- In patients with remote HIT who require VTE treatment or prophylaxis, recommend administration of a non-heparin anticoagulant (e.g., apixaban, dabigatran, danaparoid, edoxaban, fondaparinux, rivaroxaban or VKA) rather than UFH or LMWH (strong recommendation, very low certainty in the evidence about effects)

Definitions

**Primary Treatment**
Initial non-heparin anticoagulant used during treatment of acute HIT or HITT

**Secondary Treatment**
Second non-heparin anticoagulant administered after at least 1 dose of an alternative initial non-heparin anticoagulant is given for treatment of acute/subacute HIT or HITT
Linkins, et al.

- Multicenter, single-arm prospective cohort study in Canada of 22 patients with suspected or confirmed HIT

**Inclusion criteria**

- Suspected or confirmed HIT (4T score ≥4)

**Exclusion criteria**

- Pregnant or nursing
- Enrolled in this study within the past 100 days
- Presence of a mechanical heart valve
- Renal insufficiency (CrCl <30 mL/min)
- Hepatic disease (Child-Pugh B or C) associated with coagulopathy and a clinically relevant bleeding risk
- Clinically significant active bleeding or lesions at increased risk of bleeding within the last 6 months
- Ongoing requirement for systemic treatment with strong CYP3A4 and P-glycoprotein inhibitors/inducers
- Presence of a long-term indwelling epidural catheter

Linkins et al.

- **Primary outcome**
  - Incidence of new symptomatic, objectively-confirmed venous and arterial thromboembolism in the combined cohort of patients with suspected and confirmed HIT at 30 days

- **Secondary outcome**
  - Incidence of symptomatic thromboembolism while on treatment with rivaroxaban (combined cohort)
  - Incidence of venous and arterial thromboembolism, incidence of major bleeding and time to platelet recovery in SRA-positive patients while on treatment with rivaroxaban

Linkins et al.

- **Intervention**
  - Pending results of local HIT assay
    - Rivaroxaban 15 mg twice daily
  - Positive local HIT assay result
    - Rivaroxaban 15 mg twice daily until platelet recovery or until day 21 if presence of acute thrombosis (HITT) at study entry, then rivaroxaban 20 mg daily until day 30
      - Platelet recovery: platelet count $\geq 150 \times 10^9$/L (or back to baseline if the baseline count $< 150 \times 10^9$/L)

Results

### Primary outcome

Incidence of new symptomatic thromboembolism in the combined cohort at 30 days

1/22 (4.5%)

### Secondary outcomes

Incidence of symptomatic thromboembolism while on treatment with rivaroxaban (combined cohort)

1/22 (4.5%)

### SRA-positive patients

Incidence of arterial and venous thromboembolism*

1/12 (8.3%)

Incidence of major bleeding*

1/12 (8.3%)

Time to platelet recovery

9/10
Mean: 11 days
Median: 7 days

* Catheter-related DVT; resolved once catheter removed

*Major gastrointestinal bleed from gastric tumor; rivaroxaban held 9 days prior

Linkins et al. Critique

**Strengths**
- Only prospective study to date of DOAC use in HIT/HITT
- Utilized standardized dosing regimen

**Considerations**
- Primary outcome evaluated combined cohort (included HIT negative patients)
- About half of the patients received “lead-in” with parenteral non-heparin anticoagulant before rivaroxaban started
- About half of the patients who received rivaroxaban for primary treatment of HIT had platelet counts $>150 \times 10^9/L$
- Thrombosis (n=1), bleeding (n=1), mortality (n=1) unassociated with rivaroxaban
- Heterogeneous population
- Minimal arterial thrombosis patients
- Excluded critically ill and renal impairment
Hamilton Experience

■ Multicenter, retrospective cohort study (Hamilton experience) and literature review
  - Hamilton experience included patients who received rivaroxaban with suspected or confirmed HIT

■ Primary
  - 30-day incidence of new symptomatic, objectively confirmed venous and arterial thromboembolism in the cohort of patients with confirmed acute HIT

■ Secondary
  - Incidence of symptomatic thromboembolism while being treated with rivaroxaban and the following outcomes while being treated with rivaroxaban: incidence of venous and arterial thromboembolism, incidence of major bleeding and time to platelet recovery

First non-heparin anticoagulant used to treat acute HIT

Primary treatment with DOAC

- **Acute HIT**
  - **Group A₁**: DOAC started when platelet count < 150 x 10⁹/L

- **Acute HIT**
  - **Group A₂**: Platelet count never < 150 x 10⁹/L

Secondary treatment with DOAC

- **Acute HIT**
  - **Group B**: DOAC started before platelet count rose to > 150 x 10⁹/L

- **Subacute HIT**
  - **Group C**: DOAC started after platelet count rose to > 150 x 10⁹/L

Hamilton Experience

- Hamilton experience results
  - 16 patients identified
    - Group A₁: 7
    - Group A₂: 1
    - Group B: 2
    - Group C: 6
  - None experienced thrombotic events at 30-day follow up or while receiving rivaroxaban
    - Mean duration of rivaroxaban treatment: 3 months
  - None required limb amputation or developed major hemorrhage while receiving rivaroxaban
  - No deaths (up to 3-month follow up)

### Group Anticoagulant Before Rivaroxaban | Rivaroxaban Dosing (at least for first 30 days)
---|---
A₁ | None | 20 mg daily ≥30 days
A₁ | None | 15 mg BID x 3 weeks, then 20 mg daily ≥30 days
A₁ | None | 15 mg BID x 6 days, then 20 mg daily ≥30 days
A₁ | None | 15 mg BID x 3 weeks, then 20 mg daily ≥30 days
A₁ | None | 15 mg BID x 3 weeks, then 20 mg daily ≥30 days
A₁ | None | 20 mg daily ≥30 days
A₁ | None | 15 mg BID x 3 weeks, then 20 mg daily ≥30 days
A₁ | None | 10 mg daily ≥30 days
B | Fondaparinux x 1 day | 15 mg BID x 3 weeks, then 20 mg daily ≥30 days
B | Fondaparinux x 4 days | 15 mg BID x 12 weeks, then 20 mg daily ≥30 days
C | Fondaparinux x 5 days | 10 mg daily ≥30 days
C | Argatroban x 3 days, fondaparinux x 51 days | 20 mg daily ≥30 days
C | Fondaparinux x 11 days | 10 mg daily ≥30 days
C | Fondaparinux x 7 days | 10 mg daily ≥30 days
C | Fondaparinux x 5 days | 20 mg daily ≥30 days
C | Fondaparinux x 10 days | 15 mg BID x 3 weeks, then 20 mg daily ≥30 days

Rivaroxaban

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Group A₁</th>
<th>Group A₂</th>
<th>Group B</th>
<th>Median platelet count at the start of rivaroxaban</th>
<th>HITT (No.)</th>
<th>Thrombosis (No.)</th>
<th>Bleed (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary</strong></td>
<td>46</td>
<td>21</td>
<td>4</td>
<td>21</td>
<td>73</td>
<td>29/46 (63%)</td>
<td>1/46 (2.2%)</td>
<td>0/46 (0%)</td>
</tr>
</tbody>
</table>

**A₁:** Primary treatment, platelet count $<150 \times 10^9/L$

**A₂:** Primary treatment, platelet count never $<150 \times 10^9/L$

**B:** Secondary treatment, DOAC started before platelet count rose to $>150 \times 10^9/L$

### Apixaban

**A**<sub>1</sub>: Primary treatment, platelet count <150 x 10<sup>9</sup>/L  
**A**<sub>2</sub>: Primary treatment, platelet count never <150 x 10<sup>9</sup>/L  
**B**: Secondary treatment, DOAC started before platelet count rose to >150 x 10<sup>9</sup>/L

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Group A&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Group A&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Group B</th>
<th>Median platelet count at the start of rivaroxaban</th>
<th>HITT (No.)</th>
<th>Thrombosis (No.)</th>
<th>Bleed (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>10</td>
<td>90</td>
<td>5/12</td>
<td>0/12</td>
<td>0/12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(41.7%)</td>
<td></td>
<td>(0%)</td>
</tr>
</tbody>
</table>

# Dabigatran

**A1:** Primary treatment, platelet count < $150 \times 10^9$/L

**A2:** Primary treatment, platelet count never < $150 \times 10^9$/L

**B:** Secondary treatment, DOAC started before platelet count rose to > $150 \times 10^9$/L

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Group A&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Group A&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Group B</th>
<th>Median platelet count at the start of rivaroxaban</th>
<th>HITT (No.)</th>
<th>Thrombosis (No.)</th>
<th>Bleed (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>58</td>
<td>6/11 (54.5%)</td>
<td>1/11 (9.1%)</td>
<td>0/11 (0%)</td>
</tr>
</tbody>
</table>

## Putting it in Perspective

<table>
<thead>
<tr>
<th></th>
<th>New Thrombosis</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Argatroban</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIT</td>
<td>11/160 (6.9%)</td>
<td>HIT 5/160 (3.1%)</td>
</tr>
<tr>
<td>HITT</td>
<td>21/144 (14.6%)</td>
<td>HITT 16/144 (11.1%)</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>HIT/HITT 1/46 (2.2%)</td>
<td>HIT/HITT 0/46 (0%)</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>HIT/HITT 0/12 (0%)</td>
<td>HIT/HITT 0/12 (0%)</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>HIT/HITT 1/11 (9.1%)</td>
<td>HIT/HITT 0/11 (0%)</td>
</tr>
</tbody>
</table>

DOAC Studies

Factors to Consider:

- HIT vs HITT
- Platelet count on initiation of treatment with DOAC
- Primary vs. secondary treatment
- If DOAC used as secondary treatment, which non-heparin anticoagulant was used as primary treatment and for how long
- Dosing
- Renal function or organ dysfunction
- Primary endpoint
- Publication bias

Heterogeneous population
Nonrandomized, noncontrolled, retrospective
Small sample sizes
## Dosing & Considerations

<table>
<thead>
<tr>
<th>DOAC</th>
<th>MOA</th>
<th>ASH Dosing Recommendation</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| Rivaroxaban | Factor Xa inhibitor       | • **HITT:** 15 mg twice daily for 3 weeks, then 20 mg once daily  
• **Isolated HIT:** 15 mg twice daily until platelet recovery | • Does not require routine coagulation testing  
• Caution in renal impairment (avoid use if CrCl <30 mL/min)  
• Avoid in moderate or severe hepatic impairment  
• CYP3A4 and P-gp drug interactions |
| Apixaban | Factor Xa inhibitor       | • **HITT:** 10 mg twice daily for 1 week, then 5 mg twice daily  
• **Isolated HIT:** 5 mg twice daily until platelet recovery | • Does not require routine coagulation testing  
• Caution in renal impairment (no data in patients with Scr >2.5 mg/dL or CrCl <25 mL/min)  
• Not recommended in severe hepatic impairment  
• CYP3A4 and P-gp drug interactions |
| Dabigatran | Direct thrombin inhibitor | • **HITT:** 150 mg twice daily after ≥5 days of treatment with a parenteral non-heparin anticoagulant  
• **Isolated HIT:** 150 mg twice daily until platelet recovery | • Requires ≥5 days lead-in with parenteral non-heparin anticoagulation  
• Caution in renal impairment (contraindicated with CrCl <30 mL/min)  
• Dose reduction or avoidance required if using with dronedarone, ketoconazole, or P-gp inhibitors |

Summary of Guideline Recommendations

<table>
<thead>
<tr>
<th>Phase of HIT</th>
<th>American College of Chest Physicians</th>
<th>American Society of Hematology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HIT or HITT</td>
<td>▪ Normal renal function/renal insufficiency</td>
<td>▪ Critically ill, increased bleeding risk, potential for urgent procedure</td>
</tr>
<tr>
<td></td>
<td>— Argatroban</td>
<td>— Argatroban, bivalirudin</td>
</tr>
<tr>
<td></td>
<td>▪ Clinically stable, average bleeding risk</td>
<td>▪ Clinically stable, average bleeding risk</td>
</tr>
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<td></td>
<td>— Fondaparinux or DOAC</td>
<td>— Fondaparinux or DOAC</td>
</tr>
<tr>
<td></td>
<td>▪ Limb-threatening complication</td>
<td>▪ Limb-threatening complication</td>
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<tr>
<td></td>
<td>— Parenteral non-heparin anticoagulant</td>
<td>— Parenteral non-heparin anticoagulant</td>
</tr>
<tr>
<td></td>
<td>▪ Warfarin should not be initiated until platelet count recovery (≥150 x 10⁹/L)</td>
<td></td>
</tr>
<tr>
<td>Subacute HIT</td>
<td>▪ Overlap of non-heparin anticoagulant with warfarin for minimum 5 days until target INR is achieved</td>
<td>▪ DOAC preferred over warfarin</td>
</tr>
<tr>
<td>Remote HIT</td>
<td>▪ Fondaparinux until transition to warfarin is achieved</td>
<td>▪ Apixaban, dabigatran, edoxaban, fondaparinux, rivaroxaban or warfarin</td>
</tr>
</tbody>
</table>

Recommendations

- DOACs appears to be safe and effective during acute and subacute phases of HIT
  - Should be considered for patients who are clinically stable with good renal function

- Good oral alternatives to warfarin
  - Most experience reported with rivaroxaban, especially for primary treatment
  - Apixaban and dabigatran are likely safe, but were mostly studied for secondary treatment

- Dosing should follow recommendations for venous thromboembolism in patients with HITT
  - Area of uncertainty: high-intensity induction period required for rivaroxaban or apixaban if primary treatment was with parenteral non-heparin anticoagulant?
Summary

- HIT is a life-threatening, immune-mediated reaction to heparin that results in thrombocytopenia and an increased risk for thrombosis.

- Traditional approach to management required discontinuation of heparin, initiation of therapeutic anticoagulation with a parenteral non-heparin anticoagulant and transition to warfarin once platelet counts recovered.

- Latest guidelines published in 2018 by the American Society of Hematology incorporate the use of DOACs into their recommendations for the management of acute, subacute and remote phases of HIT.

- There are limited data evaluating the use of DOACs to clearly define their place in therapy, but they appear to be promising alternatives to warfarin.

- Careful consideration of patient-specific factors is required to determine if DOACs are the most appropriate option for management of HIT.
Future Studies

Efficacy and Safety of Apixaban in the Treatment of Heparin Induced Thrombocytopenia (HIT)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03594045

Recruitment Status: Recruiting
First Posted: July 20, 2018
Last Update Posted: January 25, 2019

See Contacts and Locations

Source: https://clinicaltrials.gov/ct2/show/NCT03594045
Pharmacist Assessment Question #1

Heparin-induced thrombocytopenia is differentiated into all of the following phases except:

A. Acute
B. Subacute
C. Distant
D. Suspected
Pharmacist Assessment Response #1

Heparin-induced thrombocytopenia is differentiated into all of the following phases except:

A. Acute
B. Subacute
C. Distant
D. Suspected
Pharmacist Assessment Question #2

Which of the following was a major finding of the Hamilton experience?

A. Thrombosis occurred in 8 patients who received rivaroxaban for acute HIT

B. At the 30-day follow-up, it was found that 12.5% of patients required limb amputation

C. None of the patients who received rivaroxaban for acute HIT experienced thrombosis or limb amputation

D. Major hemorrhage was seen in 6 patients who received dabigatran for subacute HIT
Pharmacist Assessment Response #2

Which of the following was a major finding of the Hamilton experience?

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B. At the 30-day follow-up, it was found that 12.5% of patients required limb amputation

C. None of the patients who received rivaroxaban for acute HIT experienced thrombosis or limb amputation

D. Major hemorrhage was seen in 6 patients who received dabigatran for subacute HIT
Pharmacist Assessment Question #3

The American Society of Hematology recommends the following dose of rivaroxaban for heparin-induced thrombocytopenia with thrombosis (HITT):

A. 15 mg twice daily for 3 weeks, then 20 mg once daily
B. 10 mg once daily
C. 10 mg twice daily for 1 week, then 5 mg twice daily
D. 15 mg once daily
Pharmacist Assessment Response #3

The American Society of Hematology recommends the following dose of rivaroxaban for heparin-induced thrombocytopenia with thrombosis (HITT):

A. 15 mg twice daily for 3 weeks, then 20 mg once daily
B. 10 mg once daily
C. 10 mg twice daily for 1 week, then 5 mg twice daily
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Pharmacy Technician Assessment Question #1

Which of the following is NOT a typical complication of HIT?

A. Bleeding
B. Arterial thromboembolism
C. Venous thromboembolism
D. Limb gangrene
Pharmacy Technician Assessment Response #1

Which of the following is NOT a typical complication of HIT?

A. Bleeding
B. Arterial thromboembolism
C. Venous thromboembolism
D. Limb gangrene
Pharmacy Technician Assessment Question #2

Current literature has evaluated the use of the following direct oral anticoagulants for HIT except for:

A. Rivaroxaban
B. Apixaban
C. Betrixaban
D. Dabigatran
Pharmacy Technician Assessment Response #2

Current literature has evaluated the use of the following direct oral anticoagulants for HIT except for:

A. Rivaroxaban
B. Apixaban
C. Betrixaban
D. Dabigatran
Thank you!

QUESTIONS?

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HIT or Miss: Direct Oral Anticoagulants For Heparin-Induced Thrombocytopenia