DOAC Utilization For Heparin-Induced Thrombocytopenia

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PGY1 Pharmacy Practice Resident

June 4, 2019
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Objectives

1) Review standard therapy for treating heparin-induced thrombocytopenia (HIT)

2) Discuss the literature supporting the use of direct oral anticoagulants (DOACs) for treating HIT

3) Outline appropriate treatment options for a patient with HIT
Poll Question 1

Which statement best describes your experience with HIT?

A. I have treated a HIT patient with a DOAC
B. I have treated a HIT patient but not with a DOAC
C. I have never treated a HIT patient
HIT Background

- Antibody-mediated adverse reaction to heparin
- >12 million inpatients exposed annually
- 600,000 cases
- 50% thromboembolism
- 15% mortality

HIT Pathophysiology

- Platelet
- Fc Receptor
- PF4
- Heparin
- IgG

HIT Pathophysiology

- Platelet
- Fc Receptor
- PF4
- Heparin
- IgG

# HIT Diagnosis – 4T Score

<table>
<thead>
<tr>
<th>Category</th>
<th>2 points</th>
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<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>&gt;50% decrease &amp; nadir ≥20 $x10^9$/L</td>
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<td>None</td>
</tr>
<tr>
<td><strong>Other causes of thrombocytopenia</strong></td>
<td>None evident</td>
<td>Possible</td>
<td>Definite</td>
</tr>
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<td>None evident</td>
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</table>

0-3 = low risk (<1%)  4-5 = intermediate risk (~10%)  6-8 = high risk (~50%)

# HIT Management

<table>
<thead>
<tr>
<th>Class</th>
<th>DTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved for HIT?</td>
<td>Yes</td>
</tr>
<tr>
<td>Initial dose and</td>
<td>1 mcg/kg/min</td>
</tr>
<tr>
<td>monitoring goal</td>
<td>IV infusion; goal aPTT 1.5-2.5x baseline</td>
</tr>
<tr>
<td>(standard intensity)</td>
<td></td>
</tr>
<tr>
<td>Initial dose and</td>
<td>1.25 mcg/kg/min</td>
</tr>
<tr>
<td>monitoring goal</td>
<td>IV infusion; goal aPTT 2-3x baseline</td>
</tr>
<tr>
<td>(high intensity)</td>
<td></td>
</tr>
<tr>
<td>Elimination Half-life</td>
<td>39-51 minutes</td>
</tr>
<tr>
<td>Dose adjustments</td>
<td>Liver dysfunction</td>
</tr>
</tbody>
</table>

DBI = Direct Thrombin Inhibitor  
aPTT = Activated Partial Thromboplastin Time
## HIT Management

<table>
<thead>
<tr>
<th></th>
<th>Argatroban</th>
<th>Bivalirudin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
<td>DTI</td>
<td>DTI</td>
</tr>
<tr>
<td><strong>Approved for HIT?</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Initial dose and monitoring goal (standard intensity)</strong></td>
<td>1 mcg/kg/min IV infusion; goal aPTT 1.5-2.5x baseline</td>
<td>0.15 mg/kg/hr IV infusion; goal aPTT 1.5-2.5x baseline</td>
</tr>
<tr>
<td><strong>Initial dose and monitoring goal (high intensity)</strong></td>
<td>1.25 mcg/kg/min IV infusion; goal aPTT 2-3x baseline</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Elimination Half-life</strong></td>
<td>39-51 minutes</td>
<td>25 minutes</td>
</tr>
<tr>
<td><strong>Dose adjustments</strong></td>
<td>Liver dysfunction</td>
<td>Renal dysfunction</td>
</tr>
</tbody>
</table>

**Notes:**
- DTI = Direct Thrombin Inhibitor
- aPTT = Activated Partial Thromboplastin Time
# HIT Management

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Argatroban</th>
<th>Bivalirudin</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
<td>DTI</td>
<td>DTI</td>
<td>Factor Xa Inhibitor</td>
</tr>
<tr>
<td><strong>Approved for HIT?</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Initial dose and</strong></td>
<td>1 mcg/kg/min IV infusion;</td>
<td>0.15 mg/kg/hr IV infusion;</td>
<td>7.5 mg SQ daily</td>
</tr>
<tr>
<td><strong>monitoring goal</strong></td>
<td>goal aPTT 1.5-2.5x baseline</td>
<td>goal aPTT 1.5-2.5x baseline</td>
<td></td>
</tr>
<tr>
<td><strong>(standard intensity)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Initial dose and</strong></td>
<td>1.25 mcg/kg/min IV infusion;</td>
<td>N/A</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>(high intensity)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Elimination Half-life</strong></td>
<td>39-51 minutes</td>
<td>25 minutes</td>
<td>17-21 hours</td>
</tr>
<tr>
<td><strong>Dose adjustments</strong></td>
<td>Liver dysfunction</td>
<td>Renal dysfunction</td>
<td>Renal dysfunction; body weight</td>
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*DTI = Direct Thrombin Inhibitor  
aPTT = Activated Partial Thromboplastin Time*
Confirmed thrombocytopenia

Discontinue heparin and calculate 4 T Score

Low HIT probability; resume heparin, monitor, & evaluate alternative causes

PF4 (+)?

4T ≥6?  

4T >3?  

SRA (+)?

HIT Treatment Options:
- Argatroban + Warfarin
- Bivalirudin + Warfarin
- Fondaparinux + Warfarin

Decision to restart heparin is based on clinical suspicion; consider heme consult

Treat for HIT; add allergy to chart

Repeat PF4; if equivocal on recheck draw SRA

Equivocal

Treat for HIT; add allergy to chart

No
Patient Case

CC: Right knee pain

HPI: 59-year-old male s/p right total knee arthroplasty

PMH: Obesity, hypertension, alcoholism

Social: No tobacco or elicit drug use; last drink 2011

Family: Sister with deep vein thrombosis

The patient is started on subcutaneous heparin the morning following his surgery. On post-op day 3 his discharge is delayed when he develops pneumonia and is started on vancomycin and piperacillin-tazobactam.
Patient Case

On post-op day 6 the patient develops new right lower leg pain, edema, erythema. An ultrasound reveals acute deep vein thrombosis and the following labs are drawn:

**POD#1 CBC:**
- HGB: 11.8 g/dL
- HCT: 35.5%
- PLT: 180 x10⁹/L
- WBC: 9.4 x10⁹/L

**POD#6 CBC:**
- HGB: 10.1 g/dL
- HCT: 33.4%
- PLT: 30 x10⁹/L
- WBC: 13.2 x10⁹/L

**POD#6 CMP:**
- SCr: 1.6 mg/dL
- CrCl: 59 mL/min
- TBili: 1.1 mg/dL
- AST: 82 IU/L
- ALT: 88 IU/L

POD = Post-Operative Day
CBC = Complete Blood Count
HGB = Hemoglobin
HCT = Hematocrit
PLT = Platelet
WBC = White Blood Cells
CMP = Complete Metabolic Panel
SCr = Serum Creatinine
CrCl = Creatinine Clearance
AST = Aspartate Aminotransferase
ALT = Alanine Aminotransferase
Poll Question 2

After calculating a 4T score of 7 you discontinue heparin and prepare to treat the patient for HIT while labs results are pending. In this patient, which agent would you recommend for initial therapy?

A. Argatroban
B. Bivalirudin
C. Fondaparinux
D. DOAC
DOAC Use in HIT

Pros

• No PF4-antibody interactions
• No hypercoagulable state
• Rapid onset of anticoagulation
• No transition from parenteral anticoagulation to oral
• No routine monitoring
• Less expensive than parenteral therapy

Cons

• Not rigorously studied in HIT
• Not all agents approved for acute thrombus
• Not ideal for patients with urgent procedures
• Not ideal for patients on dialysis

PF4 = Platelet Factor 4

Linkins, et al. Rivaroxaban for HIT

**Design**
- Multicenter, single-arm, prospective cohort study
- Patients with confirmed or suspected HIT (4T Score ≥4)
- Evaluated thrombotic events, thrombocytopenia, and major bleeding at 30 days

**Arms**
- 22 enrolled patients received rivaroxaban 15 mg PO BID
- **HIT-positive patients**: continued high-dose therapy until platelet recovery or at least therapy day 21, then decreased to 20 mg PO daily (n=12)
- **HIT-negative patients**: discontinued therapy upon final lab result (n=10)

**Results**
- **HIT positive patients**: 1/12 (4.5%) had VTE progression; 1/12 (4.5%) had major bleeding; 1/12 (4.5%) had amputation; 9/10 (90%) achieved platelet recovery
- **HIT negative patients**: No bleeding or thrombosis

VTE = Venous Thromboembolism
GI = Gastrointestinal
## Linkins, et al. Rivaroxaban for HIT

<table>
<thead>
<tr>
<th>Patient</th>
<th>HIT-related thrombosis</th>
<th>PLT at study entry</th>
<th>Treatment prior to study entry</th>
<th>Days to PLT recovery</th>
<th>Study events</th>
</tr>
</thead>
<tbody>
<tr>
<td>85 M</td>
<td>None</td>
<td>40</td>
<td>None</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>79 M</td>
<td>None</td>
<td>57</td>
<td>None</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td>80 M</td>
<td>Leg DVT; bilateral leg arterial thrombus</td>
<td>54</td>
<td>Danaparoid 1 day</td>
<td>4</td>
<td>Acute-on-chronic leg ischemic; BKA on D18</td>
</tr>
<tr>
<td>71 F</td>
<td>Leg DVT; adrenal thrombosis</td>
<td>300</td>
<td>None</td>
<td>Normal at entry</td>
<td>None</td>
</tr>
<tr>
<td>87 M</td>
<td>PE</td>
<td>111</td>
<td>Fondaparinux 3 days</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>61 M</td>
<td>Arm catheter DVT</td>
<td>28</td>
<td>Fondaparinux 2 days</td>
<td>29</td>
<td>Extension of arm apheresis catheter DVT; improved with catheter removal</td>
</tr>
<tr>
<td>82 F</td>
<td>Adrenal thrombosis</td>
<td>164</td>
<td>None</td>
<td>Normal at entry</td>
<td>None</td>
</tr>
<tr>
<td>74 F</td>
<td>No</td>
<td>81</td>
<td>Fondaparinux 2 days</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>85 F</td>
<td>Arm DVT; leg DVT; PE</td>
<td>26</td>
<td>Fondaparinux 2 days</td>
<td>8</td>
<td>None</td>
</tr>
<tr>
<td>60 M</td>
<td>No</td>
<td>21</td>
<td>Fondaparinux 2 days</td>
<td>N/A</td>
<td>Elevated LFT on D2 rivaroxaban; switched back to fondaparinux; rectal bleeding D10, death from cancer D21</td>
</tr>
<tr>
<td>55 F</td>
<td>No</td>
<td>78</td>
<td>Fondaparinux 3 days</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>65 M</td>
<td>No</td>
<td>52</td>
<td>None</td>
<td>28</td>
<td>None</td>
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PLT = Platelet Count  
DVT = Deep Vein Thrombosis  
BKA = Below the Knee Amputation  
PE = Pulmonary Embolism  
D = Study Day  
LFT = Liver Function Tests
Linkins, et al. Rivaroxaban for HIT

**Design**
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- Evaluated thrombotic events, thrombocytopenia, and major bleeding at 30 days

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**Results**
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- **HIT negative patients**: No bleeding or thrombosis

**Conclusion**
- Event rates noted in this study were similar to historical event rates that lead to the approval of argatroban
- Establishes rivaroxaban as a potential therapy option for the treatment of HIT
- Larger, head-to-head trials needed

VTE = Venous Thromboembolism
GI = Gastrointestinal
Warkentin, et al. DOACs for HIT

Design
- Multicenter, single-arm, retrospective cohort study
- Patients with confirmed acute HIT that received a DOAC
- Primary outcome: new thrombotic events at 30 days
- Also included a literature review of DOAC utilization in HIT

Arms
- **A₁**: Primary treatment with DOAC when PLT <150 (n=7)
- **A₂**: Primary treatment with DOAC but PLT was never <150 (n=1)
- **B**: Secondary treatment with DOAC, started when PLT <150 (n=2)
- **C**: Secondary treatment with DOAC, started after PLT rose >150 (n=6)

PF4 = Platelet Factor 4
SRA = Serotonin Release Assay
PLT = Platelet Count

Warkentin, et al. DOACs for HIT

First anticoagulant used to treat acute HIT?

- **DOAC**
  - A₁: DOAC started when PLT < 150 x 10⁹/L
  - A₂: PLT never < 150 x 10⁹/L

- **Non-DOAC**
  - B: DOAC started when PLT < 150 x 10⁹/L
  - C: DOAC started when PLT > 150 x 10⁹/L

PLT = Platelet Count

Primary Treatment

- Acute HIT

Secondary Treatment

- Subacute HIT

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Warkentin, et al. DOACs for HIT

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- A₂: Primary treatment with DOAC but PLT was never <150 (n=1)
- B: Secondary treatment with DOAC, started when PLT <150 (n=2)
- C: Secondary treatment with DOAC, started after PLT rose >150 (n=6)

Results
- No patient developed a new thrombotic event, required limb amputation, developed a major bleeding, or died within 30 days or while receiving rivaroxaban therapy (3 months follow-up)

PF4 = Platelet Factor 4
SRA = Serotonin Release Assay
PLT = Platelet Count
## Warkentin, et al. DOACs for HIT

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<th>Group</th>
<th>Patient</th>
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<th>PLT at DOAC start</th>
<th>Treatment prior to study entry</th>
<th>Rivaroxaban dosing during first 30 days of DOAC therapy</th>
<th>Study events</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>66 F</td>
<td>None</td>
<td>107</td>
<td>None</td>
<td>20 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>A1</td>
<td>79 F</td>
<td>None</td>
<td>78</td>
<td>None</td>
<td>15 mg BID x3 weeks; then 20 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>A1</td>
<td>60 F</td>
<td>None</td>
<td>25</td>
<td>None</td>
<td>15 mg BID x3 weeks; then 20 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>A1</td>
<td>64 F</td>
<td>Upper limb DVT</td>
<td>35</td>
<td>None</td>
<td>15 mg BID x3 weeks; then 20 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>A1</td>
<td>94 F</td>
<td>Lower limb DVT</td>
<td>56</td>
<td>None</td>
<td>15 mg BID x3 weeks; then 20 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>A1</td>
<td>62 M</td>
<td>None</td>
<td>49</td>
<td>None</td>
<td>20 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>A1</td>
<td>72 M</td>
<td>PE</td>
<td>86</td>
<td>None</td>
<td>15 mg BID x3 weeks; then 20 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>A2</td>
<td>83 F</td>
<td>Adrenal thrombosis</td>
<td>415</td>
<td>None</td>
<td>10 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>54 F</td>
<td>None</td>
<td>64</td>
<td>Fondaparinux 1 day</td>
<td>15 mg BID x3 weeks; then 20 mg daily x 3 days; then 10 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>69 F</td>
<td>MI</td>
<td>73</td>
<td>Fondaparinux 4 days</td>
<td>15 mg BID x3 weeks; then 20 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>55 F</td>
<td>None</td>
<td>163</td>
<td>Fondaparinux 5 days</td>
<td>10 mg daily x 17 days</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>78 M</td>
<td>DVT</td>
<td>203</td>
<td>Argatroban 3 days; Fondaparinux 51 days</td>
<td>20 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>56 F</td>
<td>None</td>
<td>332</td>
<td>Fondaparinux 11 days</td>
<td>10 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>92 F</td>
<td>None</td>
<td>159</td>
<td>Fondaparinux 7 days</td>
<td>10 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>72 M</td>
<td>None</td>
<td>192</td>
<td>Fondaparinux 5 days</td>
<td>20 mg daily</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>74 M</td>
<td>None</td>
<td>361</td>
<td>Fondaparinux 10 days</td>
<td>15 mg BID x3 weeks; then 20 mg daily</td>
<td>None</td>
</tr>
</tbody>
</table>

PLT = Platelet Count  
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LFT = Liver Function Tests  

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Warkentin, et al. DOACs for HIT

**Design**
- Multicenter, single-arm, retrospective cohort study
- Patients with confirmed acute HIT that received a DOAC
- Primary outcome: new thrombotic events at 30 days
- Also included a literature review of DOAC utilization in HIT

**Arms**
- **A₁**: Primary treatment with DOAC when PLT <150 (n=7)
- **A₂**: Primary treatment with DOAC but PLT was never <150 (n=1)
- **B**: Secondary treatment with DOAC, started when PLT <150 (n=2)
- **C**: Secondary treatment with DOAC, started after PLT rose >150 (n=6)

**Results**
- No patient developed a new thrombotic event, required limb amputation, developed a major bleeding, or died within 30 days or while receiving rivaroxaban therapy (3 months follow-up)

**Conclusion**
- No noted adverse event with rivaroxaban
- Reaffirms rivaroxaban as a promising potential therapy option for HIT

PF4 = Platelet Factor 4
SRA = Serotonin Release Assay
PLT = Platelet Count
Warkentin, et al. Literature Review

**Design**
- Systematic review of MEDLINE articles published 1/1/07 – 3/31/2017
- Evaluated rivaroxaban, apixaban, dabigatran, and edoxaban use in HIT
- Excluded patients with 4T score <4, negative PF4 or SRA, or incomplete data

**Arms**
- **A₁:** Primary treatment with DOAC when PLT <150 (R=11, A=2, D=2)
- **A₂:** Primary treatment with DOAC but PLT was never <150 (R=1, A=0, D=1)
- **B:** Secondary treatment with DOAC, started when PLT <150 (R=12, A=10, D=8)

**Results**
- No rivaroxaban or apixaban patients developed thrombosis or bleeding
- 1 patient had a stroke while receiving dabigatran for atrial fibrillation
- No dabigatran patients developed bleeding
- No patients received edoxaban

**Conclusion**
- Adverse event rates among DOACs consistent with historical therapy
- DOACs, particularly rivaroxaban and apixaban, remain promising for the treatment of HIT

PF4 = Platelet Factor 4  
SRA = Serotonin Release Assay  
PLT = Platelet Count  
R = Rivaroxaban  
A = Apixaban  
D = Dabigatran

Davis, et al. DOACs for HIT

**Design**
- Single center, retrospective cohort study
- Patients with confirmed HIT (4T Score ≥4, PF4 positive, SRA positive if drawn)
- Primary outcome: composite of newly diagnosed thromboembolism, gangrene, or amputation due to critical limb ischemia during hospitalization

**Arms**
- 12 total patients enrolled
- **Rivaroxaban**: 15 mg PO BID (n=3)
- **Apixaban**: 2.5 mg PO BID (n=1); 5 mg PO BID (n=7); 10 mg PO BID (n=1)

**Results**
- No patients experienced newly diagnosed thromboembolism, gangrene, or amputation due to critical limb ischemia during hospitalization

**Conclusion**
- DOACs, particularly apixaban and rivaroxaban, appear to be reasonable treatment options for HIT

PF4 = Platelet Factor 4
SRA = Serotonin Release Assay

Recommendation 3.1: When selecting an anticoagulant for acute HIT we suggest argatroban, bivalirudin, fondaparinux, or a DOAC (conditional recommendation, very low certainty)

- Consider drug factors, patient factors, and provider experience
- Parenteral anticoagulants may be preferred with critical illness, severe thromboembolism, high bleed risk, potential procedures
- DOACs are reasonable in stable patients at average bleeding risk
- Most experience is with rivaroxaban initiated at 15 mg PO BID
2018 ASH HIT Guidelines

**Recommendation 3.9:** In patients with subacute HIT, we suggest treatment with a DOAC rather than a VKA (conditional recommendation, moderate certainty)

- Consider drug factors, patient factors, and provider experience
- DOACs are preferred for clinically stable patients at average bleeding risk
- The same contraindications to their use in the treatment of acute VTE should be applied in determining their appropriateness for patients with HIT.

Confirmed thrombocytopenia

Discontinue heparin and calculate 4 Ts Score

Low HIT probability; resume heparin, monitor, & evaluate alternative causes

No

Yes

Decision to restart heparin is based on clinical suspicion; consider heme consult

HIT Treatment Options:
Argatroban + Warfarin
Bivalirudin + Warfarin
Fondaparinux + Warfarin

4T ≥6?

4T >3?

Equivocal

Repeat PF4; if equivocal on recheck draw SRA

SRA (+)?

Yes

Treat for HIT; add allergy to chart

Yes

Treat for HIT; add allergy to chart

No

No

PF4 (+)?
Casey’s HIT Algorithm

**Confirmed thrombocytopenia**
- Discontinue heparin and calculate 4 Ts Score
  - Low HIT probability; resume heparin, monitor, & evaluate alternative causes

**4T**
- **Yes**
  - Treatment options
    - Argatroban + Warfarin
    - Bivalirudin + Warfarin
    - Fondaparinux + Warfarin
    - Argatroban + DOAC
    - Bivalirudin + DOAC
    - Fondaparinux + DOAC
    - DOAC alone
- **No**
  - 4T ≥ 6?
    - **Yes**
      - Repeat PF4; if equivocal on recheck draw SRA
      - **SRA (+)?**
        - **Yes**
          - Treat for HIT; add allergy to chart
        - **No**
          - Decision to restart heparin is based on clinical suspicion; consider heme consult
    - **No**
      - 4T > 3?
        - **Yes**
          - Repeat PF4; if equivocal on recheck draw SRA
        - **No**
          - Decision to restart heparin is based on clinical suspicion; consider heme consult

**PF4 (+)?**
- **Yes**
  - Treat for HIT; add allergy to chart
- **No**
  - Equivocal
    - Repeat PF4; if equivocal on recheck draw SRA

**SRA (+)?**
- **Yes**
  - Treat for HIT; add allergy to chart
- **No**
  - Decision to restart heparin is based on clinical suspicion; consider heme consult
Treat for HIT; add allergy to chart

Critically ill or severe thromboembolism?

Yes

Initiate parenteral therapy with argatroban or bivalirudin; transition to warfarin or a DOAC when clinically stable and platelets >150 x10⁹/L

No

High bleed risk or potential for a procedure?

Yes

No

Initiate standard parenteral therapy; consider primary treatment with apixaban or rivaroxaban if the clinical situation warrants it

HIT Treatment Options:
- Argatroban + Warfarin
- Bivalirudin + Warfarin
- Fondaparinux + Warfarin
- Argatroban + DOAC
- Bivalirudin + DOAC
- Fondaparinux + DOAC
- DOAC alone
Patient Case

**CC:** Right knee pain

**HPI:** 59-year-old male s/p right total knee arthroplasty

**PMH:** Obesity, hypertension, alcoholism

**Social:** No tobacco or elicit drug use; last drink 2011

**Family:** Sister with deep vein thrombosis

The patient is started on subcutaneous heparin the morning following his surgery. On post-op day 3 his discharge is delayed when he develops pneumonia and is started on vancomycin and piperacillin-tazobactam.
Question 3

After two setbacks following total knee arthroplasty (pneumonia, HIT) the patient is eager to discharge home and is refusing parenteral anticoagulation for his newly diagnosed DVT. In this circumstance, which anticoagulation therapy would you initiate?

A. Rivaroxaban 15 mg twice daily
B. Apixaban 5 mg twice daily
C. Dabigatran 150 mg twice daily
D. Edoxaban 60 mg daily
E. Warfarin 5 mg daily
Summary

• HIT is a life-threatening adverse reaction to heparin that requires immediate heparin discontinuation and non-heparin anticoagulation

• Standard management is primary treatment with argatroban, bivalirudin, or fondaparinux and secondary treatment with warfarin

• Recent literature suggests DOACs may be effective in primary or secondary treatment

• DOACs should be limited to clinical scenarios where standard therapy is not an option
DOAC Utilization For Heparin-Induced Thrombocytopenia

Casey O’Connell, PharmD, RN
PGY1 Pharmacy Practice Resident

June 4, 2019
OConnell.Casey@mayo.edu
## HIT Characterization

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>10%</td>
<td>1-5%</td>
</tr>
<tr>
<td>Timing of Onset</td>
<td>2-3 days</td>
<td>5-10 days</td>
</tr>
<tr>
<td>Platelet Count Nadir</td>
<td>$\sim 100 \times 10^9$/L</td>
<td>$\sim 60 \times 10^9$/L</td>
</tr>
<tr>
<td>Antibody Mediated</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>No</td>
<td>Rare</td>
</tr>
<tr>
<td>Management</td>
<td>Observation</td>
<td>Heparin discontinuation; Non-heparin anticoagulation</td>
</tr>
</tbody>
</table>

HIT Risk Factors

Patient-Specific
- Female sex
- Increasing age
- Surgery
  - Ortho > Cardiac

Exposure-Specific
- UFH > LMWH
- Longer treatment duration
- Increased dosage
- No minimum safe dose
  - Heparin flushes
  - Heparin-coated catheters
  - Heparin-containing medications

UFH = Unfractionated Heparin
LMWH = Low Molecular Weight Heparin

HIT Signs and Symptoms

- Platelet count 20-150 x10^9/L
- Decrease in platelet count by >50%
- Venous or arterial thrombosis
- Necrotic skin lesions
- Systemic infusion reactions
  - Fever/chills
  - Tachycardia
  - Hypertension
  - Dyspnea

### Phases of HIT

<table>
<thead>
<tr>
<th>Phase</th>
<th>Platelet Count</th>
<th>Functional Assay</th>
<th>Immunoassay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected HIT</td>
<td>Decreased</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Acute HIT</td>
<td>Decreased</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Subacute HIT A</td>
<td>Normal</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Subacute HIT B</td>
<td>Normal</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Remote HIT</td>
<td>Normal</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
## Variants of Type II HIT

<table>
<thead>
<tr>
<th>HIT variant</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed-onset HIT</td>
<td>Begins or worsens after stopping heparin</td>
</tr>
<tr>
<td>Refractory HIT</td>
<td>Persists for &gt;1 week after stopping heparin</td>
</tr>
<tr>
<td>Spontaneous HIT</td>
<td>Occurs in the absence of recent exposure</td>
</tr>
<tr>
<td>Heparin flush HIT</td>
<td>Induced by exposure to heparin flushes</td>
</tr>
<tr>
<td>Fondaparinux-associated HIT</td>
<td>Induced by exposure to fondaparinux</td>
</tr>
<tr>
<td>Severe HIT</td>
<td>Associated with DIC, platelets &lt;20,000/microL</td>
</tr>
</tbody>
</table>
HIT Laboratory Analysis

Heparin-PF4 Antibody

- Immunoassay
- High sensitivity, lower specificity
- Serum added to enzyme-labeled secondary antibodies
- Optical density measured to quantify amount of antibodies
- Analyzed by Mayo Labs once daily Sunday-Friday
- Negative result rules-out HIT
- $278

Serotonin Release Assay

- Functional test
- High sensitivity, high specificity
- Serum added to labeled donor platelets at two heparin concentrations
- Percent platelet release measured
- Send-out to Wisconsin or California; 4-7 day turnaround
- Positive result confirms HIT
- $367

P4F = Platelet Factor 4
HIT Laboratory Analysis

**Heparin-PF4 Antibody**
- Immunoassay
- High sensitivity, lower specificity
- Negative result rules-out HIT
- Analyzed by Mayo Labs once daily Sunday-Friday
- $278

**Serotonin Release Assay**
- Functional test
- High sensitivity, high specificity
- Positive result confirms HIT
- Send-out to Wisconsin or California; 4-7 day turnaround
- $367

PF4 = Platelet Factor 4
HIT Pathophysiology

PF4 released from alpha granules of activated platelets

Heparin binds PF4 molecules forming an antigenic complex

IgG antibodies bind heparin-PF4 complex to form an immune complex

The immune complex activates other platelets via the Fc receptor

Platelets aggregate, form clots, and are cleared by macrophages

PF4 = Platelet Factor 4
IgG = Immunoglobulin G

Other Causes of Thrombocytopenia

Disease States
- Sepsis
- Disseminated intravascular clotting
- Thrombocytopenia purpura
- Antiphospholipid syndrome
- Intra-arterial devices
  - VAD
  - IABP
  - ECMO

Medications
- Chemotherapy
- Antimicrobials
  - Beta-lactams
  - Linezolid
  - Sulfamethoxazole
  - Vancomycin
- NSAIDs/acetaminophen
- Antiepileptics

VAD = Ventricular Assist Device  ECMO = Extracorporeal Membrane Oxygenation
Intra-Aortic Balloon Pump  NSAIDs = Nonsteroidal Anti-Inflammatory Drugs

### HIT Diagnosis – 4 T 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>&gt;50% decrease &amp; nadir ≥20 x10⁹/L</td>
<td>30-50% decrease or nadir 10-19 x10⁹/L</td>
<td>&lt;30% decrease or nadir &lt;10x10⁹/L</td>
</tr>
<tr>
<td>Timing of the decrease in platelet count</td>
<td>Days 5-10 or after day 1 with recent heparin exposure</td>
<td>After day 10, timing unclear, or before day 1 with recent heparin exposure</td>
<td>Before day 5 without recent heparin exposure</td>
</tr>
<tr>
<td>Thrombosis or other sequelae</td>
<td>Proven thrombosis, skin necrosis, or acute systemic reaction after heparin bolus</td>
<td>Progressive, recurrent, or silent thrombosis or erythematous skin lesions</td>
<td>None</td>
</tr>
<tr>
<td>Other causes of thrombocytopenia</td>
<td>None evident</td>
<td>Possible</td>
<td>Definite</td>
</tr>
</tbody>
</table>

0-3 = low risk (<1%)  
4-5 = intermediate risk (~10%)  
6-8 = high risk (~50%)

Rivaroxaban Indications Timeline

**Jul 1, 2011**  
DVT prophylaxis after hip or knee replacement

**Nov 2, 2012**  
Therapeutic treatment of DVT or PE

**Oct 4, 2011**  
Nonvalvular atrial fibrillation

**Nov 30, 2017**  
Reduction in DVT or PE recurrence

**Oct 11, 2018**  
Risk reduction In stable CAD or PAD
Confirmed thrombocytopenia

Discontinue heparin and calculate 4 Ts Score

Low HIT probability; resume heparin, monitor, & evaluate alternative causes

PF4 (+)?

4T ≥6?

No

Yes

Repeat PF4; if equivocal on recheck draw SRA

SRA (+)?

Yes

No

Treat for HIT; add allergy to chart

Decision to restart heparin is based on clinical suspicion; consider heme consult

My Recommended HIT Algorithm