DOACs: HIT-ting a home run for use in HIT?

October 18, 2019

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Appendices

Appendix A: Abbreviations

Presentation Slides

Appendix B: 4Ts Score
Appendix A – Abbreviations:

- PMH: past medical history
- HTN: hypertension
- VTE: venous thromboembolism
- HIT: heparin-induced thrombocytopenia
- SRA: serotonin release assay
- PTT: prothrombin time
- DOAC: direct oral anticoagulant
- IgG: immunoglobulin G
- PF4: platelet factor four
- ELISA: enzyme-linked immunosorbent assay
- HIPA: heparin-induced platelet antibody
- HITT: heparin-induced thrombocytopenia with thrombosis
- VKA: vitamin K antagonist
- ASH: American Society of Hematology
- AKI: acute kidney injury
- HTN: hypertension
- CRRT: continuous renal replacement therapy
- MOA: mechanism of action
- T½: half life
- STEMI: ST-elevation myocardial infarction
- NSTEMI: non ST-elevation myocardial infarction
- PCI: percutaneous coronary intervention
- DVT: deep vein thrombosis
- PE: pulmonary embolism
- BID: twice daily
- TIA: transient ischemic attack
- ACS: acute coronary syndrome
- GI: gastrointestinal
- Ppx: prophylaxis
- CrCl: creatinine clearance
- FDA: Food and Drug Administration
- APS: Antiphospholipid syndrome
DOACs: HIT-ting a Home Run for use in HIT?

Ava Cascone, PharmD
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Conflict of Interest

The author of this presentation has no conflicts of interest to disclose.

Objectives

• Discuss heparin-induced thrombocytopenia (HIT) and current first-line recommendations for treatment

• Review current guideline recommendations concerning DOAC use in HIT

• Evaluate current literature describing DOAC use in this setting

• Assess appropriateness of DOAC use

List of Abbreviations

- PMH: past medical history
- HTN: hypertension
- VTE: venous thromboembolism
- HIT: heparin-induced thrombocytopenia
- SRA: serotonin release assay
- PTT: prothrombin time
- DOAC: direct oral anticoagulant
- IgG: immunoglobin G
- PF4: platelet factor four
- ELISA: enzyme-linked immunosorbent assay
- HIPA: heparin-induced platelet antibody
- HIT-T: heparin-induced thrombocytopenia with thrombosis
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- ASH: American Society of Hematology
- AKI: acute kidney injury
- HTN: hypertension
- T/½: half life
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- FDA: Food and Drug Administration
- APS: Antiphospholipid syndrome

Background of HIT

Patient Case

- 65 year old male with PMH of HTN, atrial fibrillation, and gout admitted ten days ago for sepsis

- Hospital course complicated by an AKI after vancomycin and piperacillin/tazobactam use; home rivaroxaban stopped, heparin initiated

- Later diagnosed with HIT (intermediate 4Ts, heparin antibody +, SRA+); argatroban initiated

- Platelets now recovered; PTT at goal

- The attending physician asks whether the patient can be transitioned to a DOAC at this time
Heparin Induced Thrombocytopenia

- Autoimmune-mediated

- Heparin exposure → IgG antibody formation
- Platelet factor 4 (PF4) + Heparin = complex formation
- Complex binding to FcγIIa (IgG) platelet receptors
- Platelet activation → procoagulant molecules released
- Thrombin generation → venous/arterial thromboses

Guideline Recommendations

- American College of Chest Physicians, 2012
  - "In patients with HIT/HITT, we recommend the use of nonheparin anticoagulants, in particular lepirudin, argatroban, and danaparoid, over the further use of heparin or LMWH or initiation/continuation of a vitamin K antagonist (Grade 1C)"
  - "In patients with HIT/HITT and renal insufficiency, we suggest the use of argatroban over other nonheparin anticoagulants (Grade 2C)"
  - "We recommend against starting VKA until platelets have substantially recovered (ie, usually to at least 150 x 10^9/L) [Grade 1C]"

Diagnosis of HIT – 4Ts Score

- Thrombocytopenia
- Timing
- Thrombosis
- Other Causes

Guideline Recommendations

- American Society of Hematology, 2018
  - "When a non-heparin anticoagulant is being selected, the ASH guideline panel suggests argatroban, bivalirudin, danaparoid, fondaparinux, or a direct oral anticoagulant (conditional recommendation, very low certainty in the evidence)"
  - "Fondaparinux and the DOACs are reasonable options in clinically stable patients at average risk of bleeding"
  - "In patients with HIT complicated by life- or limb-threatening thromboembolism (eg, massive pulmonary embolism or venous limb gangrene), a parenteral non-heparin anticoagulant may be preferred"

Diagnosis of HIT

- Laboratory Assays
  - Antigen Assays: Detect presence of HIT antibodies
  - Functional Assays: Detect platelet activation by HIT antibodies in the presence of heparin
  - Ex. ELISA: Sensitive but not specific
  - Ex. SRA and HIPA: Sensitive + Specific

Management of HIT

- Argatroban
  - MOA
  - Indications
  - Administration in HIT
  - Pharmacokinetics
  - Direct thrombin inhibitor
    - FDA-approved HIT, PCI in adults who have or are at risk of developing HIT
    - Off-label maintenance of CRRT patency in HIT
  - IV dose adjusted based on APTT
  - Hepatic metabolism–hydroxylation and aromatization
  - T½: 39-51 minutes
  - Onset: Immediate
### Management of HIT

#### Argatroban

**MOA:** Direct thrombin inhibitor

- FDA-approved: HIT, PCI in adults who have or are at risk of developing HIT
- Off-label: maintenance of CRRT patency in HIT

**Administration in HIT:** IV, dose adjusted based on aPTT

**Pharmacokinetics:**
- Hepatic metabolism: hydrolysis and aromatization
- T1/2: 39-51 minutes
- Onset: immediate


#### Bivalirudin

**MOA:** Direct thrombin inhibitor

- FDA-approved: PCI
- Off-label: HIT, cardiac surgery with HITT

**Administration in HIT:** IV, dose adjusted based on aPTT

**Pharmacokinetics:**
- Metabolized via proteolytic cleavage
- T1/2: 25 minutes to 3.5 hours dependent on renal function
- Onset: immediate


#### Fondaparinux

**MOA:** Factor Xa inhibitor

- FDA-approved: Acute DVT, acute PE, VTE prophylaxis in surgical patients
- Off-label: HIT, STEMI, NSTEMI, acute symptomatic superficial vein thrombosis, acute thrombosis, VTE ppx in history of HIT/cancer/medical patients

**Administration in HIT:** SubQ daily dosing, dose based on weight

**Pharmacokinetics:**
- Metabolism: unchanged drug excreted in the urine
- T1/2: 17-22 hours, prolonged with renal impairment and in the elderly
- Time to peak: 2-3 hours


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**Why DOACs for HIT?**
### Management of HIT

<table>
<thead>
<tr>
<th>DOACs</th>
<th>MOA</th>
<th>Indications</th>
<th>Administration in HIT</th>
<th>Pharmacokinetics</th>
<th>T½</th>
<th>Time to peak</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Factor Xa inhibitors (apixaban, rivaroxaban, edoxaban)</td>
<td>fork in HIT, acute DVT, acute PE, VTE prophylaxis, stroke prevention in non-valvular atrial fibrillation</td>
<td>? Hepatic metabolism</td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Direct thrombin inhibitor (dabigatran)</td>
<td>fork in HIT, acute DVT, acute PE, VTE prophylaxis, stroke prevention in non-valvular atrial fibrillation</td>
<td></td>
<td>T½:</td>
<td>Apixaban ~12 hours</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Direct thrombin inhibitor (dabigatran)</td>
<td></td>
<td></td>
<td>Rivaroxaban 5-10 hours, Edoxaban 10-20 hours, Dabigatran 12-28 hours, dependent on renal function</td>
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<td></td>
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</tr>
</tbody>
</table>

### Evidence for DOAC use in HIT

- Open-label, single-arm prospective cohort study
- Population: 22 patients with HIT treated with argatroban and DOAC combination
- Inclusion/exclusion criteria:
  - HIT: recent heparin exposure + reduction of platelets to less than half of baseline or to <100 without other explainable causes
  - ELISA
  - SRA if ELISA negative

- Treatment:
  - Heparin products discontinued
  - Argatroban without a bolus initiated at 0.3-0.5 mcg/kg/min and continued for a mean of 32h
  - Dose was adjusted to keep aPTT between 50-90 sec
  - First aPTT obtained 3h after initiation and every 3h if a dose change was made; if no change, checked q24h
  - DOAC initiated 2h after discontinuation of argatroban

### Sharifi et al., 2015

- DOAC for HIT (n=22)
  - Dabigatran 150 mg BID (n=6)
  - Rivaroxaban 20 mg daily (n=11)
  - Apixaban 5 mg BID (n=5)
**Sharifi et al., 2015**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>In-hospital: N=0</td>
</tr>
<tr>
<td></td>
<td>At 1 month: N=3</td>
</tr>
<tr>
<td></td>
<td>At 19 months: N=3</td>
</tr>
<tr>
<td>New onset VTE</td>
<td>N=5</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>N=0</td>
</tr>
<tr>
<td>Limb loss</td>
<td>N=0</td>
</tr>
<tr>
<td>Bleeding</td>
<td>N=0</td>
</tr>
</tbody>
</table>

*Strengths:*
- Prospective cohort study
- 19 month follow up
- Timing of DOAC initiation discussed

*Weaknesses:*
- Small study
- No inclusion/exclusion criteria defined
- HIT not defined by 4Ts
- Dosing strategies not defined
- Time to platelet recovery not defined

**Take home points:**
- Longest follow up, prospective study, VTE in five patients

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**Kunk et al., 2017**

**Outcome Result**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>New thrombi</td>
<td>N=0</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>N=2</td>
</tr>
<tr>
<td>- GI bleed (on clopidogrel; known gastric varices)</td>
<td></td>
</tr>
<tr>
<td>- Hemoptysis (squamous cell lung cancer)</td>
<td></td>
</tr>
<tr>
<td>Time to platelet recovery</td>
<td>Range 1-8 days</td>
</tr>
</tbody>
</table>

**Strengths:**
- Follow-up period of 3-6 months
- All patients SRA positive

**Weaknesses:**
- Patient population
- Specific outcomes not defined
- Dosing of DOACs not defined
- Reports 2 of 23 patients developed severe bleeding

**Take home points:**
- Studied use of DOACs in the place of warfarin "after platelet recovery"
- Bleeding reported in two patients with HIT

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**Sharifi et al., 2015**

“The results indicate that a short course of argatroban followed by administration of DOAC is highly safe and effective in treatment of HIT”

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**Kunk et al., 2017**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>APS + HIT</td>
<td>N=23</td>
</tr>
<tr>
<td>HIT + IV bivalirudin or argatroban until platelets 50 x k/µL</td>
<td>n=12</td>
</tr>
<tr>
<td>APS</td>
<td>n=11</td>
</tr>
<tr>
<td>Apixaban</td>
<td>n=10</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>n=2</td>
</tr>
</tbody>
</table>

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**Kunk et al., 2017**

“DOACs can be safe and effective in this high risk patient population”

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**Kunk et al., 2017**

- Retrospective analysis
- Purpose: evaluation of efficacy + safety of apixaban and rivaroxaban therapy in patients with HIT or APS
- Patients: adult patients at UVA Health System with HIT or APS treated with apixaban or rivaroxaban in place of warfarin
  - HIT patients: included those with positive SRA
  - All patients had normal renal/hepatic function

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**Kunk et al., 2017**

- Strengths:
- Follow-up period of 3-6 months
- All patients SRA positive

- Weaknesses:
- Patient population
- Specific outcomes not defined
- Dosing of DOACs not defined
- Reports 2 of 23 patients developed severe bleeding

- Take home points:
- Studied use of DOACs in the place of warfarin “after platelet recovery”
- Bleeding reported in two patients with HIT
Case Reports

<table>
<thead>
<tr>
<th>Patient</th>
<th>Intervention</th>
<th>Results</th>
<th>Take Away Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 year-old male post aortic root replacement</td>
<td>Heparin → HIT → argatroban → DVT → apixaban 5 mg BID</td>
<td>Steady platelet count increase</td>
<td>Steady platelet count increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No new thrombosis</td>
<td>No new thrombosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No bleeding at 3 month follow-up</td>
<td>No bleeding at 3 month follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DOAC use following treatment with first-line parenteral therapy</td>
<td>DOAC use following treatment with first-line parenteral therapy</td>
</tr>
<tr>
<td>36 year-old male post orthopedic surgery</td>
<td>Nadroparin → HIT → fondaparinux → radial artery thrombosis 10 mg BID 2-3 days then 20 mg daily</td>
<td>Platelet count returned to normal</td>
<td>Platelet count returned to normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recanalization of thrombosis at 1 &amp; 2 months</td>
<td>Recanalization of thrombosis at 1 &amp; 2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic occlusion</td>
<td>Chronic occlusion</td>
</tr>
<tr>
<td>68 year old male with DVT after surgery</td>
<td>Enoxaparin → DVT → enoxaparin 80 mg BID → fondaparinux 2.5 mg daily → ELISA (+) → rivaroxaban 20 mg daily</td>
<td>Platelets returned to baseline 4 days after initiation of rivaroxaban</td>
<td>Platelets returned to baseline 4 days after initiation of rivaroxaban</td>
</tr>
</tbody>
</table>

Davis et al., 2017

- Retrospective analysis
- Purpose: evaluation of efficacy + safety of DOAC therapy in patients with suspected HIT
- Patients: inpatients within LA hospital network diagnosed with HIT who received apixaban, dabigatran, or rivaroxaban
  - Included intermediate-high probability of HIT with positive PF4/heparin assay
  - Excluded: SRA negative, history of HIT, admission <48h

Outcome Result

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of newly diagnosed venous or arterial thromboembolism, gangrene, or amputation</td>
<td>N=0</td>
</tr>
<tr>
<td>In-hospital major bleeding</td>
<td>N=0</td>
</tr>
<tr>
<td>Time to platelet recovery</td>
<td>3-14 days</td>
</tr>
</tbody>
</table>

"The use of DOAC therapy, specifically apixaban and rivaroxaban, was well tolerated and effective in the acute treatment of HIT during hospitalization"

Davis et al., 2017

- Strengths:
  - Systematically defined HIT
  - Dosing reported
- Weaknesses:
  - Small study
  - Only followed during hospital stay
  - SRA only reported in 4 patients
  - Results not defined based on initiation of DOAC
  - Retrospective
- Take home points:
  - DOACs used both after argatroban and as initial HIT treatment

Linkins et al., 2016

- Multicenter prospective single-arm cohort study
- Patients: adults with confirmed or suspected HIT
  - Excluded:
    - Pregnant or nursing
    - Graded in study within past 100 days
    - Mechanical heart valve
    - CrCl<30 mL/min
    - Hepatic disease with coagulopathy and clinically relevant bleed risk
    - Active bleeding or lesions at increased bleed risk within the past 6 months
    - Concurrent strong CYP3A4 inhibitor/inducer and medications
    - Long term indwelling epidural catheter
  - Active bleeding or lesions at increased bleed risk within the past 6 months
  - Concurrent strong CYP3A4 inhibitor/inducer and medications
  - Long term indwelling epidural catheter
- Purpose: to prospectively evaluate efficacy and safety of rivaroxaban in patients with suspected or confirmed HIT

Davis et al., 2017

N=12
Apixaban (n=9)
5 mg BID (n=7)
2.5 mg BID (n=1)
10 mg BID (n=1)
Rivaroxaban 15 mg BID (n=3)
Received argatroban initially (n=7)

**Linkins et al., 2016**

22 patients enrolled & given rivaroxaban 15 mg BID

12 patients SRA positive

Rivaroxaban 15 mg BID until platelet recovery or day 21 → rivaroxaban 20 mg daily

**Case Reports**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Intervention</th>
<th>Results</th>
<th>Take Away Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>54 year-old male undergoing CABG</td>
<td>Enoxaparin → HIT → rivaroxaban 20 mg BID</td>
<td>Plalet recovery → 3 month ultrasound showed no thrombus → No major bleeding</td>
<td></td>
</tr>
<tr>
<td>72 year-old female with PE</td>
<td>Dalteparin → HIT → apixaban 5 mg BID</td>
<td>Patient discharged home with phone interviews and blood samples → Platelets improved with no adverse events</td>
<td>DOAC used as primary HIT treatment in place of first-line therapies</td>
</tr>
</tbody>
</table>

**Outcome Result Take Away Points**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Result</th>
<th>Take Away Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>New symptomatic, objectively-confirmed venous and arterial thromboembolism at 30 days/hospitalized on rivaroxaban</td>
<td>N=1 (4.5%, 95% CI 0-23.5%)</td>
<td></td>
</tr>
<tr>
<td>Thrombotic event rate</td>
<td>8.3% (95% CI 0.1-37.5%)</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>N=1</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>N=4 (cancer, sepsis, COPD)</td>
<td></td>
</tr>
<tr>
<td>Time to platelet recovery</td>
<td>Mean: 11 days</td>
<td></td>
</tr>
</tbody>
</table>

**Case Series**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Intervention</th>
<th>Results</th>
<th>Take Away Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 year-old male undergoing surgical embolization</td>
<td>Enoxaparin → Heparin antibody positive → rivaroxaban 10 mg BID</td>
<td>Platelets to normal a few days after dabigatran initiation → Day 10 ultrasound showed recanalization of thrombus</td>
<td></td>
</tr>
</tbody>
</table>

**Linkins et al., 2016**

“The findings of the current study suggest that rivaroxaban may be effective in treating patients with HIT”

• Strengths:
  • Systematic HIT diagnosis
  • Prospective cohort study

• Weaknesses:
  • Study terminated early due to poor enrollment
  • Take home points:
    • Rivaroxaban used as initial treatment for HIT in place of first-line therapy

**Warkentin et al., 2017**

• Part 1 (follow-up of Hamilton study): report on post-trial experience with rivaroxaban

• Purpose: to determine frequency of thrombotic events and major bleeding in patients with a probable diagnosis of HIT treated with rivaroxaban in Hamilton

• Patient population:
  • Inclusion criteria:
    • Patients at 4 Hamilton acute care hospitals
    • 4T ≥ 4
  • Heparin antibody positive + SRA positive
Warkentin et al., 2017

- Outcome:
  - 30 day incidence of new symptomatic objectively confirmed HIT: n=0
  - Incidence of symptomatic thromboembolism: n=0
  - Incidence of venous and arterial thromboembolism: n=0
  - Incidence of major bleeding: n=0
  - Time to platelet recovery:
    - Group A1: 2-17 days
    - Group A2: N/A
    - Group B: 7 and 60 days
    - Group C: N/A

Warkentin et al., 2017

- Part 2: Systematic review/literature summary of reports on use of DOACs for treatment of patients with HIT
  - Population:
    - Exclusion criteria: patients who did not seem to have HIT, insufficient data for HIT diagnosis, SRA positive but EIA negative
  - Outcome:
    - 30 day (or last follow up) thrombotic event rate
    - Thrombotic event rate while receiving DOAC
    - Major bleeding rate while receiving DOAC
**Warkentin et al., 2017**

- Patients transitioned to a DOAC after platelet recovery: n=11
  - Rivaroxaban: n=7
  - Apixaban: n=3
  - Dabigatran: n=1

- Results:
  - No thrombosis
  - One major bleed due to known varices

**Management of HIT**

- American Society of Hematology, 2018
  - “With respect to the choice of DOAC, most of the published experience in HIT is with rivaroxaban.”
  - “Various dosing regimens have been reported.”
    - For patients with acute HIT, rivaroxaban at a dose of 15 mg BID for 3 weeks followed by 20 mg daily is preferred.
    - For patients with acute isolated HIT, rivaroxaban 15 mg BID until platelet count recovery (usually a platelet count of ≥150 x 10^9/L) followed by 20 mg daily is preferred if there is an indication for ongoing anticoagulation.

**Overall Literature Review**

<table>
<thead>
<tr>
<th>Study</th>
<th>Take Home Point</th>
<th>Major Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharif et al.</td>
<td>Longest follow up; prospective</td>
<td>HIT diagnosis</td>
</tr>
<tr>
<td>Kunk et al.</td>
<td>Studied use of DOACs after argatroban and after platelet recovery to 50 x 10^9/L</td>
<td>APS and HIT patient population</td>
</tr>
<tr>
<td>Case Reports/Series</td>
<td>DOACs used as initial treatment for HIT and after initial parenteral therapy</td>
<td>Single cases</td>
</tr>
<tr>
<td>Davis et al.</td>
<td>DOACs used as initial treatment for HIT and after argatroban</td>
<td>HIT diagnosis</td>
</tr>
<tr>
<td>Limbo et al.</td>
<td>DOACs used as initial treatment for HIT</td>
<td>Multiple apixaban dosing strategies</td>
</tr>
<tr>
<td>Warkentin et al.</td>
<td>Cited in guidelines recommending rivaroxaban’s use in HIT</td>
<td>Results not broken down based on timing of DOAC initiation</td>
</tr>
</tbody>
</table>

**“DOACs seem to be safe and effective for treatment of acute HIT, with the most experience reported for rivaroxaban”**

- Strengths:
  - Patients defined based on DOAC initiation
  - HIT definitions based on International Society of Thrombosis/Hemostasis
- Weaknesses:
  - Small study
  - Inconsistency in initiation of DOAC
  - Dosing not reported
  - Outcomes not reported for specific subgroups
- Take home points:
  - Cited in guidelines recommending rivaroxaban’s use in HIT
  - Included patients with DOACs in place of first-line treatment of HIT and in place of warfarin

**Should DOACs be recommended for use in HIT?**
### DOACs in HIT: Advantages/Disadvantages

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased monitoring</td>
<td>• Dosing inconsistent among studies</td>
</tr>
<tr>
<td>• Administration does not require IV access</td>
<td>• HIT diagnosis strategies inconsistent among studies</td>
</tr>
<tr>
<td>• Cost savings</td>
<td>• Studies inconsistent in initiation of DOAC</td>
</tr>
<tr>
<td>• Mechanism of action</td>
<td>• Randomized controlled trials lacking</td>
</tr>
<tr>
<td></td>
<td>• Renal considerations</td>
</tr>
<tr>
<td></td>
<td>• Drug-drug interactions</td>
</tr>
</tbody>
</table>

### Patient Case

A 65 year old male with a PMH of HTN, atrial fibrillation and gout was admitted ten days ago for sepsis. He was receiving heparin and was diagnosed with HIT (intermediate 4Ts, heparin antibody +, SRA +). Argatroban was initiated. The patient’s platelets are now recovered and his PTT is at goal. The attending physician asks whether the patient can be transitioned to a DOAC at this time.

#### Patient Case

**What dosing regimen of rivaroxaban would you recommend?**

A. Rivaroxaban 20 mg daily
B. Rivaroxaban 15 mg BID x 7 days, then rivaroxaban 20 mg daily
C. Rivaroxaban 10 mg daily
D. None of these, evidence is limited with rivaroxaban

### Management of HIT

#### Rivaroxaban

<table>
<thead>
<tr>
<th>MOA</th>
<th>Indications</th>
<th>Administration in HIT</th>
<th>Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor Xa inhibitor</td>
<td>FDA approved: Acute DVT, acute PE, VTE prophylaxis, stroke prevention in non-valvular atrial fibrillation</td>
<td>Off-label: HIT (apixaban), ACS + superficial vein thrombosis (rivaroxaban), VTE ppx in total knee arthroplasty (dabigatran)</td>
<td>Hepatic metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T1/2: 11-13 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time to peak:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rivaroxaban: 1-2 hours</td>
</tr>
</tbody>
</table>

### Management of HIT

#### Apixaban

<table>
<thead>
<tr>
<th>MOA</th>
<th>Indications</th>
<th>Administration in HIT</th>
<th>Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor Xa inhibitor</td>
<td>FDA approved: Acute DVT, acute PE, VTE prophylaxis, stroke prevention in non-valvular atrial fibrillation</td>
<td>Off-label: HIT (apixaban)</td>
<td>Hepatic metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T1/2:</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Apixaban: 12 hours</td>
</tr>
</tbody>
</table>

#### Dabigatran

<table>
<thead>
<tr>
<th>MOA</th>
<th>Indications</th>
<th>Administration in HIT</th>
<th>Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct thrombin inhibitor</td>
<td>FDA approved: Acute DVT, acute PE, VTE prophylaxis, stroke prevention in non-valvular atrial fibrillation</td>
<td>Off-label: HIT (apixaban)</td>
<td>Hepatic metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T1/2:</td>
</tr>
</tbody>
</table>

#### Edoxaban

<table>
<thead>
<tr>
<th>MOA</th>
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<th>Administration in HIT</th>
<th>Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor Xa inhibitor</td>
<td>FDA approved: Acute DVT, acute PE, VTE prophylaxis, stroke prevention in non-valvular atrial fibrillation</td>
<td>Off-label: HIT (apixaban)</td>
<td>Hepatic metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T1/2:</td>
</tr>
</tbody>
</table>

### Management of HIT

#### Argatroban

<table>
<thead>
<tr>
<th>MOA</th>
<th>Indications</th>
<th>Administration in HIT</th>
<th>Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct thrombin inhibitor</td>
<td>FDA approved: HIT, PTC in adults who have or are at risk of developing HIT</td>
<td>Off-label: maintenance of CRRT patency in HIT</td>
<td>Hepatic metabolism–hydroxylation and aromatization</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T1/2: 39-51 minutes</td>
</tr>
<tr>
<td></td>
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<td>Onset: immediate</td>
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</tbody>
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10/11/2019
Patient Case
When would you recommend to start the rivaroxaban?
A. Stop argatroban, initiate rivaroxaban immediately
B. Stop argatroban, initiate rivaroxaban 24 hours later
C. Stop argatroban, initiate rivaroxaban in 3-4 hours
D. None of these, evidence is limited with rivaroxaban

Conclusions

DOACs: HIT-ting a Home Run for use in HIT?
Ava Cascone, PharmD
PGY1 Pharmacy Resident, Seton Healthcare Family
October 18, 2019

Acknowledgements
- Evaluator: Ashley Castleberry, PharmD, MEd
- Neil Pan, PharmD, BCPS
- Brady Helmink, PharmD, BCPS
Appendix B:

<table>
<thead>
<tr>
<th>Table 1: 4Ts Score</th>
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<tbody>
<tr>
<td><strong>Thrombocytopenia</strong></td>
</tr>
</tbody>
</table>
| Compare the highest platelet count within the sequence of declining platelet counts with the lowest count to determine the % of platelet fall. | • >50% platelet fall AND nadir of ≥ 20 AND no surgery within preceding 3 days | • >50% platelet fall BUT surgery within preceding 3 days OR Any combination of platelet fall and nadir that does not fit criteria for Score 2 or Score 0 (eg. 30-50% platelet fall or nadir 10-19) | • < 30% platelet fall  
• Any platelet fall with nadir < 10 |
| **Timing (of platelet count fall or thrombosis)** | | | |
| Day 0 = first day of most recent heparin exposure | • Platelet fall day 5-10 after start of heparin  
• Platelet fall within 1 day of start of heparin AND exposure to heparin within past 5-30 days | • Consistent with platelet fall days 5-10 but not clear (eg. missing counts)  
• Platelet fall within 1 day of start of heparin AND exposure to heparin within past 31-100 days  
• Platelet fall after day 10 | • Platelet fall ≤ day 4 without exposure to heparin in past 100 days |
| **Thrombosis** | | | |
| • Confirmed new thrombosis (venous or arterial)  
• Skin necrosis at injection site  
• Anaphylactoid reaction to IV heparin bolus  
• Adrenal hemorrhage | • Recurrent venous thrombosis in a patient receiving therapeutic anticoagulants  
• Suspected thrombosis (awaiting confirmation with imaging)  
• Erythematous skin lesions at heparin injection sites | | • Thrombosis suspected |
| **Other cause for Thrombocytopenia** | | | |
| • No alternative explanation for platelet fall is evident | Possible other cause is evident:  
• Sepsis without proven microbial source  
• Thrombocytopenia associated with initiation of ventilator  
• Other | Probable other cause present:  
• Within 72h of surgery  
• Confirmed bacteremia/fungemia  
• Chemotherapy or radiation within past 20 days  
• DIC due to non-HIT cause  
• Posttransfusion purpura (PTP)  
• Platelet count <20 AND given a drug implicated in causing D-ITP  
• Non-necrotizing skin lesions at LMWH injection site (presumes DTH)  
• Other | |

Linkins et al. CHEST. 2012;141(2):e500S.