Modern Management of Heparin-Induced Thrombocytopenia (HIT): Focus on Direct-Acting Oral Anticoagulants (DOACs)

A presentation for HealthTrust Members

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Disclosures

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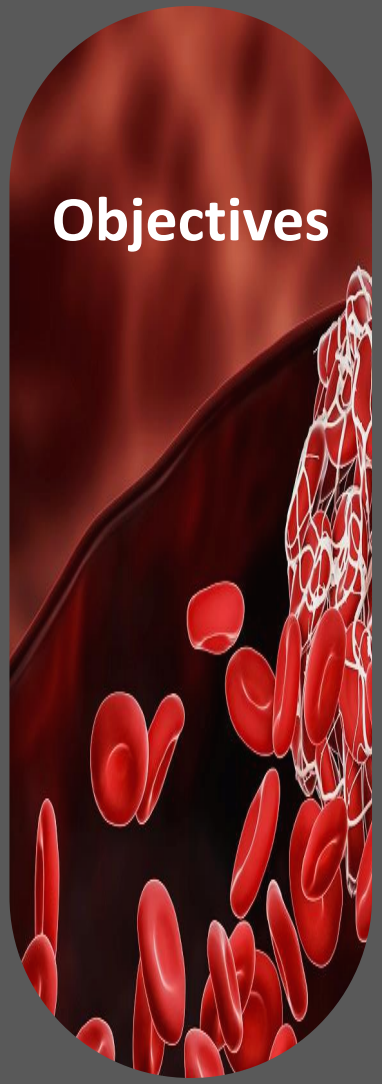
Objectives

Objectives

At the end of this presentation, participants should be able to:

Identify	Identify current guidelines for the management of HIT and recent changes from former recommendations
Recognize	Recognize patient populations that may benefit from DOAC therapy in HIT, as well as those in which DOACs may not be optimal
Recall	Recall the proper timing and dosing in the initiation of DOACs for HIT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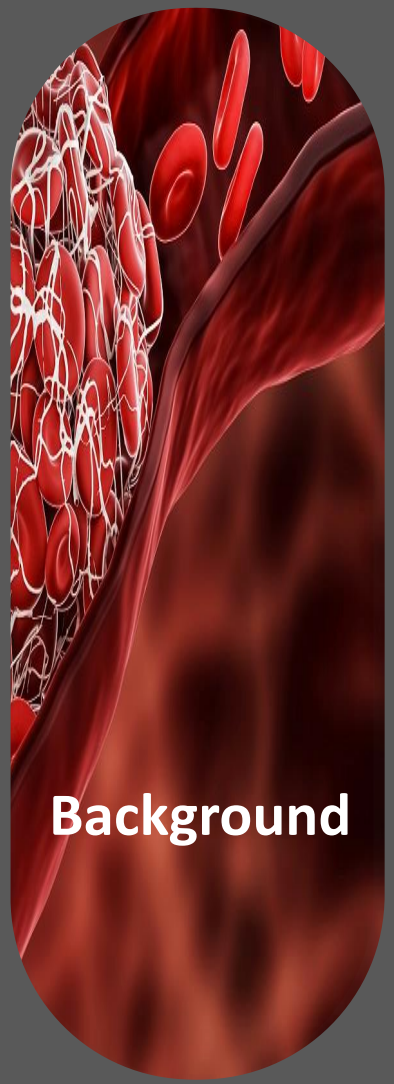

Background

Heparin Products

- Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are utilized extensively in patients for surgical and medical management in over 12 million patients per year
- Mechanism of action: Enhance the activity of antithrombin-III and inhibit factor Xa
- The most concerning adverse effect associated with heparin products is bleeding

Sources: Cureus. 2020;12(3):e7385.
Biology. 2021;41:141–152

Types of HIT

Type I HIT	Type II HIT
Non-immune mediated response	Immune-mediated response
Mild thrombocytopenia	Severe thrombocytopenia
Generally occurs within 2-3 days of heparin initiation and recovers after 2-4 days	Generally occurs 5-10 days after heparin initiation and can last for weeks
Doesn’t require heparin discontinuation or treatment	Requires heparin discontinuation and treatment
Not associated with severe complications	Associated with potentially life-threatening thromboemboli

Sources: Cureus. 2020;12(3):e7385.
Blood Adv. 2018; 2(22): 3360–3392.

Background

HIT

- Type II HIT occurs in roughly 1-5% of patients receiving UFH and 0.1-0.5% of patients receiving LMWH
- Thrombosis rate of roughly 50-60%, mortality rate as high at 20%
- Generally occurs 5-10 days after heparin initiation
  - Onset can be more rapid with heparin usage in the previous 30 days
- Twice as common in females, rare in younger adults (<40 years old), increased risk with prolonged courses of heparin and after cardiac surgery or severe trauma

Sources: Cureus. 2020;12(3):e7385.
Biology. 2021;41:141–152

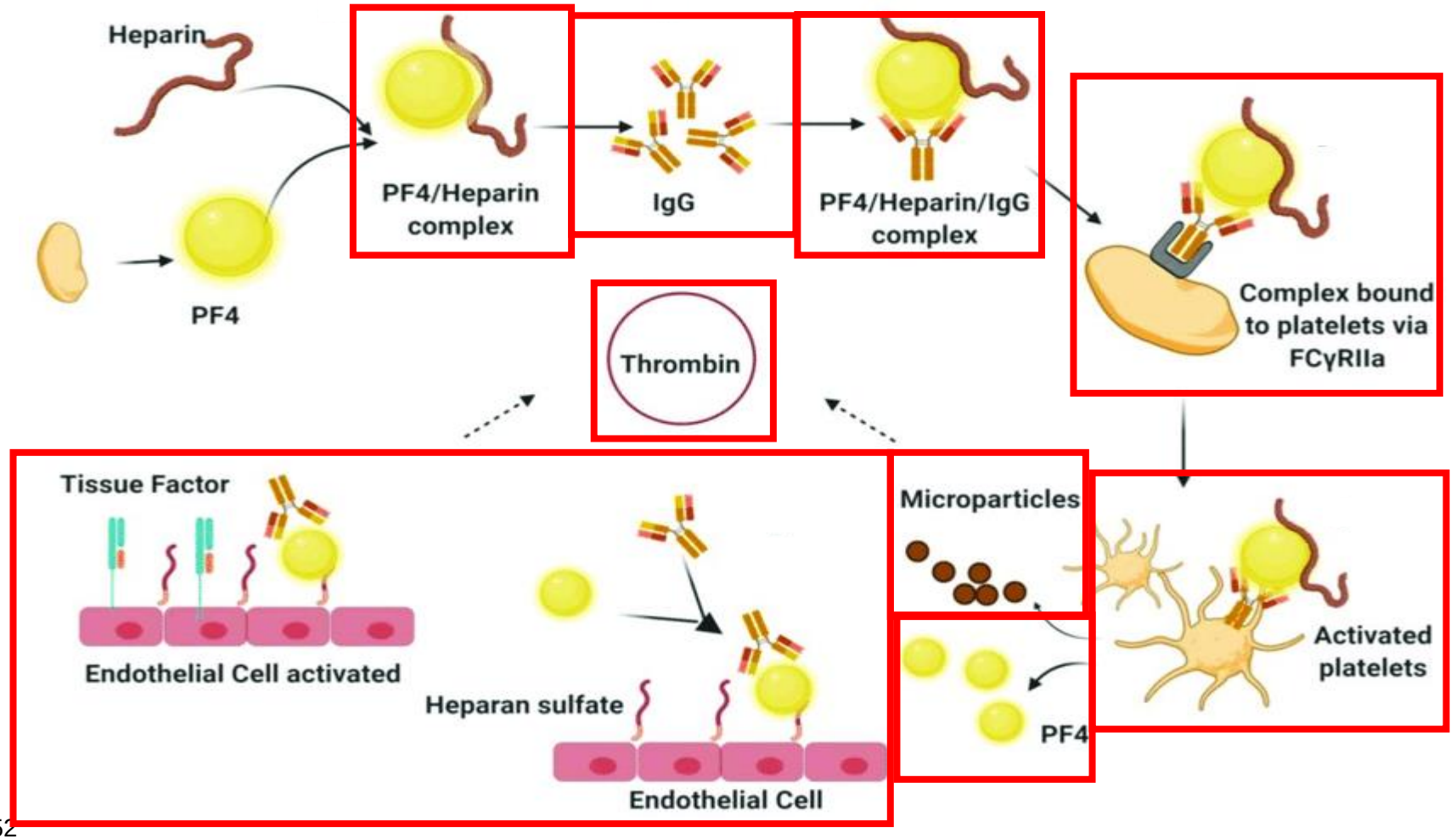
Pathophysiology

HIT is a prothrombotic adverse drug reaction (type 2 hypersensitivity reaction), mediated in most cases by immunoglobulin G antibodies that target complexes of platelet factor 4 (PF4) and heparin

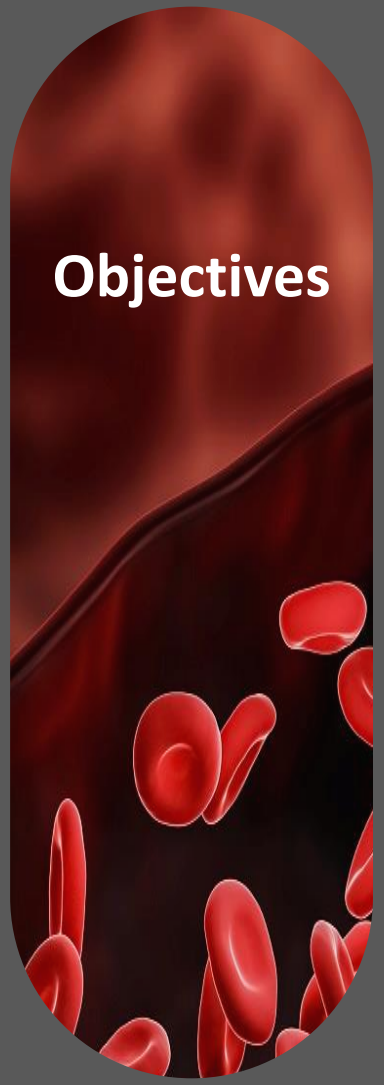
- PF4: Antigen found in platelets with various biological roles such as coagulation, inflammation, and immune cell maturation
- Immunoglobulin G (IgG) antibodies: Forms complex against the PF4/heparin complex
- Thrombin: Promotes prothrombotic state via anticoagulation cascade

Sources: Cureus. 2020;12(3):e7385.
Biology. 2021;41:141–152

Pathophysiology



Sources: *Biology*. 2021;41:141–152
Postgrad Med J. 2007;83(983):575-582.


Objectives


Background


Guidelines

4T Score

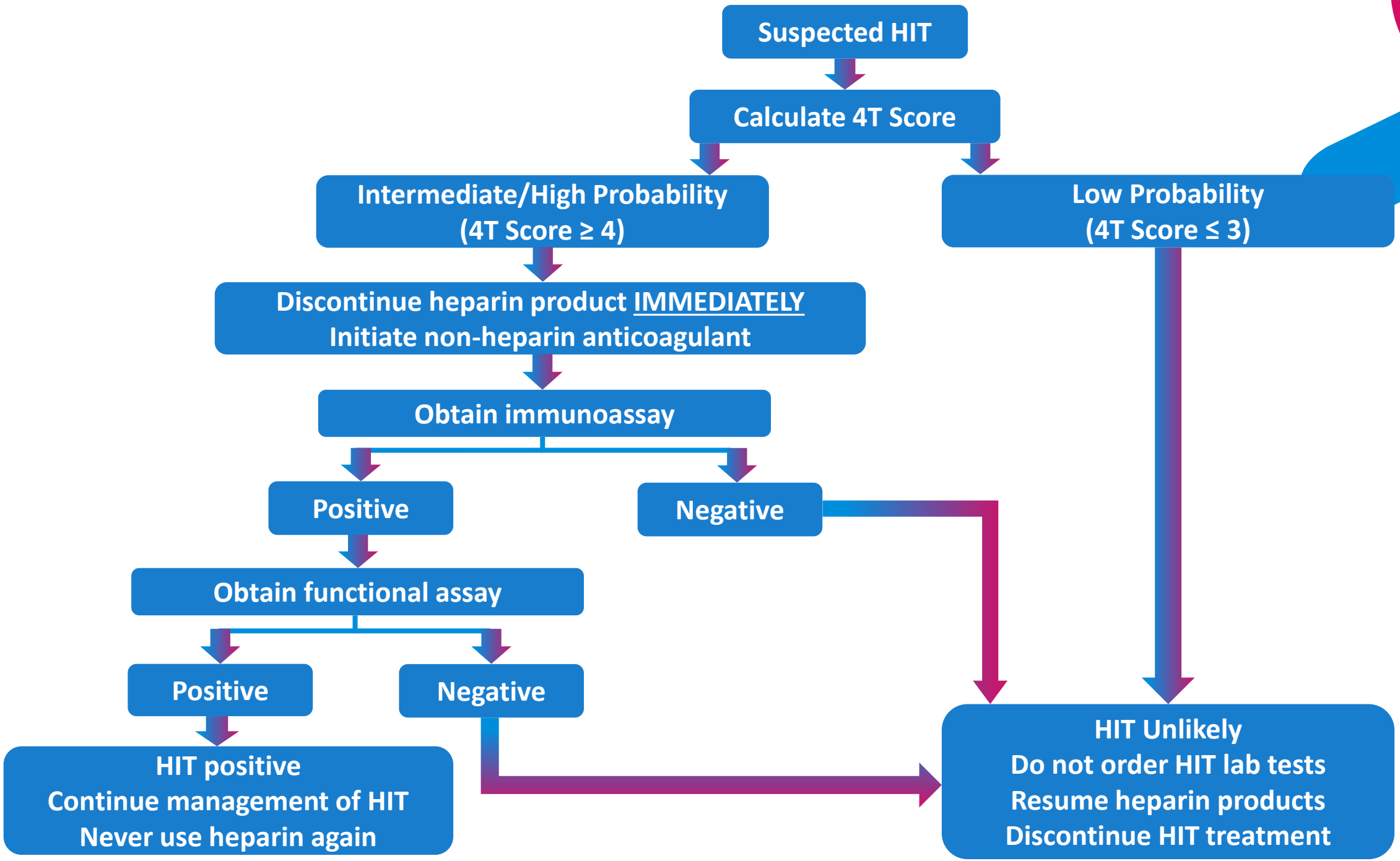
4Ts	2 points	1 point	0 points
Thrombocytopenia	PLT fall > 50% & nadir ≥ 20	PLT fall 30-50% or nadir 10-19	PLT fall < 30% or nadir <10
Timing (onset of PLT count fall)	Onset between 5-10 days or PLT fall ≤ 1 day (heparin exposure in past 30 days)	Consistent with days 5-10 fall but not clear; onset after 10th day, or fall ≤ 1 day (heparin exposure in past 30-100 days)	PLT count fall < 4 day without recent exposure
Thrombosis or other sequelae	Confirmed new thrombosis; skin necrosis; acute systemic reaction post-IV heparin bolus	Progressive or recurrent thrombosis; skin lesions (not necrotic); suspected thrombosis	None
OTher causes of thrombocytopenia	None apparent	Possible	Definite

Patients based on their score are categorized into three different probability sub-groups:

- 0-3: Low-risk group
- 4-5: Intermediate-risk group
- 6-8: High-risk group

PLT = platelet

Sources: Blood Adv. 2018; 2(22): 3360–3392.


Suspected HIT
Calculate 4T Score
Intermediate/High Probability
(4T Score ≥ 4)
Low Probability
(4T Score ≤ 3)
Discontinue heparin product IMMEDIATELY
Initiate non-heparin anticoagulant
Obtain immunoassay
Positive
Negative
Obtain functional assay
Positive
Negative
HIT positive
Continue management of HIT
Never use heparin again
HIT Unlikely
Do not order HIT lab tests
Resume heparin products
Discontinue HIT treatment

Diagnostic Assays

Immunoassays:

- Enzyme-linked immunosorbent assay (ELISA)
- Detect the presence of PF4-heparin antibodies
- Measured in optical density (OD)
  - 0.4-0.9 is weakly positive
  - >2 is strongly positive
- Sensitivity: >99%, Specificity: 40-70%

Functional assays:

- Serotonin release assay (SRA) and heparin-induced platelet activation (HIPA)
- Determines whether a patient has heparin-PF4 antibodies that have platelet-activating properties
- Specificity: >95%, Sensitivity 60-100%

Sources: *Cureus*. 2020;12(3):e7385.
Blood Adv. 2018; 2(22): 3360–3392.

Phases of HIT

Phase	Platelet Count	Functional Assay	Immunoassay
Suspected HIT	Decreased	?	?
Acute HIT	Decreased	+	+
Subacute HIT A	Normal	+	+
Subacute HIT B	Normal	-	+
Remote HIT	Normal	-	-

Sources: Cureus. 2020;12(3):e7385.
Blood Adv. 2018; 2(22): 3360–3392.

Past to Present Recommendations

Acute Phase: complicated by thrombosis (HITT) or acute HIT without thrombosis (isolated HIT)

	2012 American College of Cardiology Recommendations	2018 American Society of Hematology Recommendations
Acute	Lepirudin, argatroban, bivalirudin, danaparoid (not in US), and fondaparinux	Argatroban, bivalirudin, danaparoid (not in the US), fondaparinux, DOACs
Post-Acute	Transition to warfarin after platelet count recovery (≥150×10^9/L)[a]	Transition to warfarin after platelet count recovery (≥150×10^9/L)[a] or DOAC
Duration	Isolated HIT: VKA therapy or an alternative anticoagulant be continued for 4 weeks HITT: Vitamin K antagonist (VKA) therapy or an alternative anticoagulant be continued for 3 months	Isolated HIT: Until platelet count recovery at minimum HITT: 3 months at minimum Persistent HIT without platelet count recovery[b]: >3 months

[a]IV Direct thrombin inhibitor (DTI) or fondaparinux is overlapped with warfarin for about 5 days, until INR is at goal (generally 2-3)
[b]Doesn't apply to acute HITT

Sources: Blood Adv. 2018; 2(22): 3360–3392.

Why DOACs?

Unlike VKAs, DOACs have a rapid onset and do not cause reductions in protein C anticoagulant activity, thus potentially providing benefit during the acute phase of HIT	DOACs should also be effective during longer-term anticoagulation after platelet count recovery, therefore avoiding the risk and expense of transition from parenteral to oral VKA anticoagulation	There is no potentially deleterious immunologic interaction between these agents and HIT antibodies

DOAC Recommendations

Acute Phase: complicated by thrombosis (HITT) or acute HIT without thrombosis (isolated HIT)

- DOACs are reasonable options in clinically stable patients at average risk of bleeding
- In patients with HIT complicated by life- or limb-threatening thromboembolism, a parenteral non-heparin anticoagulant may be preferred

Sources: Blood Adv. 2018; 2(22): 3360–3392.

Assessment Question #1

True or False: A patient with suspected HIT was recently found to have a DVT. Suddenly, the patient develops shortness of breath, chest pain, palpitations, diaphoresis, and hypotension. Platelets are within a normal range. CTA chest revealed a large saddle PE, and the echocardiogram showed evidence of right heart strain. Rivaroxaban is a primary treatment option based on guidelines and clinical trial data.

A. True
B. False

Assessment Question #1

True or False: A patient with suspected HIT was recently found to have a DVT. Suddenly, the patient develops shortness of breath, chest pain, palpitations, diaphoresis, and hypotension. Platelets are within a normal range. CTA chest revealed a large saddle PE, and echocardiogram showed evidence of right heart strain. Rivaroxaban is a primary treatment option based on guidelines and clinical trial data.

A. True

B. False

Assessment Question #2

AB is a 50-year-old black male that weighs 75 kg. He is in the remote phase of HIT, currently treated with an argatroban infusion. Past medical history includes heart failure, atrial fibrillation, and chronic kidney disease stage IV (creatinine clearance of ~28 mL/min). INR is 1.3. The patient is being prepared for discharge and the attending asks to switch to more concrete therapy. What is the most appropriate monotherapy treatment course?

A. Switch to enoxaparin 80 mg SQ daily
B. Switch to warfarin 5 mg PO daily
C. Switch to apixaban 5 mg PO twice daily
D. Switch to fondaparinux 7.5 mg SQ daily

Assessment Question #2

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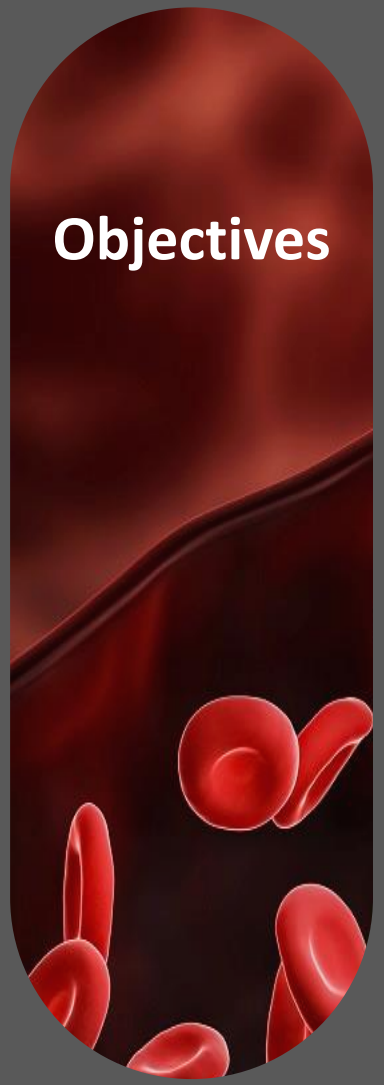
Dosing

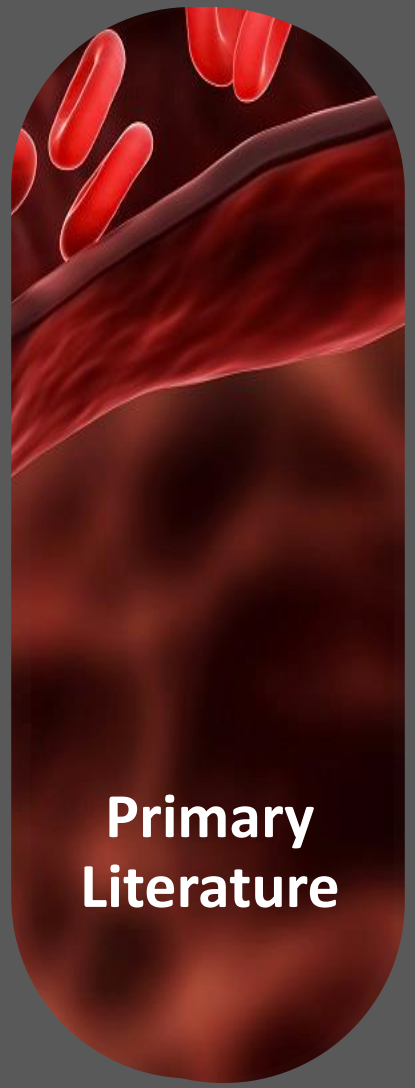
Medication	Route	Dosing	Half-life	Mechanism of Action	Considerations (for VTE)
Apixaban	PO	HITT: 10 mg BID x 1 week, then 5 mg BID Isolated HIT: 5 mg BID until platelet recovery	Hepatic/Renal (8-15 h)	Factor Xa inhibition	Avoid use in CrCl <15 mL/min
Rivaroxaban	PO	HITT: 15 mg BID x 3 weeks, then 20 mg QD Isolated HIT: 15 mg BID until platelet recovery	Renal (5-9 h)	Factor Xa inhibition	Avoid use in CrCl <15 mL/min
Dabigatran	PO	HITT: 150 mg BID after ≥ 5 days of treatment with a parental non-heparin agent Isolated HIT: 150 mg BID until platelet recovery	Renal (12-17 h)	Thrombin inhibition	Prodrug Avoid use in CrCl <30 mL/min or BMI ≥ 40 kg/m^2

Sources: Blood Adv. 2018; 2(22): 3360–3392.


Objectives


Background


Guidelines

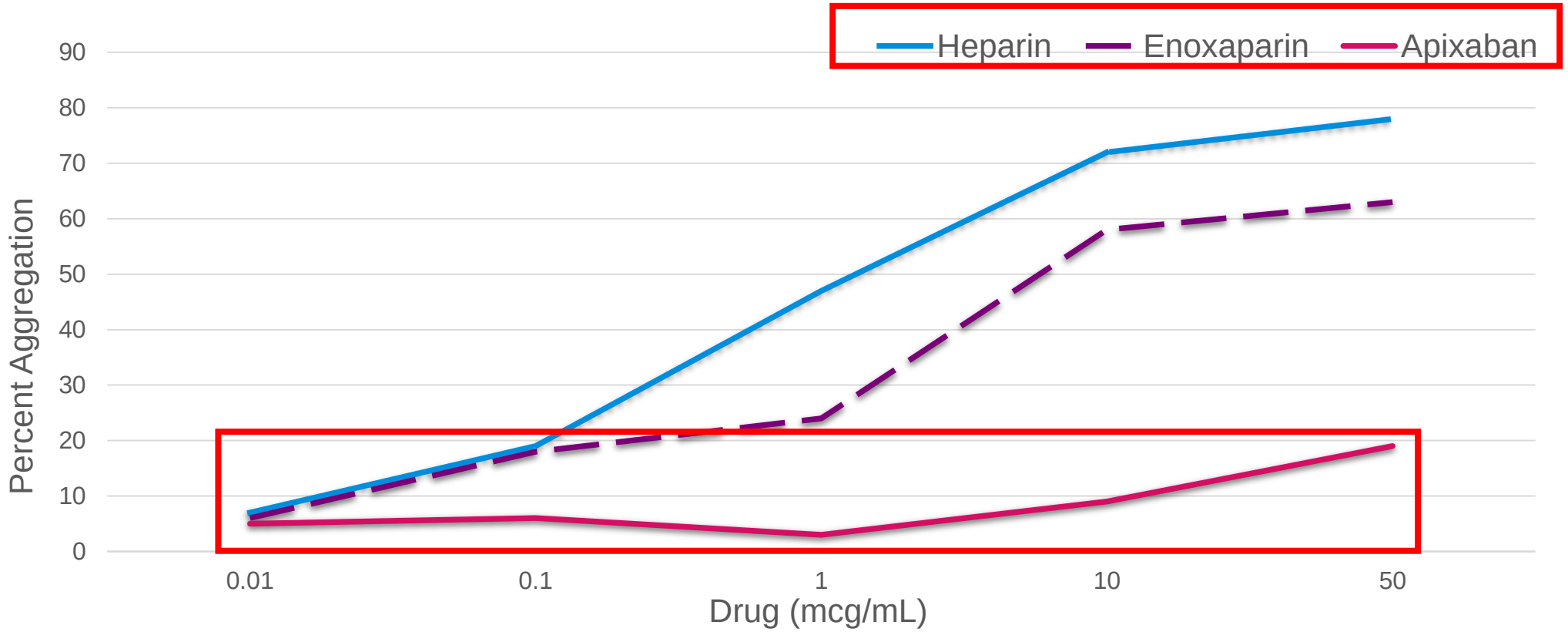

Primary
Literature

Apixaban as an Alternative for Management of HIT

- **Objective:** To assess the cross-reactivity of apixaban with HIT antibodies
- **Outcomes:** Apixaban was compared to UFH and LWMH for reactivity to HIT antibodies
- **Findings:** Apixaban was unreactive to HIT antibodies and did not lead to platelet aggregation. Thus, it is a feasible option for the management of HIT

Sources: Clin Appl Thromb Hemost. 2013;19(5):482-487.

HIT Cross-Reactivity with DOACs



Cross-reactivity of apixaban, LMWH, and heparin with HIT antibodies
<20% is negative

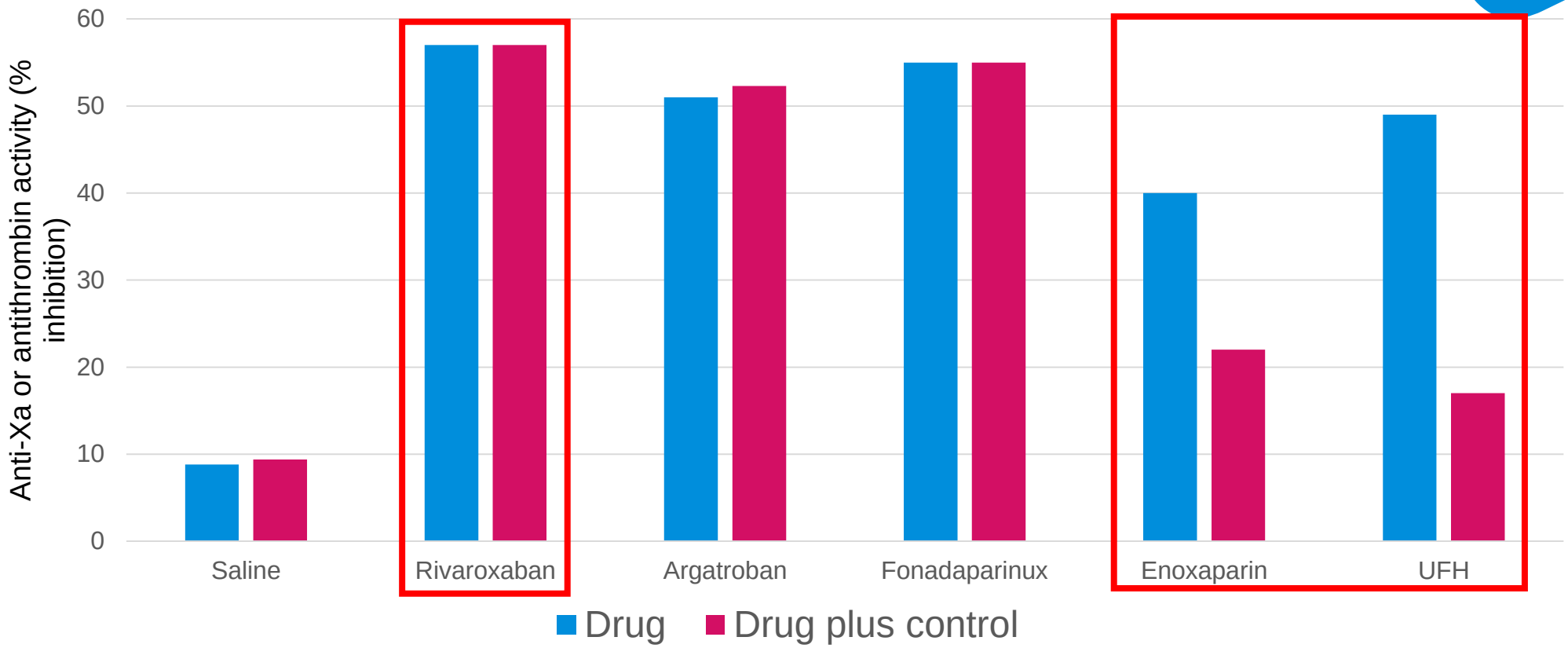
Sources: Clin Appl Thromb Hemost. 2013;19(5):482-487.

Potential of Rivaroxaban for the Management of HIT

- **Objective:** To determine if rivaroxaban interacts with PF4
- **Outcomes:** Non-heparin anticoagulants were compared to heparin and LMWH to observe their anticoagulant effects with and without the PF4 complex
- **Findings:** Rivaroxaban's anticoagulant activity was unaffected by the PF4 complex, and rivaroxaban does not increase PF4 release

Sources: *Eur J Haematol*. 2017;99:332–335.

Results



The effect of PF4 on the anticoagulant activity of rivaroxaban, fondaparinux, argatroban, LMWH and UFH

Sources: *Eur J Haematol*. 2017;99:332–335.

DOACs for Treatment of HIT: Update of Hamilton Experience and Literature Review

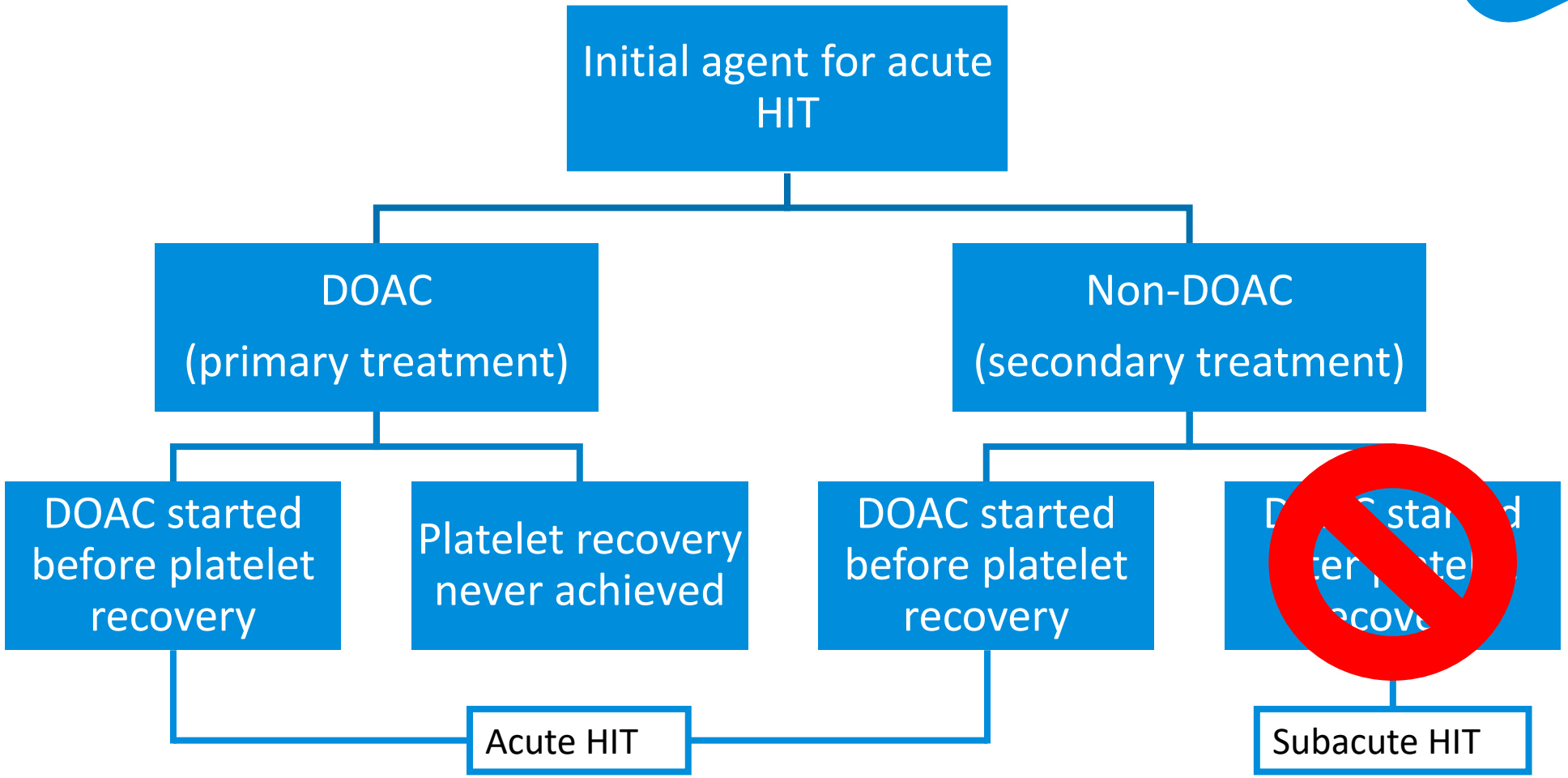
Objective: To assess the efficacy of DOACs throughout the stages of HIT

Inclusion: Positive test for HIT: (1) positive IgG–specific anti-PF4/heparin enzyme immunoassay and (2) positive SRA (≥50%), clinical picture consistent with HIT (4T score ≥ 4), and no diagnosis more compelling than HIT

Exclusion: SRA positive but immunoassay negative

Sources: *Blood*. 2017;130(9):1104-1113.

Design



Sources: *Blood*. 2017;130(9):1104-1113.

Outcomes

Primary: The 30-day incidence of new symptomatic, objectively confirmed venous and arterial thromboembolism

Secondary: Incidence of major bleeding

Sources: *Blood*. 2017;130(9):1104-1113.

Results

Drug	Primary DOAC before PLT recovery	Primary DOAC no PLT recovery	Secondary DOAC before PLT recovery	Mean Platelet Count at DOAC start	HITT, N (%)	Thrombus, N (%)	Bleeding, N (%)
Rivaroxaban (n = 46)	21	4	21	73	29 (63)	1 (2.2)	0 (0)
Apixaban/ Dabigatran (n = 11)	2	1	8	58	6 (54.5)	1 (9.1)	0 (0)

PLT = Platelet

Sources: *Blood*. 2017;130(9):1104-1113.

Summary

Strengths

- Strict inclusion of patients with confirmed HIT
- Evaluates the utilization of multiple DOACs
- Evaluates DOAC use in various stages of HIT

Weaknesses

- Small patient population
- No assessment of subacute phase

Conclusion: DOACs seem to be safe and effective for treatment of acute HIT, with the most experience reported for rivaroxaban. DOACs seemed to be effective regardless of the patient have HIT or HIT, and with or without previous treatment with a parental agent. Although this study provided promising results, further studies with more patients must be conducted.

Sources: *Blood*. 2017;130(9):1104-1113.

DOACs for the Treatment of Suspected HIT

Objective: Retrospective cohort study to evaluate the efficacy and safety of DOAC therapy in hospitalized patients with suspected HIT in the remote phase

Inclusion: Inpatient diagnosis of HIT who received apixaban, dabigatran, or rivaroxaban; an intermediate or high pretest probability for HIT (4T score ≥ 4) and a positive IgG-specific anti-PF4/heparin complex assay

Exclusion: Negative SRA (≤20%), previous history of HIT prior to admission, admitted for less than 48 hours

Sources: Eur J Haematol. 2017;99:332–335.

Outcomes

Primary: Newly diagnosed venous or arterial thromboembolism during hospitalization

Secondary: In-hospital major bleeding (fatal bleeding, bleeding in a critical organ, transfusion of ≥2 units of packed red blood cells, reduction in hemoglobin of ≥2 g/dL)

Sources: Eur J Haematol. 2017;99:332–335.

Results

Drug	Median Hours on Argatroban	Days on DOAC Prior to Discharge	HITT, N (%)	Bleeding, N (%)	Recurrent Thrombosis, N (%)
Apixaban 2.5 mg BID n = 1	206.5	2	0 (0)	0 (0)	0 (0)
Apixaban 5 mg BID n = 7	105.8	6.8	3 (43)	0 (0)	0 (0)
Apixaban 10 mg BID n = 1	0	2	0 (0)	0 (0)	0 (0)
Rivaroxaban 15 mg BID n = 3	249	20	2 (67)	0 (0)	0 (0)

Sources: Eur J Haematol. 2017;99:332–335.

Summary

Strengths

- Only includes confirmed HIT patients
- Assessed multiple DOACs
- Compares multiple dosing strategies

Weaknesses

- Low enrollment
- Only assessed outcome occurrence during admission
- No assessment of long-term outcomes

Conclusion: In the management of acute HIT, with or without confirmed thrombosis prior to initiating a DOAC, treatment with DOAC therapy was not associated with in-hospital thrombotic or hemorrhagic events. None of the patients experienced an outcome during hospitalization. Platelet recovery was achieved in all patients during hospitalization.

Sources: Eur J Haematol. 2017;99:332–335.

Rivaroxaban and Apixaban for the Treatment of Suspected or Confirmed HIT

Objective: Retrospective analysis to evaluate the prescribing patterns of rivaroxaban and apixaban for the treatment of suspected or confirmed HIT

Inclusion: 18 years or older, have a clinical suspicion or confirmed HIT based upon PF4 testing, and initiated on a DOAC

Exclusion: Patients with a negative PF4 (OD <0.4) or a negative SRA (≤20%)

Sources: J Clin Pharm Ther. 2022;47:112–118.

Outcomes

Primary: Recurrent thrombosis after DOAC initiation

Secondary: Mean platelet count at DOAC initiation and at discharge

Sources: J Clin Pharm Ther. 2022;47:112–118.

Results

Drug	Median Days on Argatroban	Mean Platelet Count at DOAC Initiation ($\times 10^9$/L)	Mean Platelet Count at Discharge ($\times 10^9$/L)	Confirmed HIT, N (%)	Recurrent Thrombosis N (%)
Apixaban 5 mg BID n = 4	8.3	182	222	2 (50)	0 (0)
Apixaban 10 mg BID x 7 days, followed by 5 mg BID n = 1	4	200	200	1 (100)	0 (0)
Rivaroxaban 15 mg BID x 21 days, followed by 20 mg QDay n = 5	8	262	366	3 (60)	0 (0)
Rivaroxaban 20 mg QDay n = 2	2.5	120	125	0 (0)	0 (0)

Sources: J Clin Pharm Ther. 2022;47:112–118.

Summary

Strengths

- Provides data on dosing of DOACs
- Multiple dosing strategies
- Follow-up phase

Weaknesses

- Missing data on multiple HIT diagnostic tests
  - Specifically 4T score and SRA confirmation
- Low enrollment

Conclusion: Rivaroxaban and apixaban were successfully used in patients with suspected HIT, including four with confirmed HIT and two confirmed with HITT. Eight patients (unclear which regimen) followed up at 6 months, no new thrombi were reported. This study provided more literature to assist with proper dosing of DOACs in HIT. This study, as with previous studies, had a miniscule patient population.

Sources: J Clin Pharm Ther. 2022;47:112–118.

Assessment Question #3

BC is a 50-year-old black male that has been diagnosed with acute isolated HIT. His most recent platelet count is 101×10^9/L. PMH includes hypertension and atrial fibrillation. What is the most appropriate dosing strategy for Rivaroxaban in this patient?

A. Rivaroxaban 15 mg twice daily until platelet count reaches $\geq 150 \times 10^9$/L, then switch to 20 mg daily
B. Rivaroxaban 15 mg twice daily until platelet count reaches $\geq 150 \times 10^9$/L, then discontinue anticoagulation
C. Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg daily
D. Rivaroxaban is not indicated in this patient. A parental anticoagulant should be utilized.

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D. Rivaroxaban is not indicated in this patient. A parental anticoagulant should be utilized.

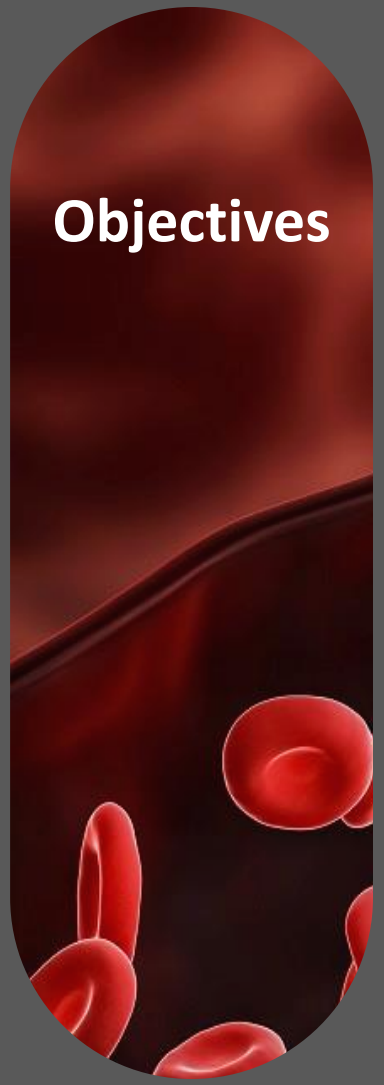
DOAC Treatment Summary

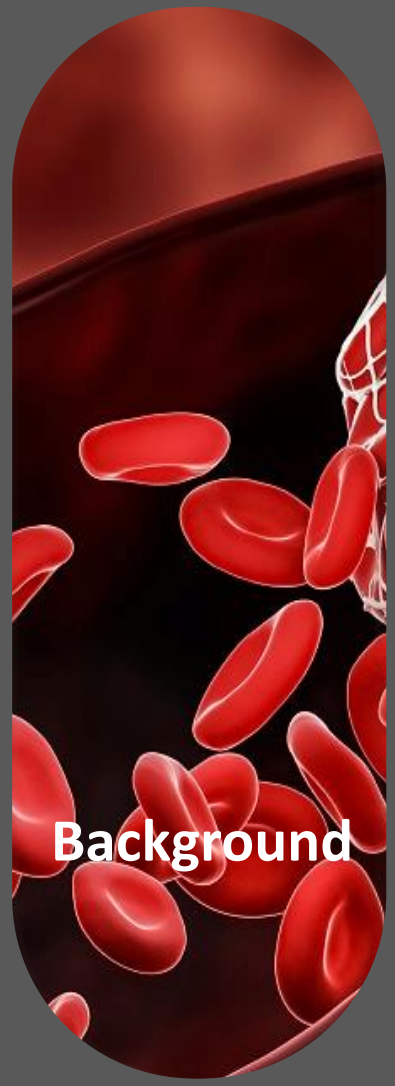
Acute Phase: complicated by thrombosis (HITT) or acute HIT without thrombosis (isolated HIT)

- With respect to the choice of DOAC, the most published literature involves rivaroxaban
  - Acute HITT: Rivaroxaban 15 mg twice per day for 3 weeks followed by 20 mg daily
  - Acute isolated HIT: Rivaroxaban 15 mg twice daily until platelet recovery, followed by 20 mg daily (if there is an indication for anticoagulation).

- In patients with subacute HIT A, the ASH guideline panel suggests treatment with a DOAC rather than a VKA.

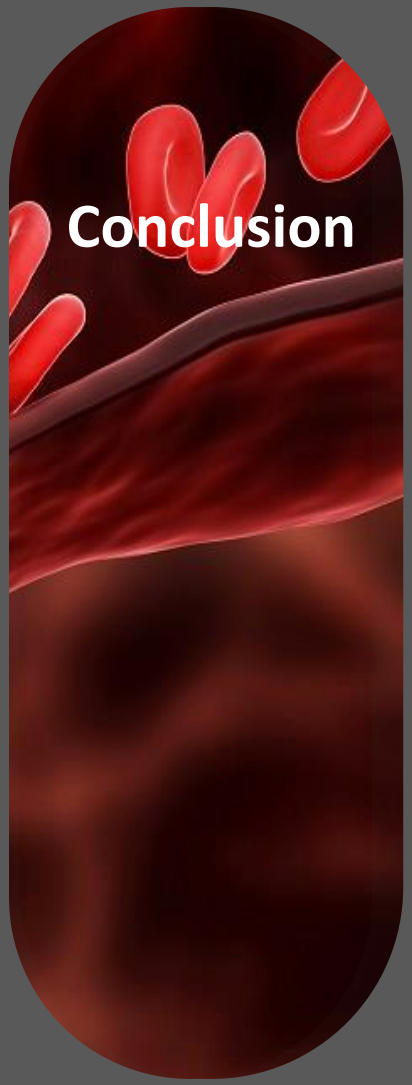
Blood Adv. 2018; 2(22): 3360–3392.


Objectives


Background

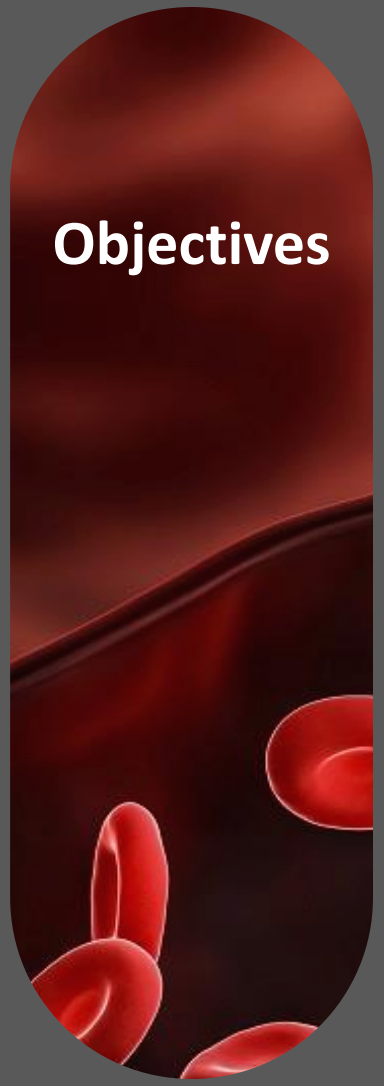

Guidelines


Primary
Literature


Conclusion

Conclusion

- Guideline updates now recommende the utilization of DOACs for the management of HIT as they have low cross-reactivity, decrease hospital length of stay, and have increasing literature supporting their efficacy
- Primary literature on this topic is still scarce. Rivaroxaban is currently the recommended DOAC
- Scenarios in which DOACs may not be optimal include life- or limb-threatening thrombus and end-stage kidney disease
- Warfarin is still the primary agent in certain situations such as mechanical heart valves, antiphospholipid syndrome, and increased risk of gastrointestinal bleeding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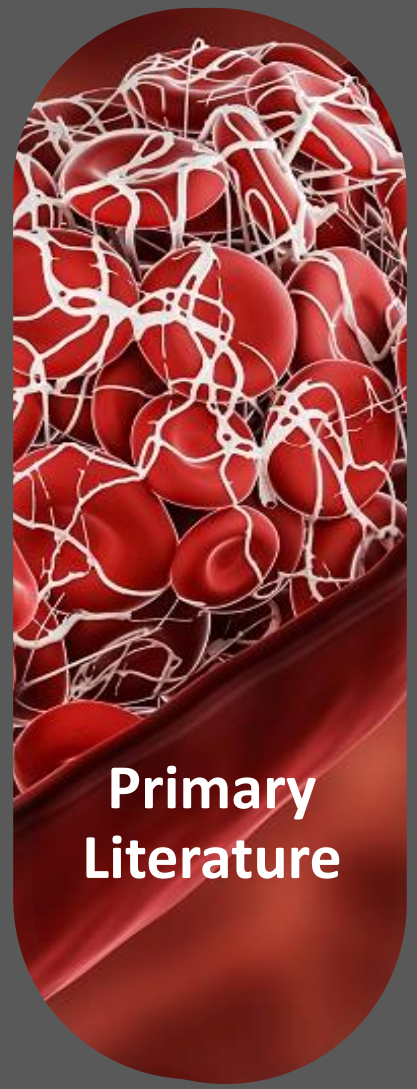
Primary
Literature


Conclusion


Application

Application to the Role of a Pharmacist

- Pharmacists are the medication experts and primary educators in most healthcare facilities
- Many physicians still view warfarin as a primary oral option, despite the complicated monitoring, drug-drug interactions, and diet changes required
- It’s crucial that pharmacists provide evidence-based recommendations and encourage the utilization of DOACs when deemed appropriate
- Order sets for HIT should include DOACs as a viable option and be pharmacy-driven

Abbreviations Guide

- ASH: American Society of Hematology
- BMI: Body mass index
- CrCl: Creatinine clearance
- DOAC: Direct-Acting Oral Anticoagulant
- DVT: Deep vein thrombosis
- ELISA: Enzyme-linked immunosorbent assay
- HIPA: Heparin-induced platelet activation
- HIT: Heparin-induced thrombocytopenia
- HITT: HIT with thrombosis
- IgG: Immunoglobulin G
- INR: International normalized ratio
- IV: Intravenous
- LMWH: Low molecular weight heparin
- OD: Optical density
- PE: Pulmonary embolism
- PF4: Platelet factor 4
- PLT: Platelet
- PMH: Past medical history
- PO: By mouth
- SRA: Serotonin release assay
- UFH: Unfractionated heparin
- VKA: Vitamin K antagonist

References

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Thank you!

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