



DOAC Utilization For Heparin-Induced Thrombocytopenia

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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

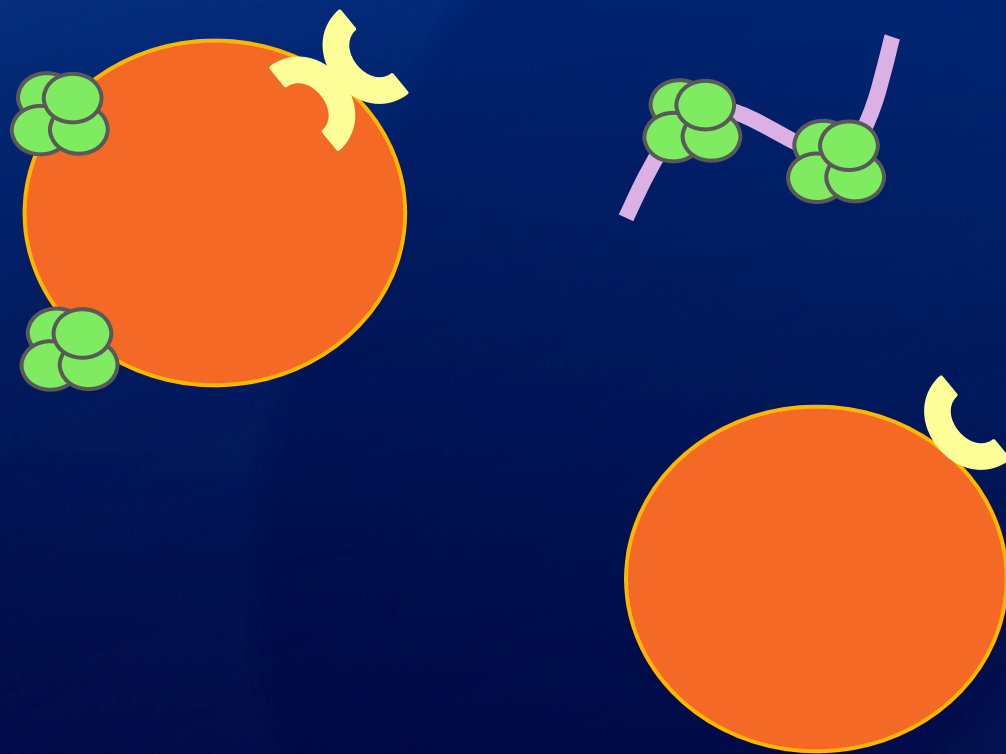
Which statement best describes your experience with HIT?

- 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

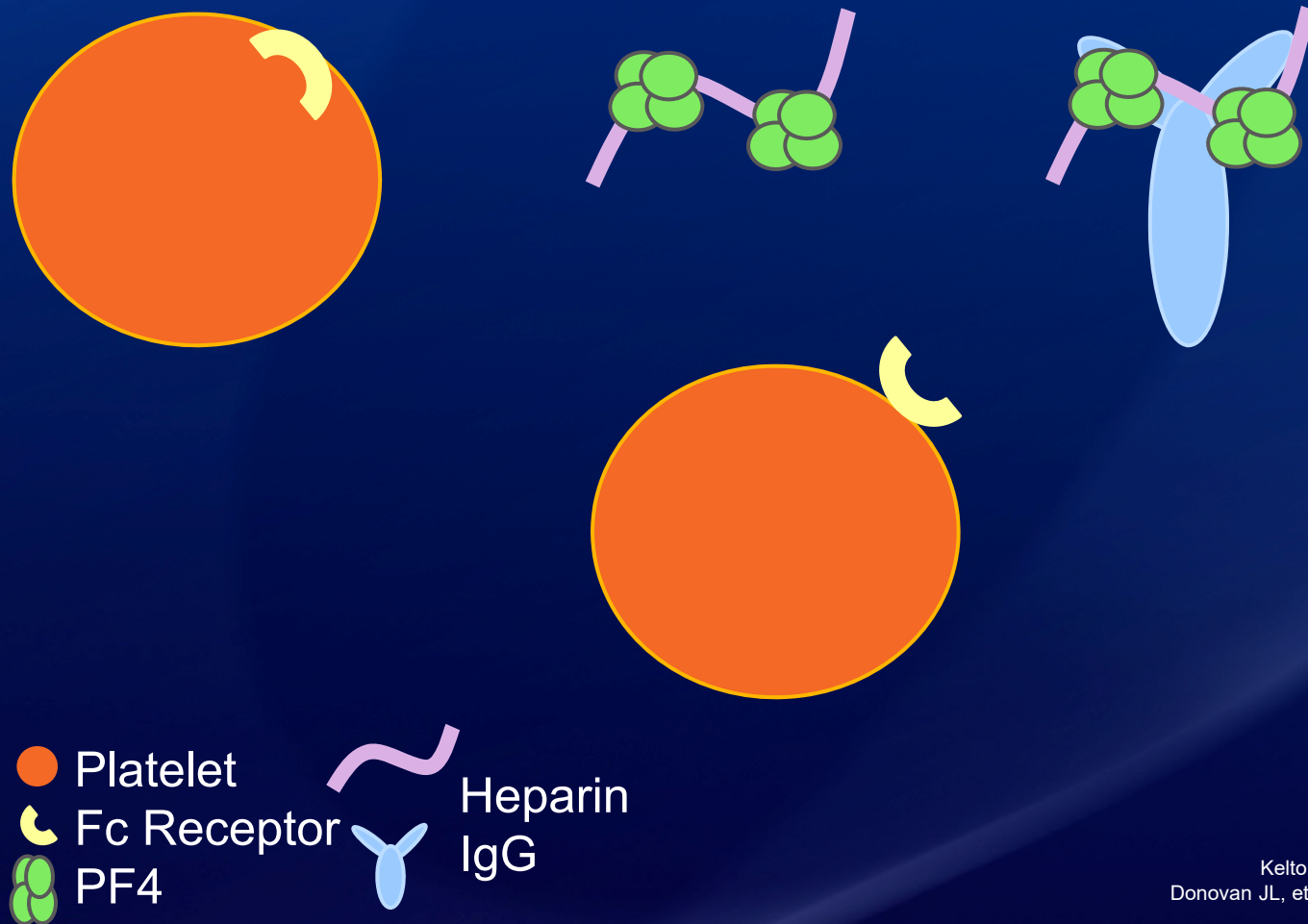
HIT Background

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

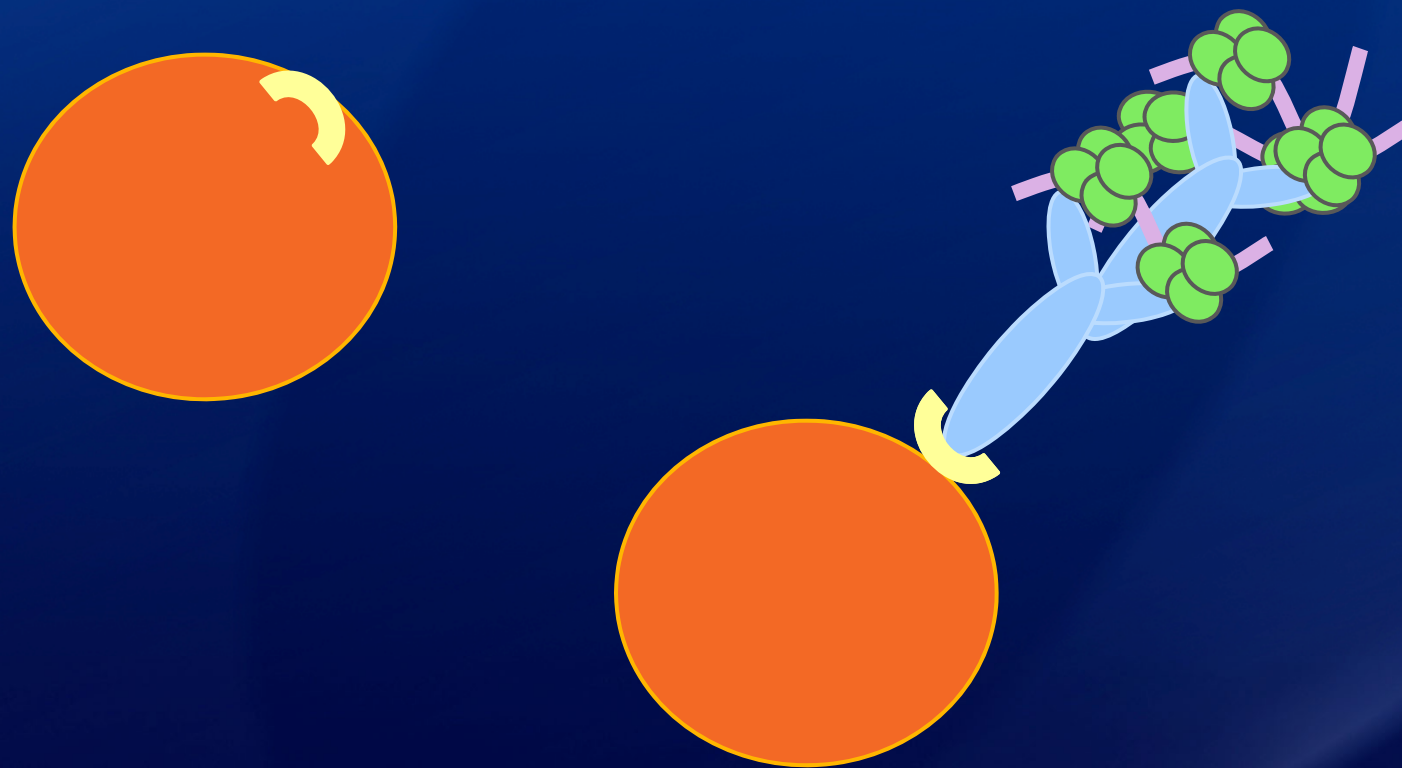
HIT Pathophysiology



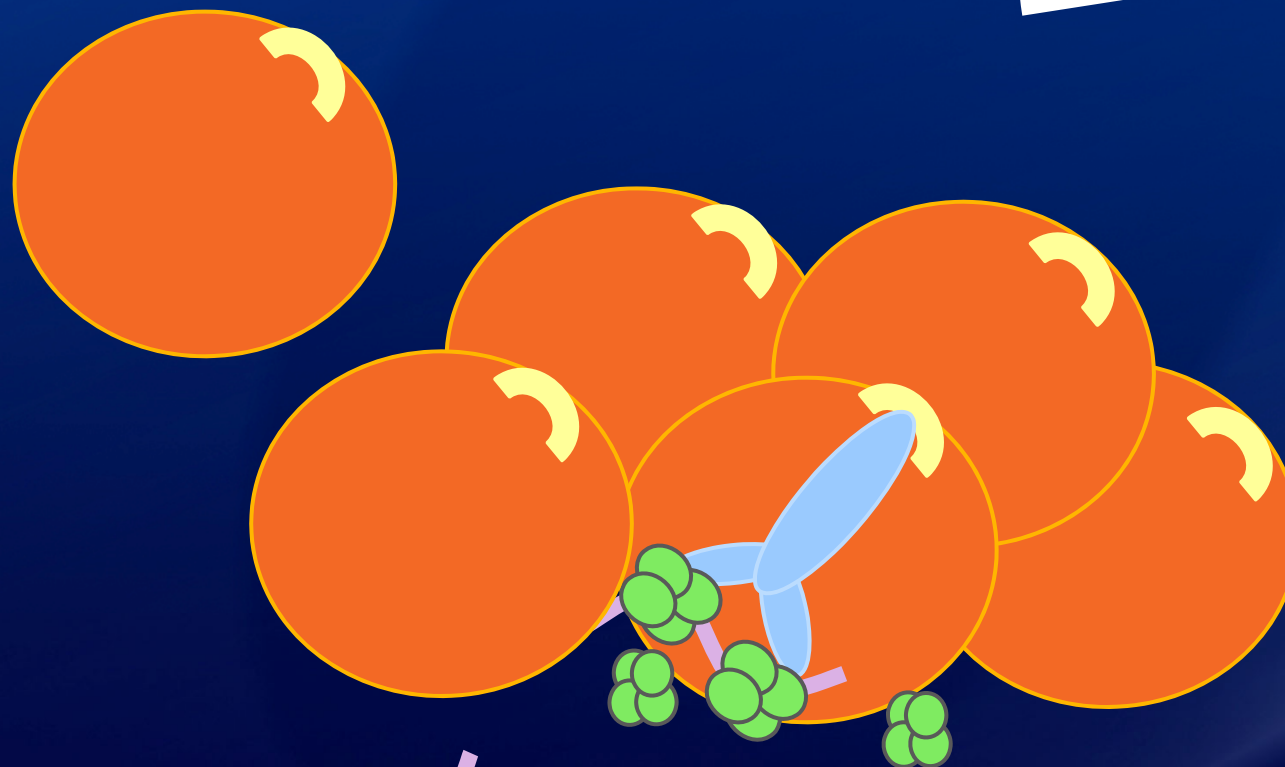
HIT Pathophysiology



HIT Pathophysiology



HIT Pathophysiology



● Platelet

☞ Fc Receptor

● PF4

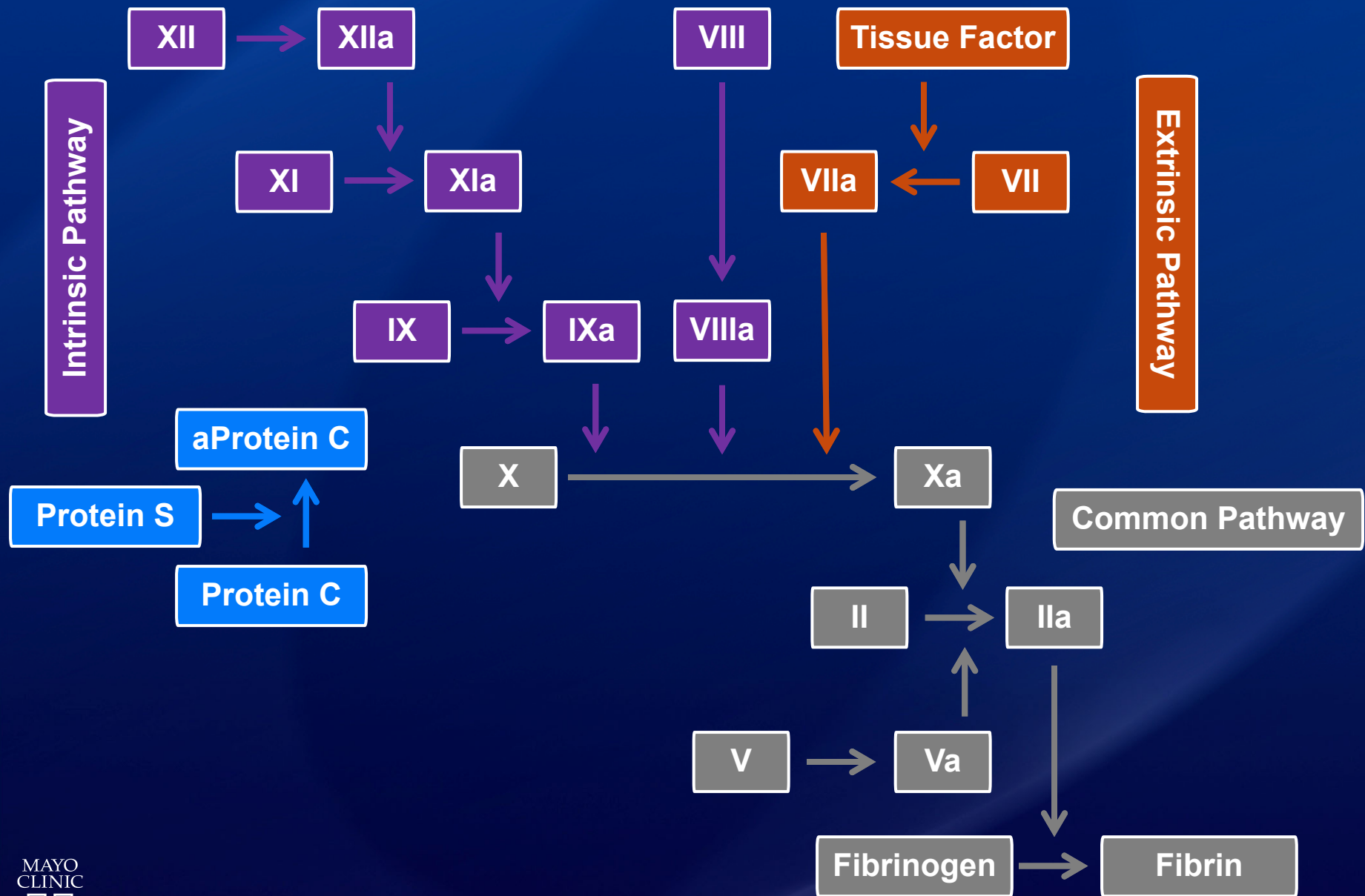


Heparin
IgG

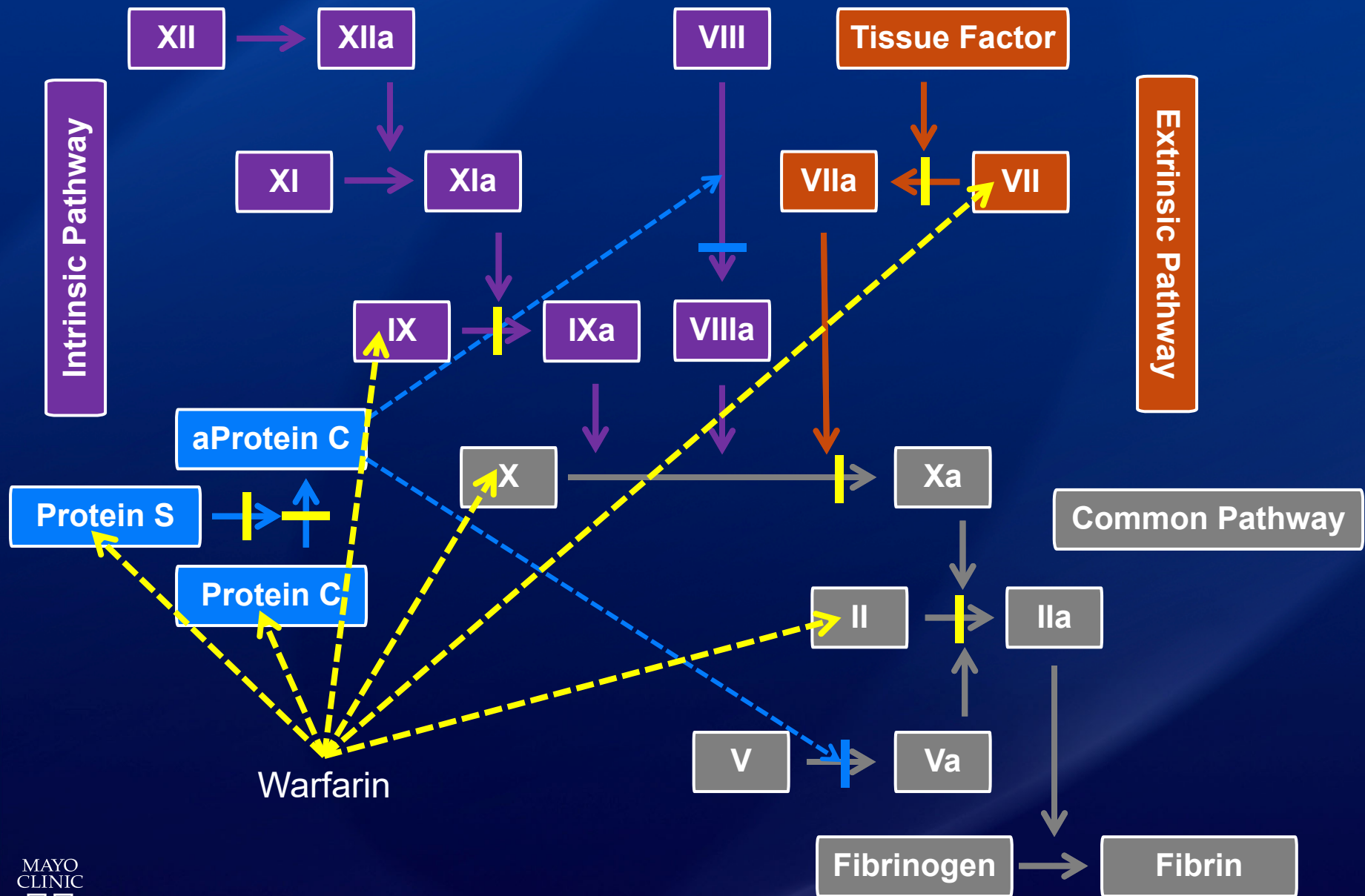


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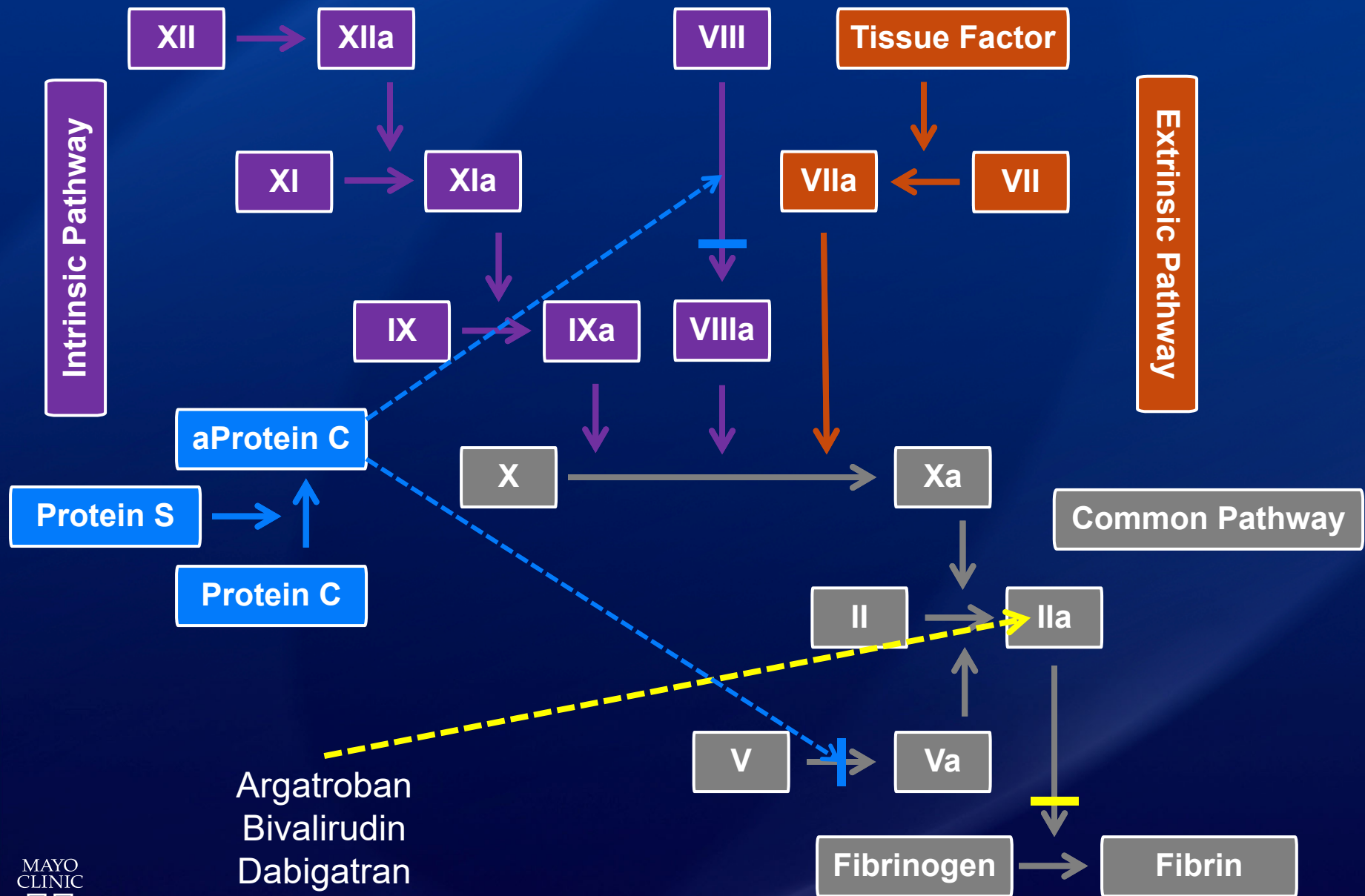
Clotting Cascade



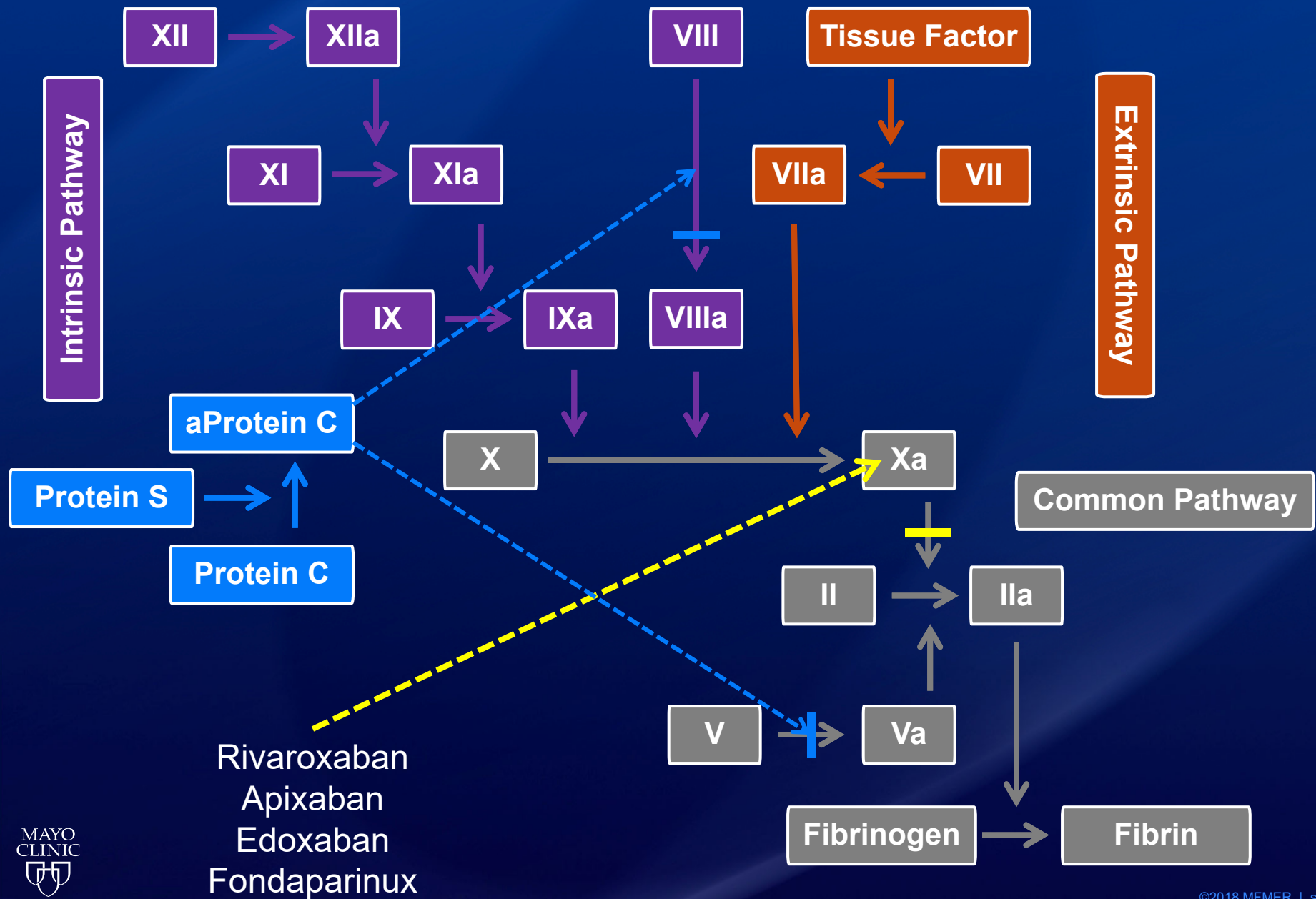
Clotting Cascade



Clotting Cascade



Clotting Cascade



HIT Diagnosis – 4T Score

Category	2 points	1 point	0 points
Thrombocytopenia	>50% decrease & nadir $\geq 20 \times 10^9/L$	30-50% decrease or nadir $10-19 \times 10^9/L$	<30% decrease or nadir $< 10 \times 10^9/L$

HIT Diagnosis – 4T Score

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Timing of the decrease in platelet count	Days 5-10 or after day 1 with recent heparin exposure	After day 10, timing unclear, or before day 1 with recent heparin exposure	Before day 5 without recent heparin exposure

HIT Diagnosis – 4T Score

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Timing of the decrease in platelet count	Days 5-10 or after day 1 with recent heparin exposure	After day 10, timing unclear, or before day 1 with recent heparin exposure	Before day 5 without recent heparin exposure
Thrombosis or other sequelae	Proven thrombosis, skin necrosis, or acute systemic reaction after heparin bolus	Progressive, recurrent, or silent thrombosis or erythematous skin lesions	None

HIT Diagnosis – 4T Score

Category	2 points	1 point	0 points
Thrombocytopenia	>50% decrease & nadir $\geq 20 \times 10^9/L$	30-50% decrease or nadir $10-19 \times 10^9/L$	<30% decrease or nadir $< 10 \times 10^9/L$
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Thrombosis or other sequelae	Proven thrombosis, skin necrosis, or acute systemic reaction after heparin bolus	Progressive, recurrent, or silent thrombosis or erythematous skin lesions	None
Other causes of thrombocytopenia	None evident	Possible	Definite

HIT Diagnosis – 4T Score

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Thrombocytopenia	>50% decrease & nadir $\geq 20 \times 10^9/L$	30-50% decrease or nadir $10-19 \times 10^9/L$	<30% decrease or nadir $< 10 \times 10^9/L$
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Thrombosis or other sequelae	Proven thrombosis, skin necrosis, or acute systemic reaction after heparin bolus	Progressive, recurrent, or silent thrombosis or erythematous skin lesions	None
Other causes of thrombocytopenia	None evident	Possible	Definite
0-3 = low risk (<1%) 4-5 = intermediate risk (~10%) 6-8 = high risk (~50%)			

HIT Management

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



DTI = Direct Thrombin Inhibitor
aPTT = Activated Partial Thromboplastin Time

McBane RD, et al. *AskMayoExpert*. Reviewed 2018 Jul 26. Accessed 2019 May 25.

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HIT Management

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



DTI = Direct Thrombin Inhibitor
aPTT = Activated Partial Thromboplastin Time

McBane RD, et al. *AskMayoExpert*. Reviewed 2018 Jul 26. Accessed 2019 May 25.

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HIT Management

	Argatroban	Bivalirudin	Fondaparinux
Class	DTI	DTI	Factor Xa Inhibitor
Approved for HIT?	Yes	No	No
Initial dose and monitoring goal (standard intensity)	1 mcg/kg/min IV infusion; goal aPTT 1.5-2.5x baseline	0.15 mg/kg/hr IV infusion; goal aPTT 1.5-2.5x baseline	7.5 mg SQ daily
Initial dose and monitoring goal (high intensity)	1.25 mcg/kg/min IV infusion; goal aPTT 2-3x baseline	N/A	N/A
Elimination Half-life	39-51 minutes	25 minutes	17-21 hours
Dose adjustments	Liver dysfunction	Renal dysfunction	Renal dysfunction; body weight

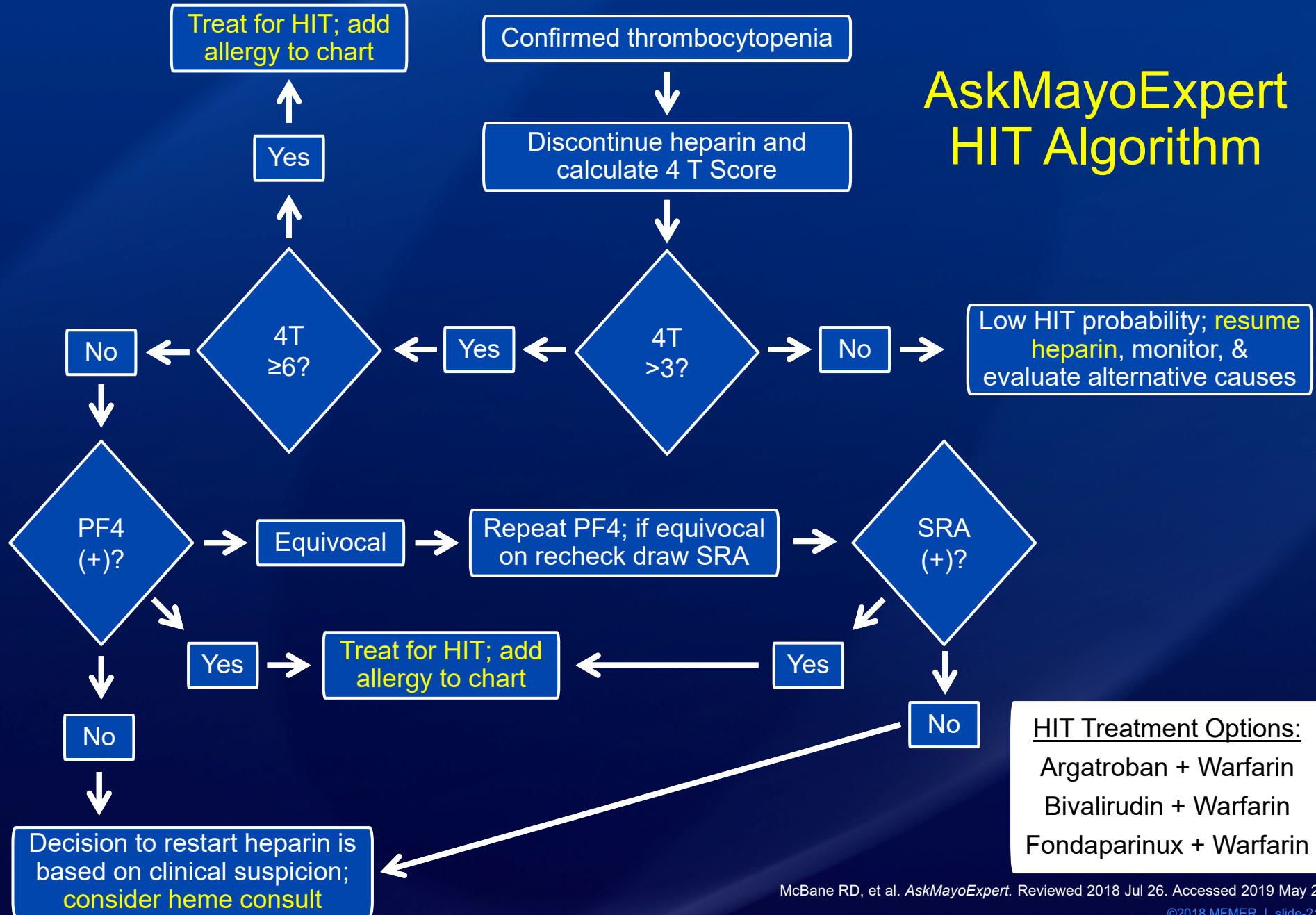


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McBane RD, et al. *AskMayoExpert*. Reviewed 2018 Jul 26. Accessed 2019 May 25.

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AskMayoExpert HIT Algorithm



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 illicit 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: $180 \times 10^9/L$

WBC: $9.4 \times 10^9/L$

POD#6 CBC:

HGB: 10.1 g/dL

HCT: 33.4%

PLT: $30 \times 10^9/L$

WBC: $13.2 \times 10^9/L$

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

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

Patient	HIT-related thrombosis	PLT at study entry	Treatment prior to study entry	Days to PLT recovery	Study events
85 M	None	40	None	4	None
79 M	None	57	None	15	None
80 M	Leg DVT; bilateral leg arterial thrombus	54	Danaparoid 1 day	4	Acute-on-chronic leg ischemic; BKA on D18
71 F	Leg DVT; adrenal thrombosis	300	None	Normal at entry	None
87 M	PE	111	Fondaparinux 3 days	2	None
61 M	Arm catheter DVT	28	Fondaparinux 2 days	29	Extension of arm apheresis catheter DVT; improved with catheter removal
82 F	Adrenal thrombosis	164	None	Normal at entry	None
74 F	No	81	Fondaparinux 2 days	7	None
85 F	Arm DVT; leg DVT; PE	26	Fondaparinux 2 days	8	None
60 M	No	21	Fondaparinux 2 days	N/A	Elevated LFT on D2 rivaroxaban; switched back to fondaparinux; rectal bleeding D10, death from cancer D21
55 F	No	78	Fondaparinux 3 days	3	None
65 M	No	52	None	28	None



PLT = Platelet Count
DVT = Deep Vein Thrombosis
PE = Pulmonary Embolism

BKA = Below the Knee Amputation
D = Study Day
LFT = Liver Function Tests

Linkins LA, et al. *J Thromb Haemost.* 2016 Jun;14(6):1206-10.

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Linkins, et al. Rivaroxaban for HIT

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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

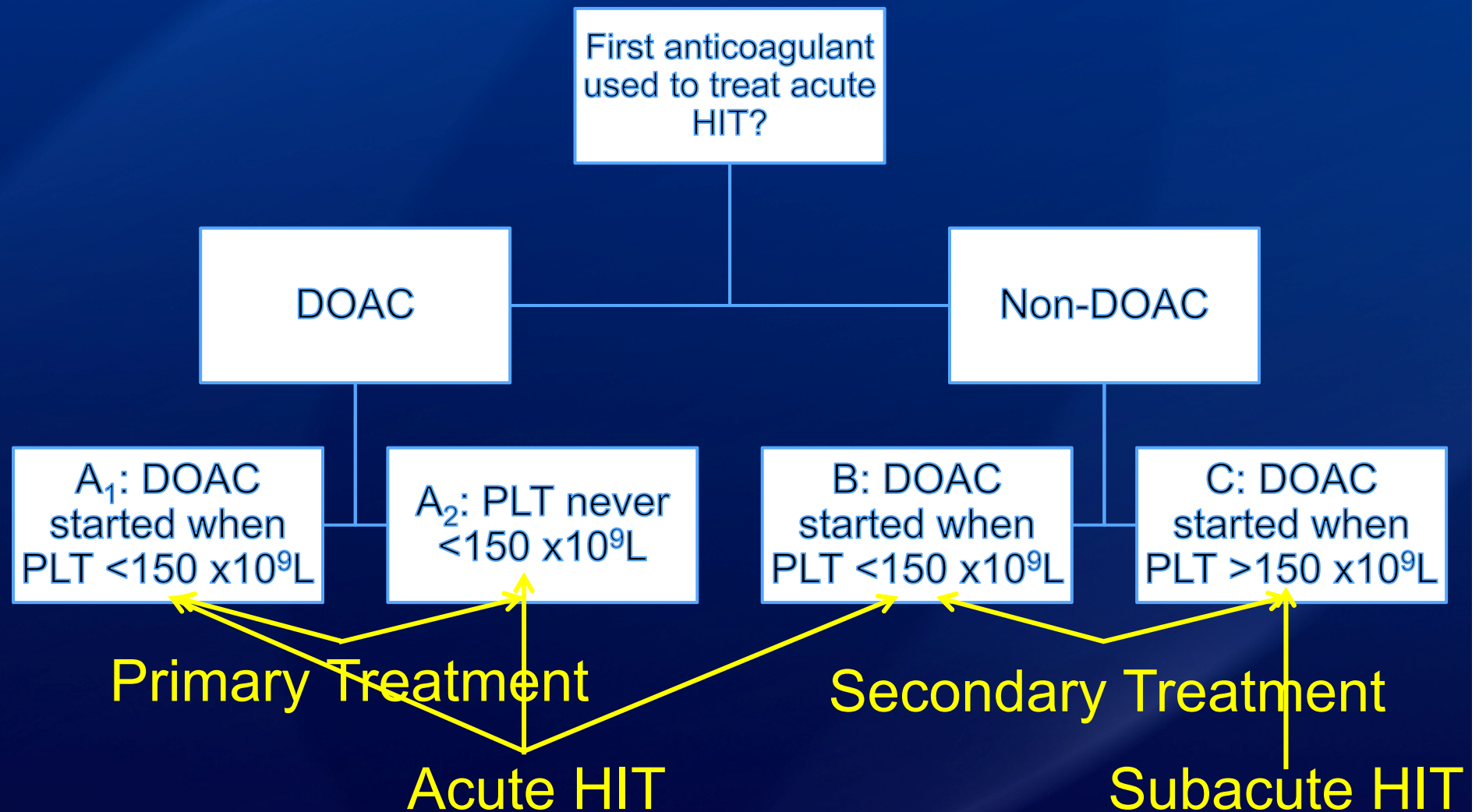
Design

- 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)

Warkentin, et al. DOACs for HIT



Warkentin, et al. DOACs for HIT

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- **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)

Warkentin, et al. DOACs for HIT

Group	Patient	HIT-related thrombosis	PLT at DOAC start	Treatment prior to study entry	Rivaroxaban dosing during first 30 days of DOAC therapy	Study events
A ₁	66 F	None	107	None	20 mg daily	None
A ₁	79 F	None	78	None	15 mg BID x3 weeks; then 20 mg daily	None
A ₁	60 F	None	25	None	15 mg BID x6 days; then 20 mg daily	None
A ₁	64 F	Upper limb DVT	35	None	15 mg BID x3 weeks; then 20 mg daily	None
A ₁	94 F	Lower limb DVT	56	None	15 mg BID x3 weeks; then 20 mg daily	None
A ₁	62 M	None	49	None	20 mg daily	None
A ₁	72 M	PE	86	None	15 mg BID x3 weeks; then 20 mg daily	None
A ₂	83 F	Adrenal thrombosis	415	None	10 mg daily	None
B	54 F	None	64	Fondaparinux 1 day	15 mg BID x3 weeks; then 20 mg daily x 3 days; then 10 mg daily	None
B	69 F	MI	73	Fondaparinux 4 days	15 mg BID x3 weeks; then 20 mg daily	None
C	55 F	None	163	Fondaparinux 5 days	10 mg daily x 17 days	None
C	78 M	DVT	203	Argatroban 3 days; Fondaparinux 51 days	20 mg daily	None
C	56 F	None	332	Fondaparinux 11 days	10 mg daily	None
C	92 F	None	159	Fondaparinux 7 days	10 mg daily	None
C	72 M	None	192	Fondaparinux 5 days	20 mg daily	None
C	74 M	None	361	Fondaparinux 10 days	15 mg BID x3 weeks; then 20 mg daily	None



PLT = Platelet Count
DVT = Deep Vein Thrombosis
PE = Pulmonary Embolism

BKA = Below the Knee Amputation
D = Study Day
LFT = Liver Function Tests

Linkins LA, et al. *J Thromb Haemost.* 2016 Jun;14(6):1206-10.

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Warkentin, et al. DOACs for HIT

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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

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

2018 ASH HIT Guidelines

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

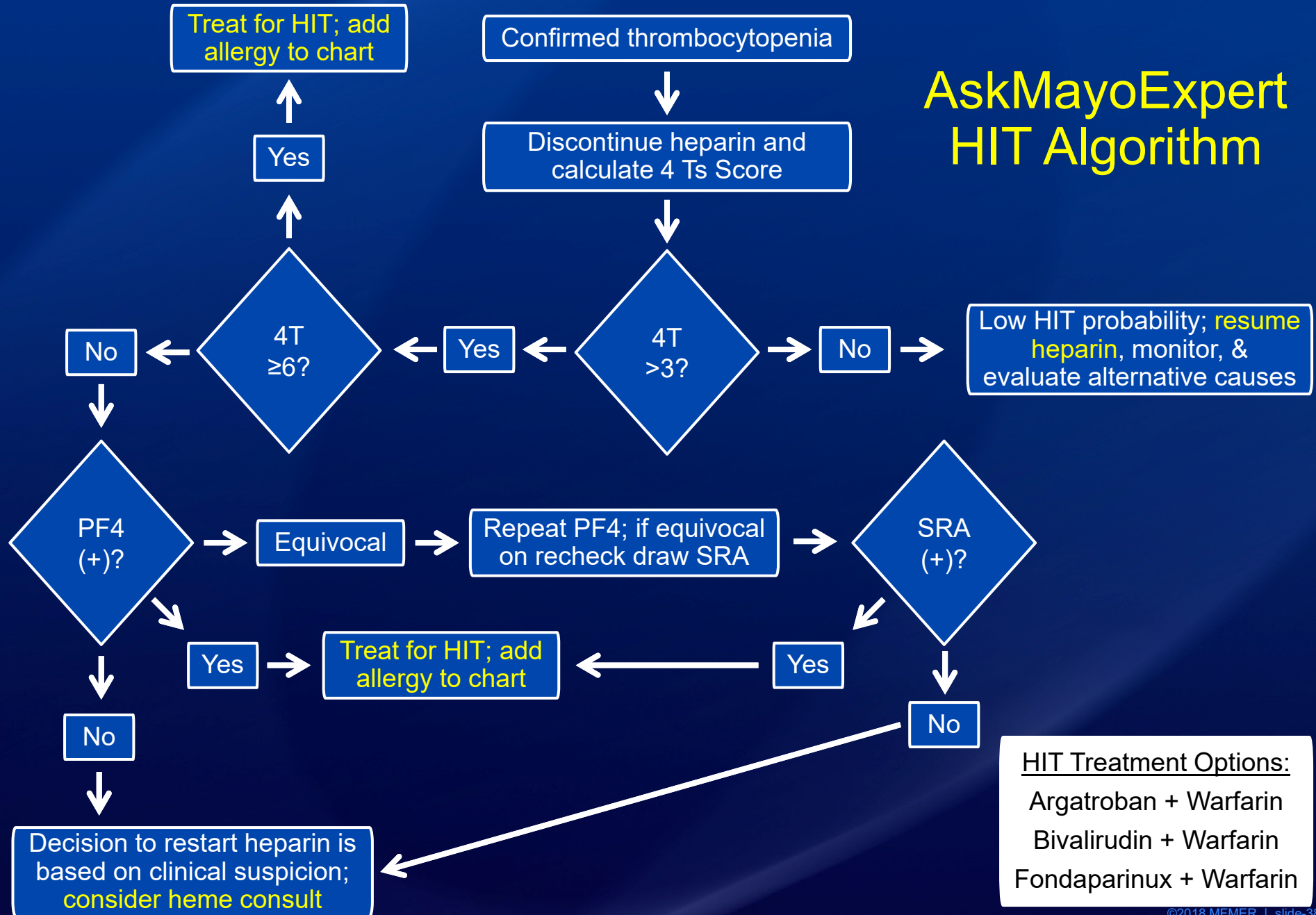
Recommendation 3.9: In patients with subacute HIT, we suggest treatment with a DOAC rather than a VKA (conditional recommendation, moderate certainty)

- 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.



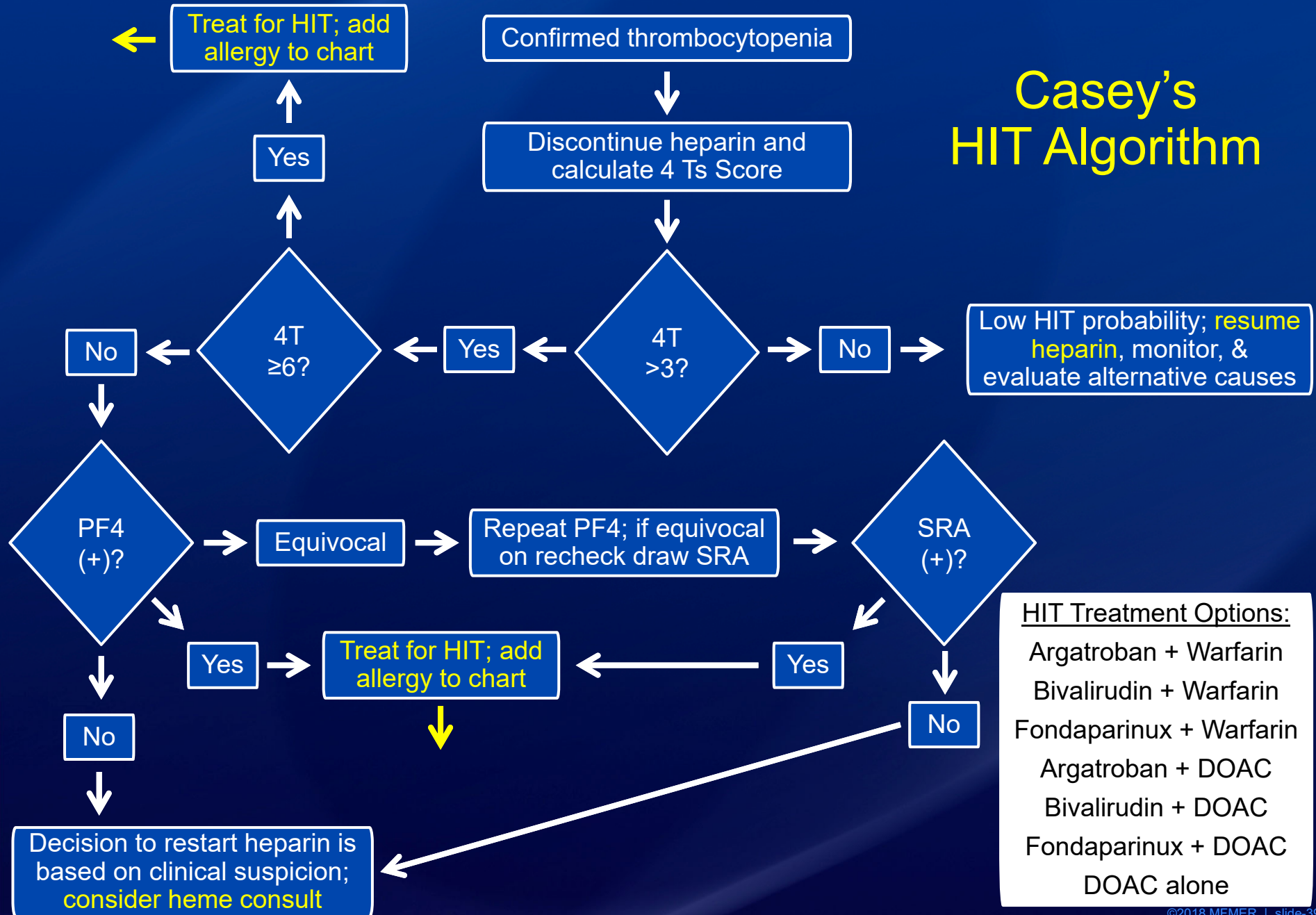
ASH = American Society of Hematology
VKA = Vitamin K Antagonist

AskMayoExpert HIT Algorithm



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

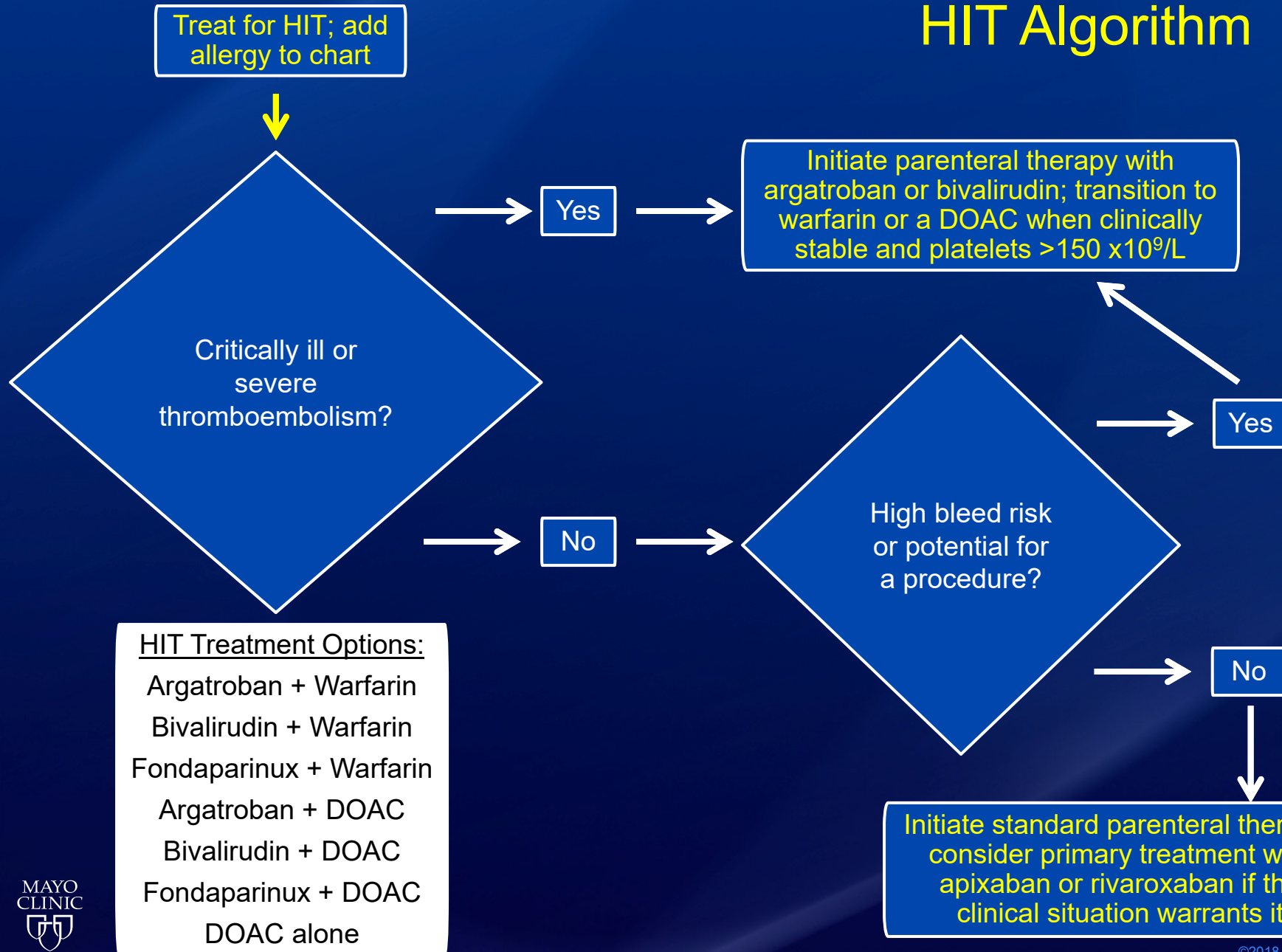
Casey's HIT Algorithm



HIT Treatment Options:

- Argatroban + Warfarin
- Bivalirudin + Warfarin
- Fondaparinux + Warfarin
- Argatroban + DOAC
- Bivalirudin + DOAC
- Fondaparinux + DOAC
- DOAC alone

Casey's HIT Algorithm



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 illicit 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
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HIT Characterization

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

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

Martel, et al. *Blood*. 2005 Oct 15;106(8):2710-5.
Warkentin TE, et al. *Blood*. 2006;108(9):2937.
Smythe MA, et al. *Chest*. 2007 Jun;131(6):1644-9.
Donovan JL, et al. *J Pharm Pract*. 2010 Jun;23(3):226-34.
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HIT Signs and Symptoms

- Platelet count 20-150 x10⁹/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

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

Variants of Type II HIT

HIT variant	Description
Delayed-onset HIT	Begins or worsens after stopping heparin
Refractory HIT	Persists for >1 week after stopping heparin
Spontaneous HIT	Occurs in the absence of recent exposure
Heparin flush HIT	Induced by exposure to heparin flushes
Fondaparinux-associated HIT	Induced by exposure to fondaparinux
Severe HIT	Associated with DIC, platelets <20,000/microL

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

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

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

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

HIT Diagnosis – 4 T Score

Category	2 points	1 point	0 points
Thrombocytopenia	>50% decrease & nadir $\geq 20 \times 10^9/L$	30-50% decrease or nadir $10-19 \times 10^9/L$	<30% decrease or nadir $< 10 \times 10^9/L$
Timing of the decrease in platelet count	Days 5-10 or after day 1 with recent heparin exposure	After day 10, timing unclear, or before day 1 with recent heparin exposure	Before day 5 without recent heparin exposure
Thrombosis or other sequelae	Proven thrombosis, skin necrosis, or acute systemic reaction after heparin bolus	Progressive, recurrent, or silent thrombosis or erythematous skin lesions	None
Other causes of thrombocytopenia	None evident	Possible	Definite
0-3 = low risk (<1%) 4-5 = intermediate risk (~10%) 6-8 = high risk (~50%)			



Rivaroxaban Indications Timeline



DVT = Deep Vein Thrombosis
PE = Pulmonary Embolism

CAD = Coronary Artery Disease
PAD = Coronary Artery Disease

Xarelto (rivaroxaban) [prescribing information]. Titusville, NJ:
Janssen Pharmaceuticals Inc; January 2019.

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My Recommended HIT Algorithm

