Advanced Anticoagulation Training

TMS Slide Set

2017

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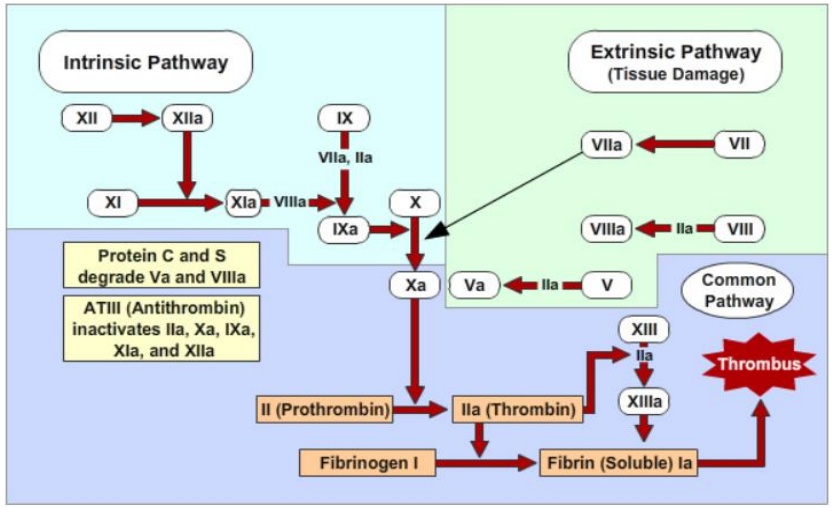
The Coagulation Cascade

The key point in examining the Coagulation Cascade is appreciating that two different pathways can lead to the formation of a fibrin clot. Both pathways, intrinsic and extrinsic, are complex and initiated by distinct mechanisms. Agents used to prevent clotting act at different sites of the Coagulation Cascade. Examine the Coagulation Cascade below, and then proceed to the next screen where you will be able to observe the sites of action for various anticoagulants.



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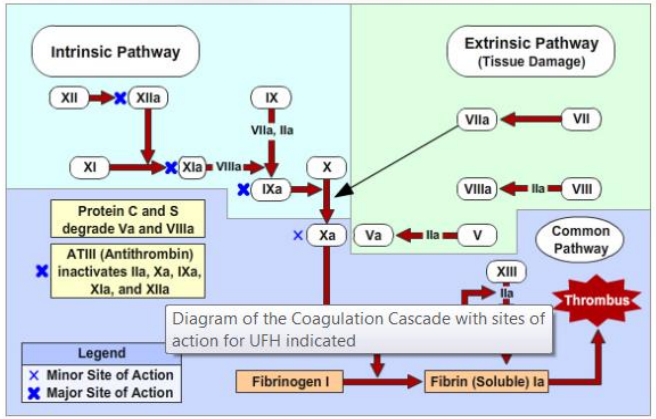
Sites of Action

Select each item on the toggle list to learn more about the pathways and sites of action for different anticoagulants in the Coagulation Cascade.

- Sites of Action: UFH
- Sites of Action: LMWH
- Sites of Action: Fondaparinux
- Sites of Action: Warfarin
- Sites of Action: TSOACs

Sites of Action: UFH

Select the image for more information about the sites of action for UFH.



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Sites of Action: UFH

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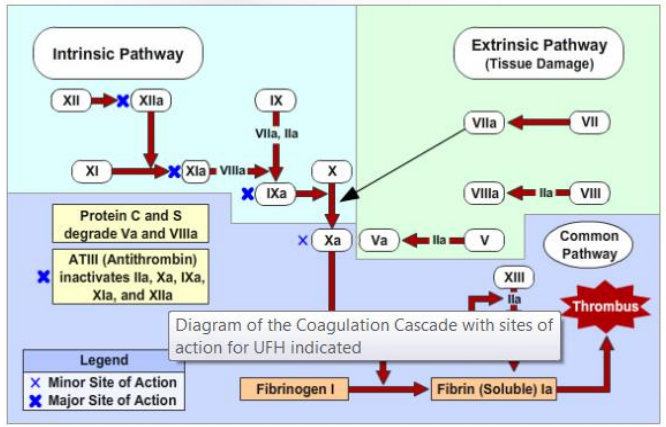

Diagram of the Coagulation Cascade with sites of action for UFH indicated

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Sites of Action

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- Sites of Action: UFH
- Sites of Action: LMWH
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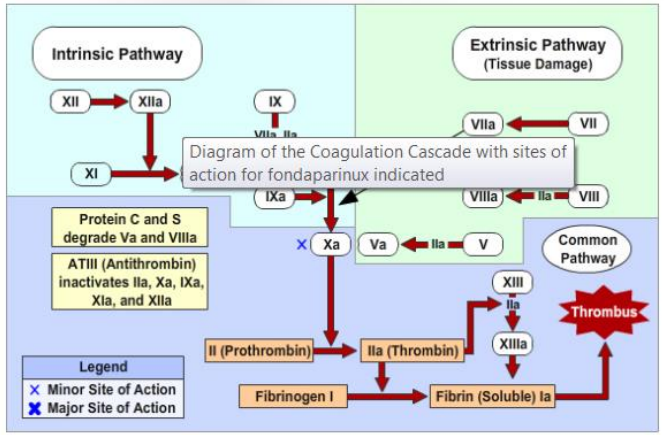
- Sites of Action: Warfarin
- Sites of Action: TSOACs

Sites of Action: Fondaparinux

Select the image for more information about the sites of action for fondaparinux.



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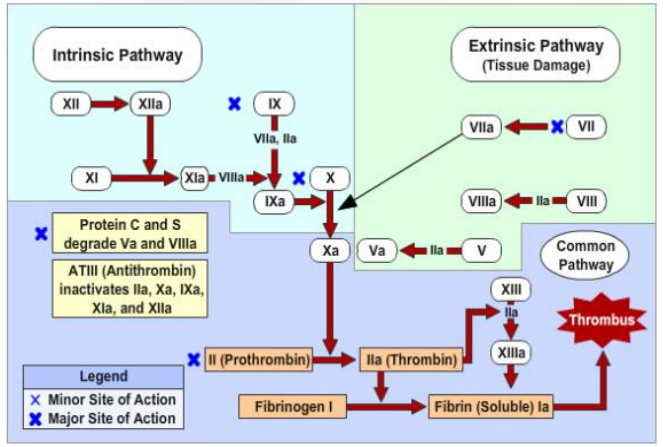
Sites of Action

Select each item on the toggle list to learn more about the pathways and sites of action for different anticoagulants in the Coagulation Cascade.

- Sites of Action: UFH
- Sites of Action: LMWH
- Sites of Action: Fondaparinux
- Sites of Action: Warfarin
- Sites of Action: TSOACs

Sites of Action: Warfarin

Remember, warfarin inhibits the vitamin K dependent clotting factors.
Select the image for more information about the sites of action for warfarin.



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Sites of Action

Select each item on the toggle l

- Sites of Action: UFH
- Sites of Action: LMWH
- Sites of Action: Fondaparin
- Sites of Action: Warfarin
- Sites of Action: TSOACs

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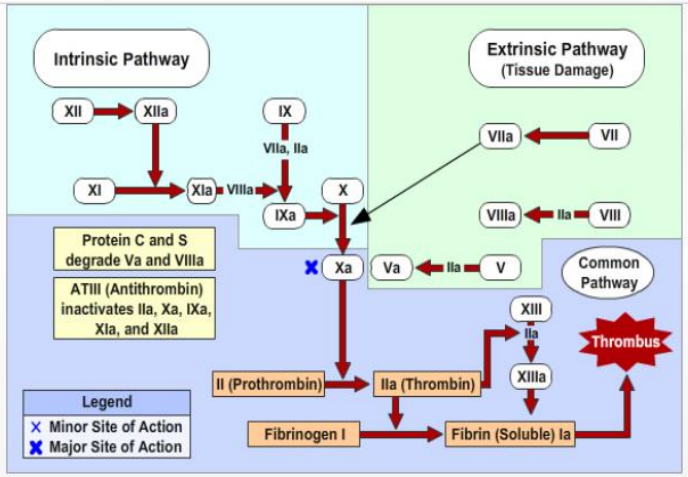
and any TSOACs
TSOAC for more

Sites of Action: Apixaban/Rivaroxaban



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- Sites of Action: UFH
- Sites of Action: LMWH
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- Sites of Action: TSOACs

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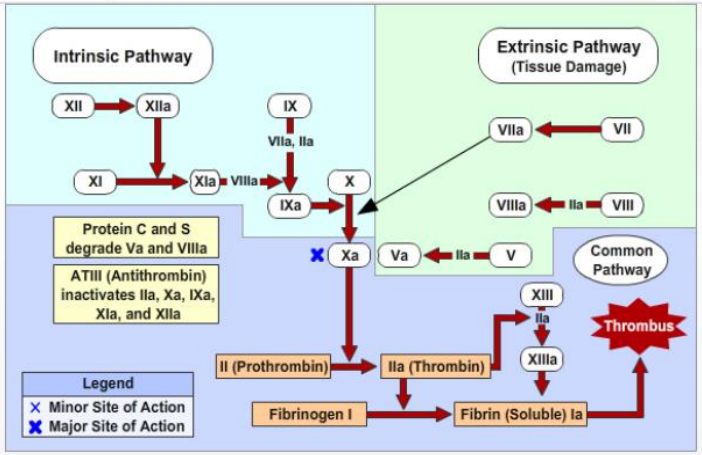
Sites of Action: Apixaban/Rivaroxaban



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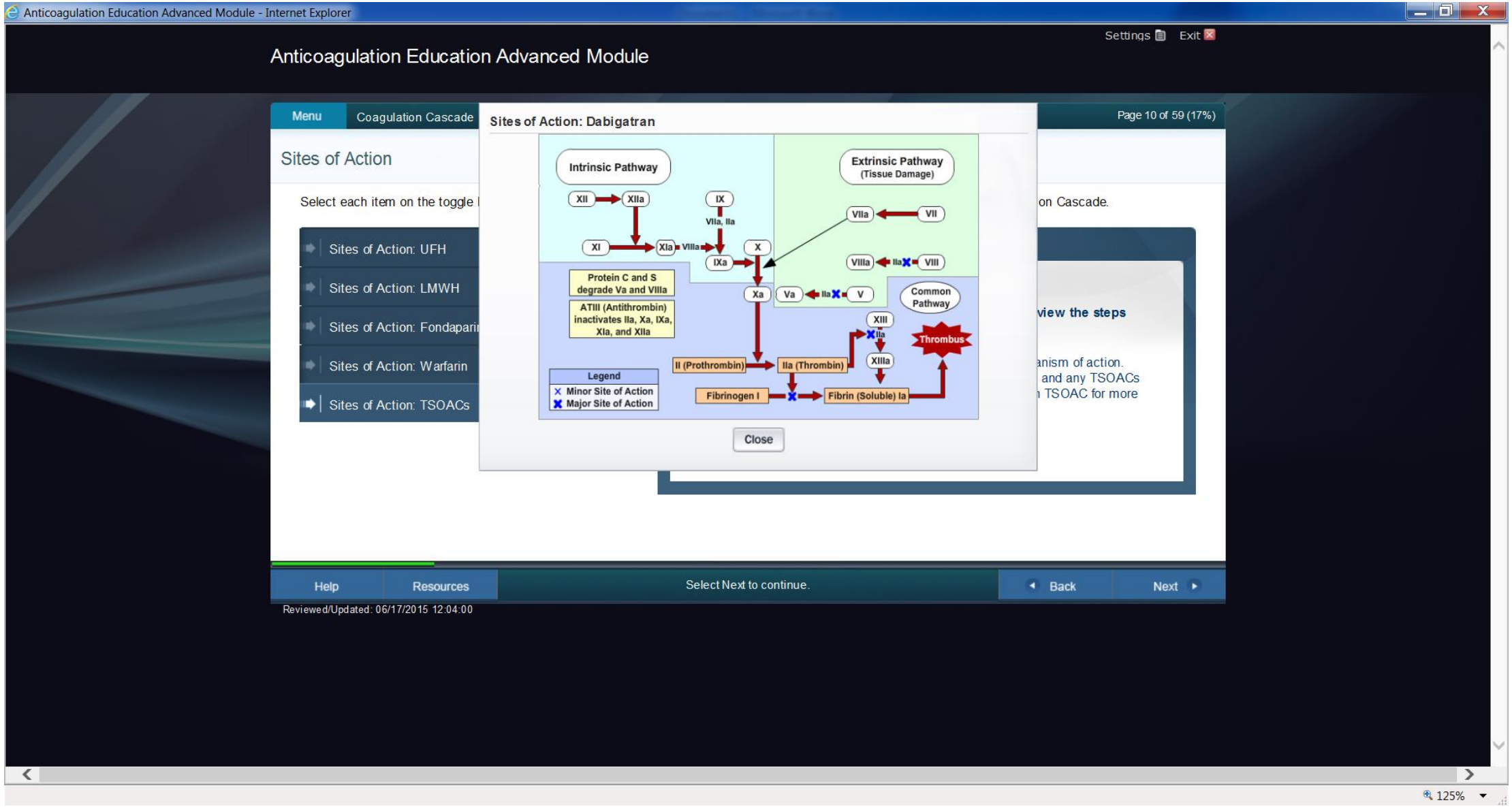
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Sites of Action: TSOACs
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and any TSOACs
TSOAC for more
Sites of Action: Dabigatran
Intrinsic Pathway
Extrinsic Pathway
(Tissue Damage)
XII
XIIa
IX
VIIa, IIa
VIIa
VII
XI
XIa
VIIIa
X
IXa
VIIIa
IIa
VIII
Protein C and S
degrade Va and VIIIa
ATIII (Antithrombin)
inactivates IIa, Xa, IXa,
XIa, and XIIa
Xa
Va
IIa
V
Common
Pathway
XIII
IIa
Thrombus
II (Prothrombin)
IIa (Thrombin)
XIIIa
Legend
Minor Site of Action
Major Site of Action
Fibrinogen I
Fibrin (Soluble) Ia
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Injectable Anticoagulants

The following are the anticoagulants available as injectables.

- Heparin (unfractionated heparin or sometimes referred to as UFH)

Low Molecular Weight Heparin (LMWH)

- Enoxaparin (Lovenox)
- Dalteparin (Fragmin)
- Tinzaparin (Innohep)

Factor Xa Inhibitors:

- Fondaparinux (Arixtra)

Direct Thrombin Inhibitors:

- Argatroban (Acova)
- Bivalirubin (Angiomax)

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UFH, LMWH, Fondaparinux: Dosing Considerations

	UFH	LMWH	Fondaparinux
Plasma ½ life (Dose Dependent)	0.5 – 3 hours	3 – 6 hours	17 – 21 hours
Clearance	Renal and Hepatic	Renal (dose needs to be adjusted when CrCl < 30)	Renal (contraindicated when CrCl < 30)
Onset of action	1 – 2 hours (peak 3 hours)	3 – 5 hours (peak 3.5 hours)	2 – 3 hours (peak 3 hours)
Route	subcutaneous, continuous IV infusion, intermittent IV	subcutaneous; IV (ACS loading dose only)	subcutaneous
Neutralized with IV protamine	Yes	Not completely	No

Check the manufacturer's full prescribing information, the Pharmacy Benefits Management website, and/or local VA pharmacy for current information and additional updates.

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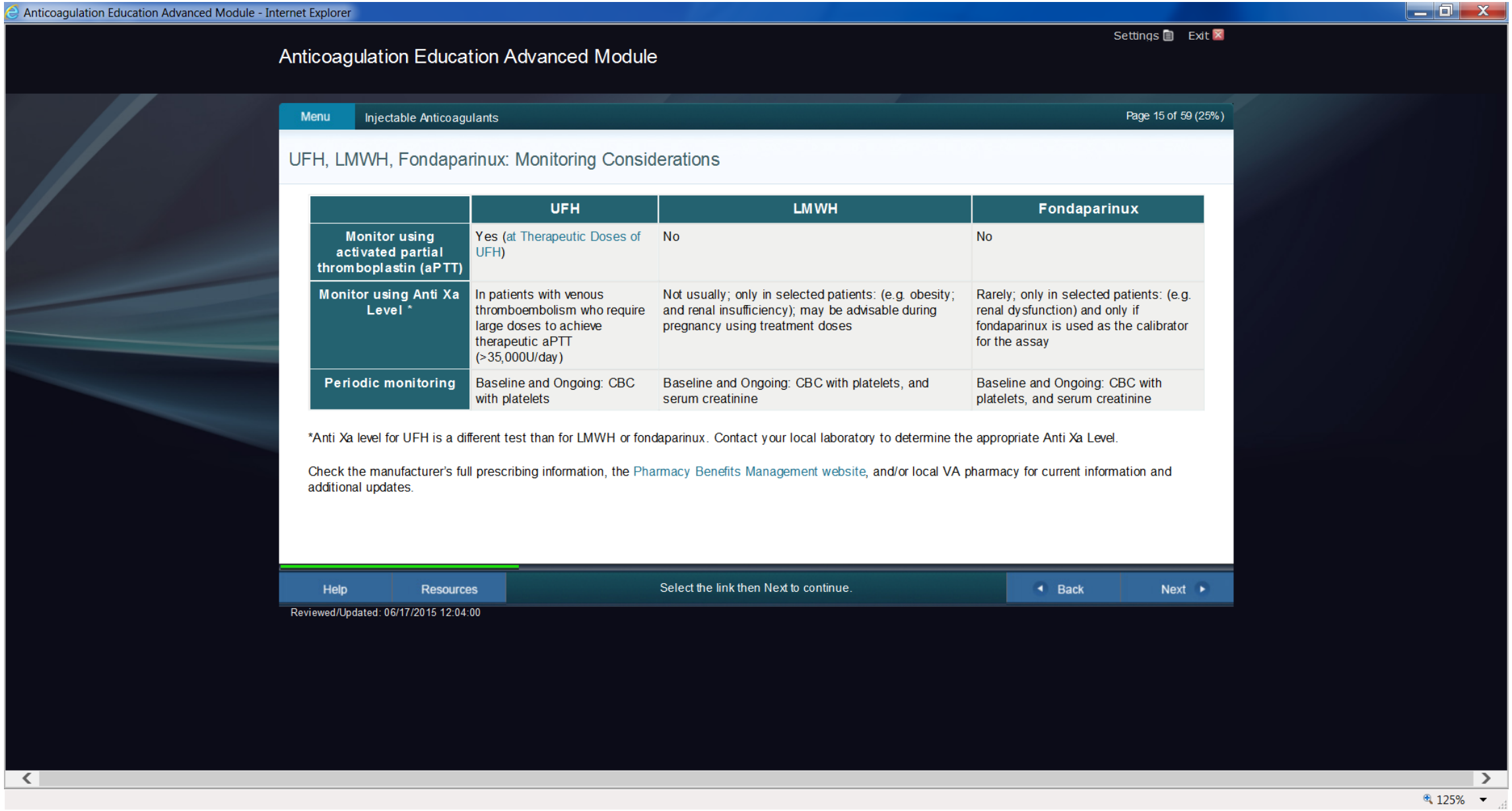
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UFH, LMWH, Fondaparinux: Monitoring Considerations
UFH
LMWH
Fondaparinux
Monitor using activated partial thromboplastin (aPTT)
Yes (at Therapeutic Doses of UFH)
No
No
Monitor using Anti Xa Level *
In patients with venous thromboembolism who require large doses to achieve therapeutic aPTT (>35,000U/day)
Not usually; only in selected patients: (e.g. obesity; and renal insufficiency); may be advisable during pregnancy using treatment doses
Rarely; only in selected patients: (e.g. renal dysfunction) and only if fondaparinux is used as the calibrator for the assay
Periodic monitoring
Baseline and Ongoing: CBC with platelets
Baseline and Ongoing: CBC with platelets, and serum creatinine
Baseline and Ongoing: CBC with platelets, and serum creatinine
*Anti Xa level for UFH is a different test than for LMWH or fondaparinux. Contact your local laboratory to determine the appropriate Anti Xa Level.
Check the manufacturer's full prescribing information, the Pharmacy Benefits Management website, and/or local VA pharmacy for current information and additional updates.
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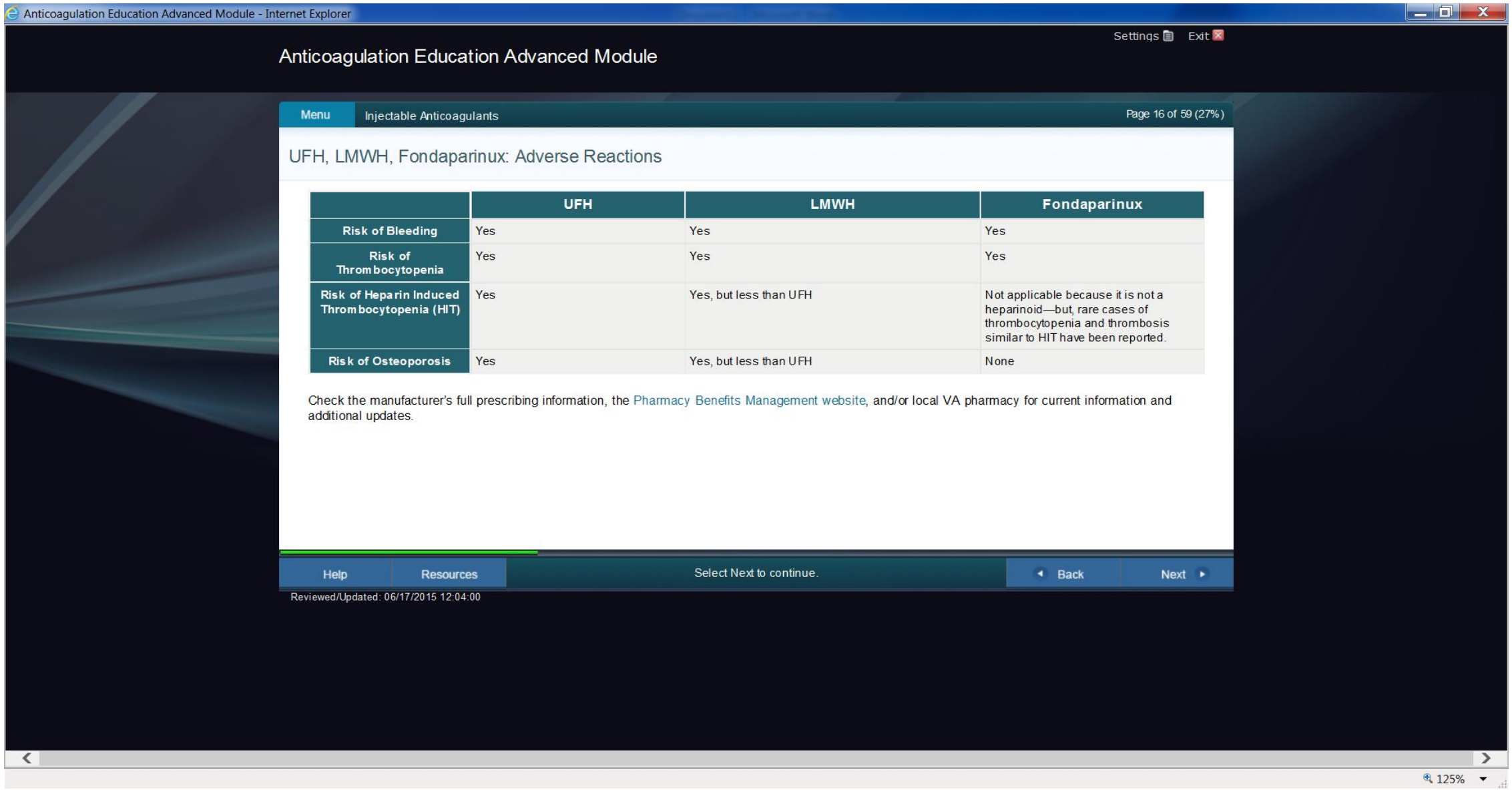

	UFH	LMWH	Fondaparinux
Risk of Bleeding	Yes	Yes	Yes
Risk of Thrombocytopenia	Yes	Yes	Yes
Risk of Heparin Induced Thrombocytopenia (HIT)	Yes	Yes, but less than UFH	Not applicable because it is not a heparinoid—but, rare cases of thrombocytopenia and thrombosis similar to HIT have been reported.
Risk of Osteoporosis	Yes	Yes, but less than UFH	None

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Heparin Induced Thrombocytopenia (HIT): Background and Treatment

Heparin induced thrombocytopenia is a complication of heparin therapy. There are two types of heparin induced thrombocytopenia (HIT)—Type 1 and Type 2. Some patients may experience an unexplained drop of platelet count after being exposed to heparin, however the clinical sequelae differ between the two types.

Note: Normal platelet count does not preclude the diagnosis of HIT.

HIT TYPE 1	HIT TYPE 2
Occurs in up to 10% of patients on heparin and characterized by a mild and transient asymptomatic thrombocytopenia (rarely less than 100 K platelets/uL).	Occurs in up to 8% of patients on heparin and characterized by an unexplained drop in platelet of at least 30-50% from baseline and develop antibodies without becoming thrombocytopenic.
No presence of heparin-dependent antibodies.	The presence of immune mediated, abnormal antibodies against heparin–platelet factor (PF4) complex causing further activation of the coagulation cascade with thrombin generation.
Clinical course is benign. Not associated with an increased risk of thrombosis.	Increased risk for venous and/or arterial thromboembolism. Skin necrosis may occur at heparin injection sites.

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Note: Normal platelet count does not preclude the diagnosis of HIT.

HIT TYPE 1	HIT TYPE 2
Occurs in up to 10% of patients on heparin and characterized by a mild and transient asymptomatic thrombocytopenia (rarely less than 100 K platelets/uL).	Occurs in up to 8% of patients on heparin and characterized by an unexplained drop in platelet of at least 30-50% from baseline and develop antibodies without becoming thrombocytopenic.
No presence of heparin-dependent antibodies.	The presence of immune mediated, abnormal antibodies against heparin–platelet factor (PF4) complex causing further activation of the coagulation cascade with thrombin generation.
Clinical course is benign. Not associated with an increased risk of thrombosis.	Increased risk for venous and/or arterial thromboembolism. Skin necrosis may occur at heparin injection sites.
Develops within the first two days of starting heparin and disappears quickly once the heparin is withdrawn. Platelet returns to normal within 5 days despite continued heparin use (or within 2 days if heparin is stopped)	Decrease in platelet count begins typically between 5-14 days after exposure to heparin.
Bleeding is rare.	Despite thrombocytopenia, bleeding is rare.

In HIT Type 2, the decrease in platelet count may be immediate if patient has been exposed to heparin before.

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Heparin Induced Thrombocytopenia (HIT): Diagnosis

Before ordering expensive laboratory tests to diagnose HIT, one way of predicting whether a patient may have HIT is to use a probability 4 T score.

The score is based on 4 items: percentage fall in the platelet count, onset of the platelet count fall, presence of thrombosis or other sequelae, and whether other causes of thrombocytopenia exists. Using the following table, determine the number of points associated with the respective situations. See the note below to determine the probability of testing positive for HIT.

The 4 T score predicts a positive HIT antibody test

J Thrombos Haemost 2006; 4:759

4Ts	2 points	1 point	0 points
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥ 20K*	Platelet count fall 30–50% or platelet nadir 10–19	Platelet count fall <30% or platelet nadir <10
Timing of platelet count fall	Clear onset between days 5–10 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)†	Consistent with days 5–10 fall, but not clear (e.g. missing platelet counts); onset after day 10‡, or fall ≤ 1 day (prior heparin exposure 30–100 days ago)	Platelet count fall <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis §, acute systemic reaction postintravenous unfractionated heparin (UFH) bolus	Progressive or recurrent thrombosis¶, non-necrotizing (erythematous) skin lesions §, suspected thrombosis (not proven)**	None
Other causes for thrombocytopenia	Non-apparent	Possible ††	Definite††

*Greifswald, Germany (GW): platelet count fall >50% or nadir 20-100; Hamilton, Canada (but not GW): platelet count fall >50% directly resulting from surgery counts as 1, rather than 2, point. † GW: onset from days 5–14 (rather than days 5–10); platelet fall within 1 day (heparin exposure within 100 days). ‡ GW: onset after day 14. § Skin lesions at heparin injection sites. ¶ Progression refers to objectively documented increase in thrombus size (usually, extension of deep-vein thrombosis by ultrasonography); recurrence refers to newly formed thromboembolus in previously affected region (usually, new perfusion defects in a patient with previous pulmonary embolism.) ** In GW< "suspected thrombosis (not proven)" was not included as a criterion. †† Determination of whether the presence of another apparent cause of thrombocytopenia was "possible" or "definite" was at the discretion of the investigator.

NOTE:

If the 4 T score is low (i.e. < 4), it is unlikely that the patient has HIT and additional work up may not be required.

If the 4 T score is higher than 4, then based on clinical judgment, screening the patient with rapid ELISA-PF4 assay may be warranted. If additional confirmation is needed, ordering a SRA assay may be required.

Score	% Testing positive
<4	0.8%
4–5	11%
>5	34%

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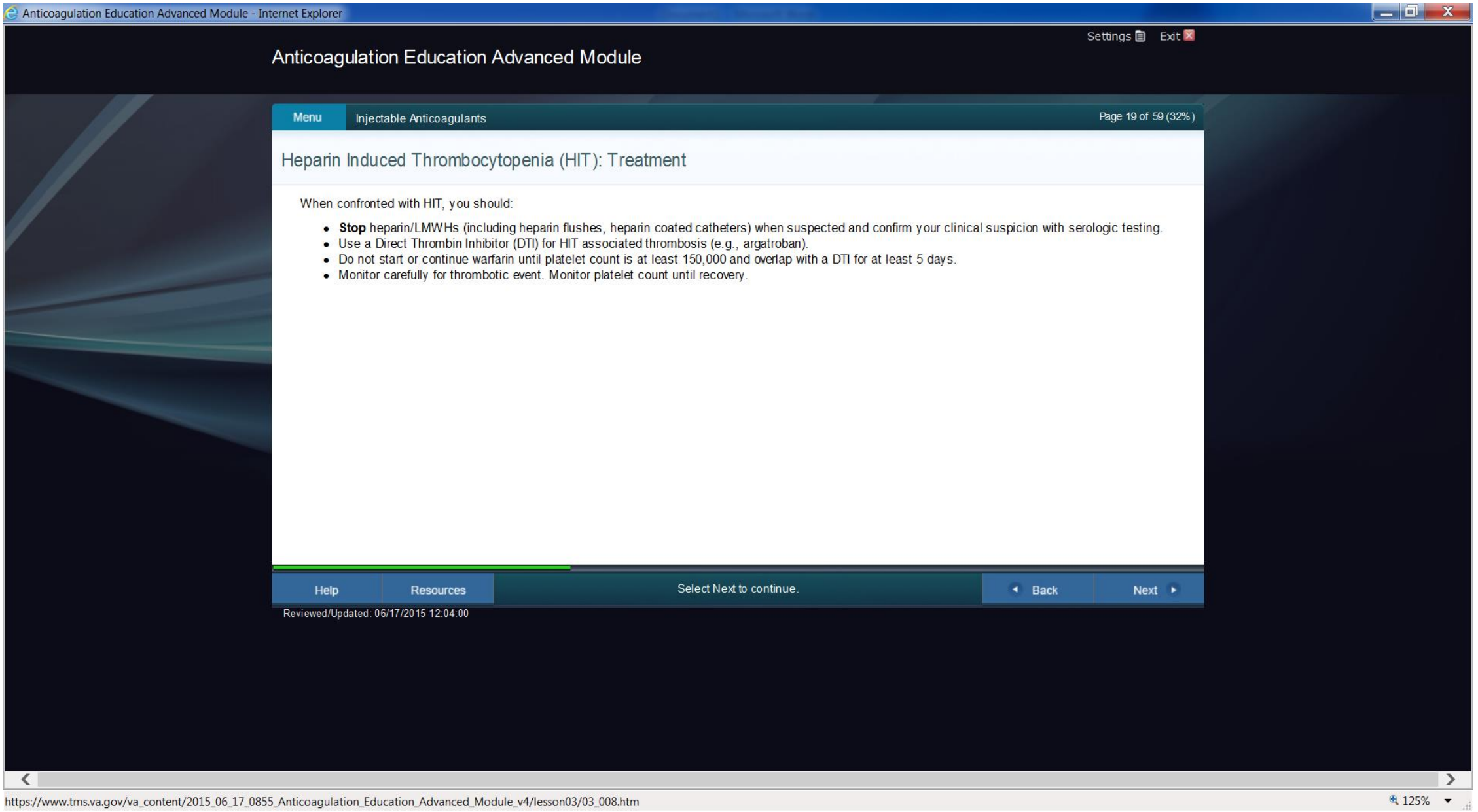
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Heparin Induced Thrombocytopenia (HIT): Treatment
When confronted with HIT, you should:
Stop heparin/LMWHs (including heparin flushes, heparin coated catheters) when suspected and confirm your clinical suspicion with serologic testing.
Use a Direct Thrombin Inhibitor (DTI) for HIT associated thrombosis (e.g., argatroban).
Do not start or continue warfarin until platelet count is at least 150,000 and overlap with a DTI for at least 5 days.
Monitor carefully for thrombotic event. Monitor platelet count until recovery.
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