Saudi MoH Protocol for

Heparin Induced Thrombocytopenia (HIT)

(Version 1), 17/04/2021

Disclaimer: **This is a living guidance that is subject to change as more evidence accumulates. It will be updated regularly and whenever needed.**

INTRODUCTION:

Heparin-induced thrombocytopenia (HIT) is a life-threatening complication of exposure to heparin (e.g. unfractionated heparin, low molecular weight [LMW] heparin) that occurs in a small percentage of patients exposed, regardless of the dose, schedule, or route of administration.

HIT results from an autoantibody directed against endogenous platelet factor 4 (PF4) in complex with heparin. This antibody activates platelets and can cause catastrophic arterial and venous thrombosis.

Untreated HIT has a mortality rate as high as 20%; although with improved recognition and early intervention, mortality rates have been reported as below 2%.

RISK FACTORS:

Heparin-related	**Host-related**
Type of heparin (UFH > LMWH)	Age (older adults > young adults and children
Duration of heparin (5-10 days > shorter course)	Sex (female > male)
Patient population (surgical > medical > obstetric)	

- NB: All patients given heparin is at risk to develop HIT

EVALUATION:

The 4 Ts score should be used as a guide for clinicians and should not substitute for clinical judgment (Refer to table)

Suspecting HIT — Any one of the following scenarios should raise the possibility of HIT in patients who are currently receiving heparin or who received heparin in the preceding 5 to 10 days:

- ●New onset of thrombocytopenia (i.e. platelet count <150,000/microL).
- ●A decrease in platelet count by 50% or more, even if the platelet count exceeds 150,000/microL.
- ●Venous or arterial thrombosis.
- ●Necrotic skin lesions at heparin injection sites.
- ● Rapid onset HIT, drop of platelet within 24 hours for those with recent exposure to heparin within a month.

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4Ts Score for Heparin-Induced Thrombocytopenia			
4T's	**2 Points**	**1 Point**	**0 Points**
Thrombocytopenia	Platelet count fall > 50% **and** Platelet nadir ≥ 20x 10^9/L	Platelet count fall > 50% (30 to 50% or nadir 10 to 19,000/microL) **and** Platelet nadir ≥ 20 x 10^9/L	Platelet count fall < 30% **or** Platelet nadir <10 x 10^9/L
Timing of platelet count fall	Clear onset between days 5-14 **or** Platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5-14 (10) fall, but not clear (e.g. missing platelet counts) or onset after day 14 (10) **or** fall ≤ 1 day (prior heparin exposure 30-100 days ago)	Platelet count fall ≤ 4 days without recent exposure
Thrombosis or other squeal	New thrombosis (confirmed) Skin necrosis at heparin injection sites Anaphylactoid reaction after IV heparin bolus	Progressive or recurrent thrombosis Non-necrotizin (erythematous) skin lesions Suspected thrombosis (not confirmed)	None
other causes of thrombocytop-enia	None apparent	Possible	Definite
High probability: 6-8 points; intermediate probability: 4-5 points; low probability: ≤3 Points For intermediate or high probability 4 Ts score only, we do HIT antibody testing, ([ELISA], rapid immunoassay)			

- Consult hematology if available

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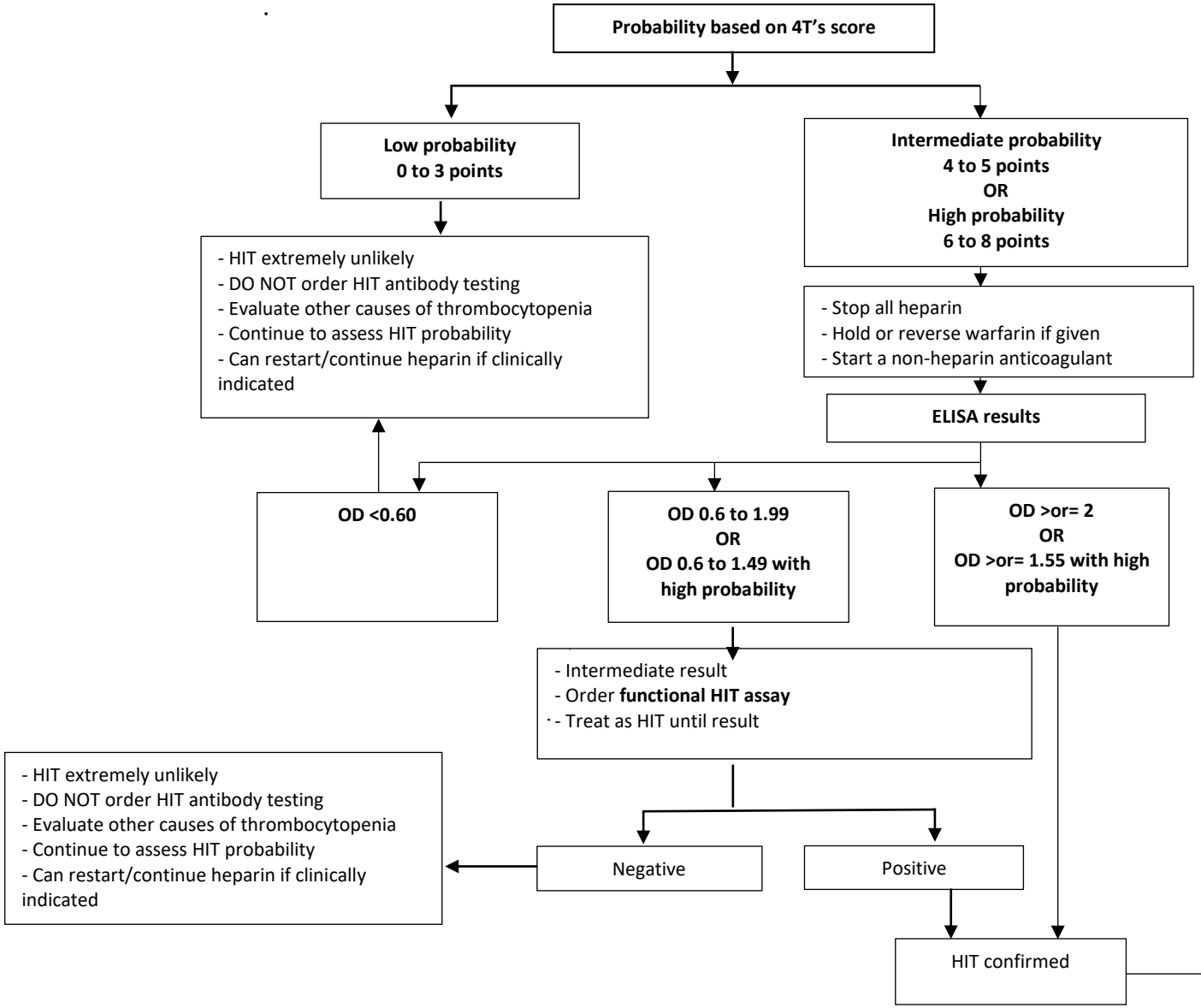

□ **Fondaparinux (first line):**
<50kg → 5mg SC OD
50-100kg → 7.5mg SC OD
100kg → 10mg SC OD
CrCl 30-50 mL/min) use caution)
CrCl < 30 mL/min) contraindicated)

□ **Argatroban (If fondaparinex is contraindicated):**
In patients with critical illness, increased bleeding risk, increased potential need for urgent procedures or HIT complicated by life- or limb-threatening thromboembolism (eg, massive pulmonary embolism or venous limb gangrene):
In clinically stable patients at average risk of bleeding (refer to nomogram for doses and monitoring):
Normal organ function → 1mcg/kg/min IV
Liver dysfunction (bilirubin.1.5mg/dL) →0.2- 0.5 mcg/kg/min
Heart failure, anasarca, postcardiac surgery → 0.2-0.5 mcg/kg/min

□ **Bivalirudin**:
Restricted for PCI patient
- During PCI: Initial: 0.75 mg/kg bolus immediately prior to procedure, followed by 1.75 mg/kg/hour
- Prior to PCI: Initial: Administer an initial 0.1 mg/kg bolus, followed by 0.25 mg/kg/hour

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DATE AND TIME

ARGATROBAN NOMOGRAM FOR HEPARIN-INDUCED THROMBOCYTOPENIA

Patient weight: _____Kg • **Actual** • **Estimate**

LABORATORY:
Baseline PTT (contact prescriber if elevated), INR, AST, AALT, total bilirubin, ALP, Urea and creatinine
CBC daily x 3 days

MEDICATIONS:
Discontinue all heparin, low molecular weight heparin, heparin flushes, locks
No intramuscular injections

Initiate argatroban therapy:
Initiate argatroban 1mg/mL IV infusion at:
• 0.2 mcg/kg/min (If liver or heart failure) *OR • 1 mcg/kg/min

PTT-adjusted argatroban therapy: (select dosing intensity)
Measure PTT 2 hours after starting argatroban, then adjust infusion rate and repeat PTT based on sliding scale below:

	CRITICALLY ILL HEPATIC INSUFFICIENCY	**NORMAL INTENSITY DOSING**
PTT (sec)	**Rate change and PTT Monitoring**	**Rate change and PTT Monitoring**
Less than 45	Increase rate by 0.2 mcg/kg/min Repeat PTT in 2 hours ***Call physician if 2 consecutives PTTs less than 45sec or infusion rate is greater than 4mcg/kg/min***	Increase rate by 1 mcg/kg/min Repeat PTT in 2 hours ***Call physician if 2 consecutives PTTs less than 45sec or infusion rate is greater than 4mcg/kg/min***
45 to 59	Increase rate by 0.1 mcg/kg/min Repeat PTT in 2 hours ***Call physician if infusion rate is greater than 4mcg/kg/min***	Increase rate by 0.5 mcg/kg/min Repeat PTT in 2 hours ***Call physician if infusion rate is greater than 4mcg/kg/min***
60 to 90 therapeutic	No change in infusion rate Repeat PTT Q4H until 3 consecutive PTTs are within therapeutic range then monitor PTT daily	No change in infusion rate Repeat PTT Q4H until 3 consecutive PTTs are within therapeutic range then monitor PTT daily
91 to 100	Decrease rate by 0.1 mcg/kg/min Repeat PTT in 2 hours	Decrease rate by 0.5 mcg/kg/min Repeat PTT in 2 hours
Above 100	HOLD infusion x 120 minutes Decrease rate by 0.3 mcg/kg/min Repeat PTT in 4 hours after re-initiation of infusion ***Call physician if 2 consecutives PTTs above 100 seconds***	HOLD infusion x 120 minutes Decrease rate by 1 mcg/kg/min Repeat PTT in 4 hours after re-initiation of infusion ***Call physician if 2 consecutives PTTs above 100 seconds***

Physician name Signature ID no. Pager

Child-Pugh Score			
Measure	**1 point**	**2 points**	**3 points**
Total bilirubin (micromol/L)	Less than 34	34 to 50	Greater than 50
Serum albumin (g/L)	Greater than 35	28 to 35	Less than 28
INR	Less than 1.7	1.7 to 2.2	Greater than 2.2
Ascites	None	Suppressed with medication	Refractory
Hepatic encephalopathy	None	Grade I to II (or suppressed with medication)	Grade III to IV (or refractory)

Preparation for administration:

The 2.5 ml (100 mg/ml) concentrated vial must be diluted to 1 mg/ml prior to administration. The premixed 50 ml or 125 ml vials and 250 ml bag (1 mg/ml) require no further dilution.

Argatroban should be diluted in 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/ml.

Stability after preparation

Solutions prepared are stable at 25°C (77°F), with in ambient indoor light for 24 hours; therefore, light-resistant measures such as foil protection for intravenous lines are unnecessary. Solutions are physically and chemically stable for up to 96 hours when protected from light and stored at controlled room temperature, 20° to 25°C or at refrigerated conditions, 5° ± 3°C.

TRANSITION TO WARFARIN:

Conversion to Warfarin If the decision is made to continue anticoagulation with oral therapy (warfarin) after argatroban infusion, several steps should be taken to avoid the pro-thrombotic effects of warfarin:

- Do not use warfarin as monotherapy in acute HIT
- Do not initiate warfarin until the platelet count has rebounded to >150 K/μL
- Do not use a loading dose of warfarin, initiate therapy with expected maintenance dose
- **Overlap** warfarin and argatroban therapy for at least 5 days – to allow for the half–lives of all the clotting factors
- Measure INR daily; INR will be significantly affected by argatroban as well as by warfarin; however increased INR may not correspond to an increased risk of bleeding
- To stop argatroban infusion, see table below:

For doses ≤ 2 mcg/kg/min	For doses > 2 mcg/kg/min
• Discontinue argatroban when the INR is > 4 on combined therapy (& and least 5 days of overlap) • Check INR 4 to 6 hours after stopping argatroban to assure therapeutic goal (INR 2 -3) is maintained • If repeat INR is below desired therapeutic range (2 -3) resume argatroban & repeat procedure daily until desired therapeutic range on warfarin alone is reached	• INR cannot be reliably predicted at argatroban doses > 2 mcg/kg/min • Temporarily reduce dose of argatroban to 2 mcg/kg/min (in order to predict INR on warfarin alone) • Repeat INR 4 to 6 hours after reduction and follow the process outlined for doses up to 2 mcg/kg/min

- **Conversion to a direct-acting oral anticoagulant after argatroban infusion**: Start direct-acting oral anticoagulant when argatroban infusion is stopped.

- **Transitioning from fondaparinux to warfarin**: Overlap fondaparinux and warfarin until a therapeutic INR has been established. For acute DVT and PE treatment, INR should be ≥2 for at least 24 hours and parenteral therapy should be continued for at least 5 days for initial treatment.

- **Transitioning from fondaparinux to non-warfarin oral anticoagulant (DOAC)**: Start DOAC within 0 to 2 hours of when the next dose of fondaparinux is scheduled to be given

- **Duration of therapy**

  - Heparin-induced thrombocytopenia without thrombosis: Typically, 4 weeks to 3 months
  - Heparin-induced thrombocytopenia with thrombosis: Typically, 3 to 6 months

Medication Related Information:				
Medication	**Contraindication**	**Major Drug Interactions**	**Required dose adjustment**	**Pregnancy**
Fondaparinux (first line) **Dose:** **(2.5 mg/0.5 mL,** **5 mg/0.4 mL** **7.5 mg/0.6 mL** **and** **10 mg/0.8 mL)** **injection**.	Active major bleeding Body weight less than 50 kg in patients requiring prophylaxis for venous thromboembolism History of serious hypersensitivity reaction (e.g. angioedema, anaphylactoid or anaphylactic reactions) Severe renal impairment (i.e. CrCl less than 30 mL/minute) Thrombocytopenia associated with positive in vitro test for antiplatelet antibody in the presence of fondaparinux sodium	• **Avoid combination** ○ **Apixaban:** May enhance the anticoagulant effect of Anticoagulants. ○ **Dabigatran Etexilate:** May enhance the anticoagulant effect of Anticoagulants. ○ **Edoxaban:** May enhance the anticoagulant effect of Anticoagulants ○ **Hemin:** May enhance the anticoagulant effect of Anticoagulants. ○ **Mifepristone:** May enhance the adverse/toxic effect of Anticoagulants. ○ **Omacetaxine:** Anticoagulants may enhance the adverse/toxic effect of Omacetaxine. ○ **Rivaroxaban:** Anticoagulants may enhance the anticoagulant effect of Rivaroxaban. ○ **Urokinase:** May enhance the anticoagulant effect of Anticoagulants. ○ **Vorapaxar:** May enhance the adverse/toxic effect of Anticoagulants. • **To Consider therapy modification.** ○ **Desirudin:** Discontinue treatment with other anticoagulants prior to desirudin initiation. If concomitant use cannot be avoided, monitor patients receiving these combinations closely for clinical and laboratory evidence of excessive anticoagulation. ○ **Estrogen Derivatives:** Carefully weigh the prospective benefits of estrogens against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations. ○ **Herbs (Anticoagulant/Antiplatelet Properties):** Avoid such combinations when possible. If used concomitantly, increase diligence in monitoring for adverse effects (e.g. bleeding, bruising, altered mental status due to CNS bleeds). ○ **Progestins:** Carefully weigh the prospective benefits of progestins against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations.	Renal impairment, CrCl 30 to 50 mL/min: Use with caution (manufacturer dosing) Renal impairment, CrCl 20 to 50 mL/min (VTE prophylaxis): 1.5 mg subQ once daily starting 6 hours or more (ideally 8 hours) postoperatively for10 days for total hip or knee replacement or 28 to 35 days for hip fracture surgery (study dosing) Geriatric: Use with caution Hemodiafiltration in patients with heparin-induced thrombocytopenia: Initiate at 0.03 mg/kg postdialysis body weight, administered via the efferent line of the dialyzer; titrate in increments of 0.01 mg/kg postdialysis body weight based on postdialysis anti-Xa activity (study dosing) Body weight less than 50 kg (VTE prophylaxis): Contraindicated Body weight less than 50 kg (VTE treatment): Use with caution	Pregnancy Considerations Based on case reports, small amounts of fondaparinux have been detected in the umbilical cord following multiple doses during pregnancy (Dempfle2004). Use of fondaparinux in pregnancy should be limited to those women who have severe allergic reactions to heparin, including heparin-induced thrombocytopenia, and who cannot receive danaparoid (Guyatt 2012).

Medication Related Information:				
Medication	**Contraindication**	**Major Drug Interactions**	**Required dose adjustment**	**Pregnancy**
			□ Body weight greater than 100 kg (DVT treatment): 10 mg subQ daily (guideline dosing)	
Argatroban (second line) **(Refer to nomogram for doses)**	□ Hypersensitivity to argatroban or to any component of the product □ Major bleeding	○ **Apixaban:** May enhance the anticoagulant effect of Anticoagulants**.** ○ **Dabigatran Etexilate:** May enhance the anticoagulant effect of Anticoagulants ○ **Edoxaban:** May enhance the anticoagulant effect of Anticoagulants ○ **Hemin:** Hemin may enhance the anticoagulant effect of Anticoagulants ○ **Mifepristone:** MiFEPRIStone may enhance the adverse/toxic effect of Anticoagulants. Specifically, the risk of bleeding may be increased. ○ **Omacetaxine:** Anticoagulants may enhance the adverse/toxic effect of Omacetaxine. ○ **Rivaroxaban:** Anticoagulants may enhance the anticoagulant effect of Rivaroxaban. ○ **Urokinase:** May enhance the anticoagulant effect of Anticoagulants. ○ **Vorapaxar:** May enhance the adverse/toxic effect of Anticoagulants. • **To Consider therapy modification.** ○ **Desirudin:** Anticoagulants may enhance the anticoagulant effect of Desirudin. Management: Discontinue treatment with other anticoagulants prior to desirudin initiation. If concomitant use cannot be avoided, monitor patients receiving these combinations closely for clinical and laboratory evidence of excessive anticoagulation. ○ **Estrogen Derivatives:** Carefully weigh the prospective benefits of estrogens against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations. ○ **Herbs (Anticoagulant/Antiplatelet Properties):** Avoid such combinations when possible. If used concomitantly, increase diligence in monitoring for adverse effects (eg, bleeding, bruising, altered mental status due to CNS bleeds). ○ **Progestins:** Carefully weigh the prospective benefits of progestins against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations.	□ Hepatic impairment (moderate to severe, Child-Pugh class B and C) in heparin-induced thrombocytopenia (HIT): Avoid use or use a reduced dose. □ In patients with bilirubin of greater than 1.5 mg/dL, use a dose of 0.5 to 1.2 mcg/kg/min. Adjust aPTT to 1.5 to 3 times baseline □ Hepatic impairment (moderate to severe) in (HIT): Initial dose 0.5 mcg/kg/min; monitor aPTT closely and adjust dosage as clinically indicated. Achievement of steady state aPTT levels may take longer and require more dose adjustments in patients with hepatic impairment compared to patients with normal hepatic function □ Hepatic impairment in percutaneous coronary intervention (PCI): Avoid use with clinically	Pregnancy Considerations Information related to Argatroban in pregnancy is limited. Use of parenteral direct thrombin inhibitors in pregnancy should be limited to those women who have severe allergic reactions to heparin, including heparin-induced thrombocytopenia, and who cannot receive danaparoid (Guyatt 2012).

Medication Related Information:				
Medication	**Contraindication**	**Major Drug Interactions**	**Required dose adjustment**	**Pregnancy**
			significant hepatic disease or AST/ALT levels 3 or more times the ULN. In other patients, titrate carefully until the desired level of anticoagulation is achieved Critically ill patients without organ failure in HIT: Initial, 1 mcg/kg/min Critically ill patients with multiple organ failure or heart failure in HIT: Initial, 0.5 to 0.6 mcg/kg/min Critically ill patients with multiple organ failure in HIT: Initial, 0.2 mcg/kg/min Heart failure, multiple organ system failure, or severe anasarca, or post-cardiac surgery in HIT: Initial, 0.5 to 1.2 mcg/kg/min Obesity (BMI up to 51 kg/m(2)): No dosing adjustment required when actual body weight-based dosing to target coagulation response is utilized	
Bivalirudin	Active major bleeding	• **Avoid combination.** ○ **Apixaban:** May enhance the anticoagulant effect of Anticoagulants. ○ **Dabigatran Etexilate:** May enhance the anticoagulant effect of Anticoagulants.	Renal impairment (CrCl less than 30 mL/min): Reduce	Pregnancy Considerations

Medication Related Information:				
Medication	**Contraindication**	**Major Drug Interactions**	**Required dose adjustment**	**Pregnancy**
(Restricted for PCI patient with HIT)	□ Hypersensitivity to bivalirudin or its components □ Acute gastric or duodenal ulcer □ Cerebral hemorrhage □ Bacterial endocarditis □ Diabetic or hemorrhagic retinopathy □ Proximal use of spinal/epidural anesthesia	○ **Edoxaban:** May enhance the anticoagulant effect of Anticoagulants. ○ **Hemin:** May enhance the anticoagulant effect of Anticoagulants. ○ **Mifepristone:** May enhance the adverse/toxic effect of Anticoagulants. ○ **Omacetaxine:** Anticoagulants may enhance the adverse/toxic effect of Omacetaxine. ○ **Rivaroxaban:** Anticoagulants may enhance the anticoagulant effect of Rivaroxaban. ○ **Urokinase:** May enhance the anticoagulant effect of Anticoagulants ○ **Vorapaxar**: May enhance the adverse/toxic effect of Anticoagulants. • **To Consider therapy modification.** ○ **Desirudin:** Discontinue treatment with other anticoagulants prior to desirudin initiation. If concomitant use cannot be avoided, monitor patients receiving these combinations closely for clinical and laboratory evidence of excessive anticoagulation. ○ **Estrogen Derivatives:** Carefully weigh the prospective benefits of estrogens against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations. ○ **Herbs (Anticoagulant/Antiplatelet Properties):** Avoid such combinations when possible. If used concomitantly, increase diligence in monitoring for adverse effects (e.g. bleeding, bruising, altered mental status due to CNS bleeds). ○ **Progestins:** Carefully weigh the prospective benefits of progestins against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations.	infusion rate to 1 mg/kg/hr; monitor the anticoagulant status more frequently □ Hemodialysis: Reduce infusion rate to 0.25 mg/kg/hr; no bolus dose reduction is necessary □ Obesity: The actual measured body weight (total body weight) should be used for dose calculations, according to a retrospective review in patients with heparin-induced thrombocytopenia (HIT) (n=135); in the obese group, the mean total body weight was 105 +/- 21.2 kg (range, 78 to 176 kg) and mean BMI 37.7 +/- 6.7 kg/m(2) (range, 30.1 to 56.2 kg/m(2))	Bivalirudin is used in conjunction with aspirin, which may lead to maternal or fetal adverse effects, especially during the third trimester. Use of parenteral direct thrombin inhibitors in pregnancy should be limited to those women who have severe allergic reactions to heparin, including heparin-induced thrombocytopenia, and who cannot receive danaparoid (Guyatt 2012).

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