INDIRECT PARENTERAL ANTICOAGULANTS

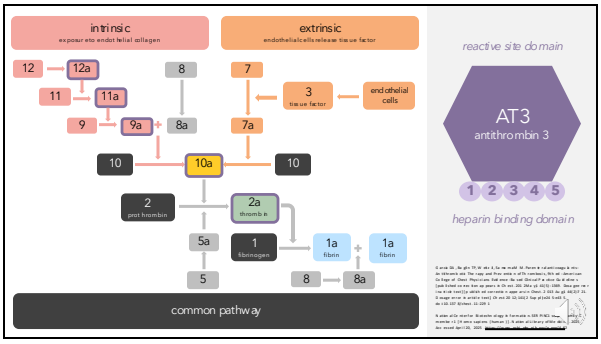
Angela Su, PharmD

LEARNING OBJECTIVES

Discuss the **pharmacology** of unfractionated heparin, low molecular weight heparin, and fondaparinux.

Identify **indications and contraindications** for unfractionated heparin, low molecular weight heparin, and fondaparinux.

PHARMACOLOGY


intrinsic
exposure to endothelial collagen
extrinsic
endothelial cells release tissue factor
12
12a
11
11a
9
9a
8
8a
7
3
tissue factor
endothelial cells
7a
10
10a
10
2
prothrombin
2a
thrombin
5a
1
fibrinogen
1a
fibrin
1a
fibrin
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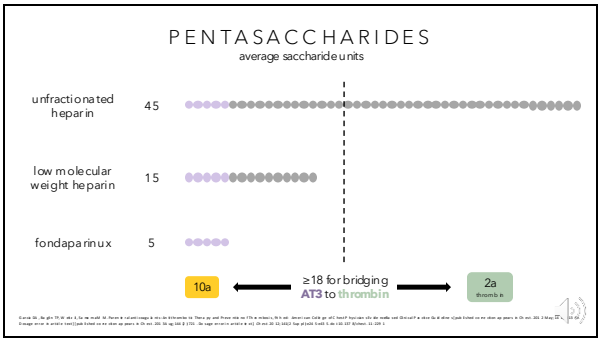
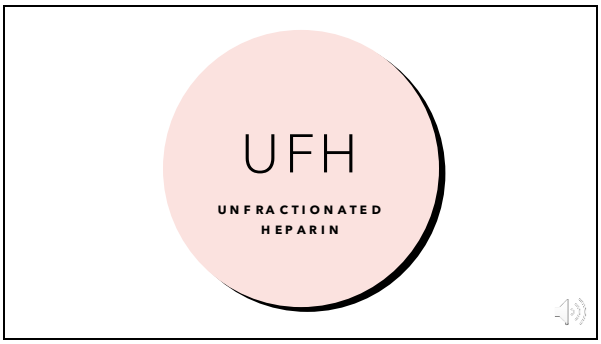
8
8a
common pathway
reactive site domain
AT3
antithrombin 3
1 2 3 4 5
heparin binding domain


PENTASACCHARIDES
average saccharide units
unfractionated heparin
45
low molecular weight heparin
15
fondaparinux
5
10a
≥18 for bridging
AT3 to thrombin
2a
thrombin


UFH
UNFRACTIONATED
HEPARIN

UFH: PHARMACOKINETICS

Onset of Action
- SC: ~30 min
- IV: immediate

Absorption
- SC: erratic
- IV: rapid and complete

t½: 1.5 hr → continuous infusion

Metabolism: liver and reticuloendothelial cells → no renal adjustment

Table 3—*Example of a Heparin Dose Adjustment Nomogram*

Initial dose	80 units/kg bolus, then 18 units/kg/h
aPTT, < 35 s	80 units/kg bolus, then increase 4 units/kg/h
aPTT, 35-45 s	40 units/kg bolus, then increase 2 units/kg/h
aPTT, 46-70 s[a]	No change
aPTT, 71-90 s	Decrease infusion rate by 2 units/kg/h
aPTT, > 90 s	Hold infusion 1 h, then decrease infusion rate by 3 units/kg/h

aPTT = activated partial thromboplastin time. (Adapted with permission from Raschke et al.[65])
[a]Therapeutic aPTT range of 46-70 s corresponded to anti-Xa activity of 0.3-0.7 units/mL. The target aPTT range in a particular institution should reflect what is known about the local reagents and equipment used to perform the assay.

Heparin sodium injection. Prescribing information. Fresenius Kabi; 1939. Updated December 2019. Accessed April 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cb1c1e7a-c9ca-4a07-8833-e45ce436d287

Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published correction appears in Chest. 2012 May;141(5):1369. Dosage error in article text] [published correction appears in Chest. 2013 Aug;144(2):721. Dosage error in article text]. *Chest*. 2012;141(2 Suppl):e24S-e43S. doi:10.1378/chest.11-2291

UFH: INDICATIONS

VTE Prophylaxis: 5000 units SC Q8-12 hr

VTE Treatment: 80 units/kg IV bolus + 18 units/kg/hr infusion

ACS/STEMI Treatment: 60 units/kg IV bolus + 12 units/kg/hr infusion*

* off-label

Heparin sodium injection. Prescribing information. Fresenius Kabi; 1939. Updated December 2019. Accessed April 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cb1c1e7a-c9ca-4a07-8833-e45ce436d287

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Rao SV, O'Donoghue ML, Ruel M, et al. 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2025 Apr;151(13):e865. doi:10.1161/CIR.0000000000001328] [published correction appears in Circulation. 2025 Jun 24;151(25):e1098. doi:10.1161/CIR.0000000000001346]. *Circulation*. 2025;151(13):e771-e862. doi:10.1161/CIR.0000000000001309

UFH: SAFETY

Contraindications
- uncontrolled active bleed
- severe thrombocytopenia
- history of HIT
- hypersensitivity to pork products

Monitoring
- aPTT or anti-Xa level
  - 6 hr after initiation
  - Q6 hr until therapeutic
  - Q24 hr
  - Every dose change
- platelets
- hemoglobin
- hematocrit

Heparin sodium injection. Prescribing information. Fresenius Kabi; 1939. Updated December 2019. Accessed April 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cb1c1e7a-c9ca-4a07-8833-e45ce436d287

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UFH: FORMULATIONS

IV Bag

Vial

Syringe

SPOT THE DIFFERENCE

SPOT THE DIFFERENCE

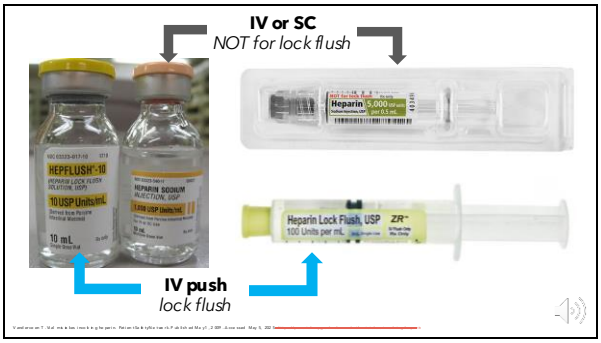
of units

SPOT THE DIFFERENCE

of units bag size

SPOT THE DIFFERENCE

of units bag size diluent



HIGH ALERT

- concentration
- route of administration

LMWH

LOW MOLECULAR WEIGHT HEPARINS

LMWH: PHARMACOKINETICS

More Predictable Than UFH

- 1 mg enoxaparin = 100 units anti-Xa activity
- anti-Xa monitoring generally not required
- bioavailability: rapid and complete

Maximum Anti-Xa & -IIa Activities: 3-5 hr

t½: 3-6 hours (dose independent)

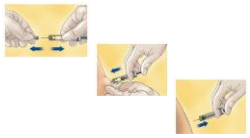
Metabolism: primarily renal → adjustment

LMWH: INDICATIONS

VTE Prophylaxis
- 30 mg SC Q12 hr
- 40 mg SC daily
- CrCl < 30 mL/min: 30 mg SC daily

VTE Treatment
- 1 mg/kg SC Q12 hr
- 1.5 mg/kg SC daily
- CrCl < 30 mL/min: 1 mg/kg SC daily

UA/NSTEMI Treatment
- 1 mg/kg SC Q12 hr
- CrCl < 30 mL/min: 1 mg/kg SC daily



STEMI Treatment

< 75 yo
- 30 mg IV bolus + 1 mg/kg SC dose
- then 1 mg/kg SC Q12 hr*
- *CrCl < 30 mL/min: 1 mg/kg SC daily

maximum 100 mg for 1st two SC doses

≥ 75 yo

- no bolus
- 0.75 mg/kg SC Q12 hr
- CrCl < 30 mL/min: 1 mg/kg SC daily

maximum 75 mg for 1st two SC doses

LMWH: SAFETY

Boxed Warning: Spinal/Epidural Hematomas
- neuraxial anesthesia
- spinal puncture

Contraindications
- active major bleed
- history of HIT
- hypersensitivity to pork products

Monitoring
- platelets
- hemoglobin
- hematocrit
- serum creatinine
- anti-Xa in pregnancy

do NOT expel air bubble

lower dose prefilled syringes tend to lack graduations

KNOWLEDGE CHECK

Low molecular weight heparin is approved for all of the following indications EXCEPT:

A. Prevention of venous thromboembolism
B. Treatment of venous thromboembolism
C. Anticoagulation in patients with a history of HIT
D. All of the above are true

KNOWLEDGE CHECK

Low molecular weight heparin is approved for all of the following indications EXCEPT:

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FONDAPARINUX

25

FONDAPARINUX: PHARMACOKINETICS

Bioavailability: ~100%

Maximum Concentration: ~2 hr

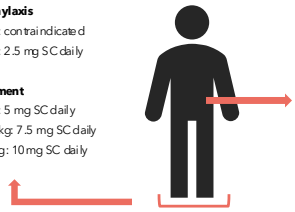
t½: 17-21 hr → once daily dosing

Metabolism: renal → contraindicated if CrCl < 30 mL/min

FONDAPARINUX: INDICATIONS

VTE Prophylaxis
- < 50 kg: contraindicated
- ≥ 50 kg: 2.5 mg SC daily

VTE Treatment
- < 50 kg: 5 mg SC daily
- 50-100 kg: 7.5 mg SC daily
- > 100 kg: 10 mg SC daily



CrCl 30-50 mL/min
- caution
- total clearance ↓ by 40%

CrCl < 30 mL/min
- contraindicated
- total clearance ↓ by 55%

FONDAPARINUX: SAFETY

<u>Boxed Warning</u>: Spinal/Epidural Hematomas
- neuraxial anesthesia
- spinal puncture

Contraindications
- severe renal impairment (CrCl < 30 mL/min)
- active major bleed
- bacterial endocarditis
- thrombocytopenia with positive test for anti-platelet antibody in presence of fondaparinux

Monitoring
- serum creatinine
- *coagulation monitoring not routinely recommended*
  - *anti-Xa levels 3 hr post-dose*
  - *platelets*
  - *hemoglobin*
  - *hematocrit*

ARIXTRA (fondaparinux sodium) injection. Prescribing information. Mylan; 2001. Updated December 2024. Accessed April 7, 2025. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=d3b30c68-cf45-4b46-8ba6-72090f7ba01a&type=display

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do NOT expel air bubble

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KNOWLEDGE CHECK

TY is admitted to your hospital for community-acquired pneumonia. You notice that he is a candidate for VTE prophylaxis. He is a 70 year-old male, 5'5", and 75 kg. Labs include INR 1.1, BUN 30, and SCr 2.9. What is the most appropriate recommendation?

A. Enoxaparin 40 mg SC daily
B. Heparin IV per thromboembolic protocol
C. Fondaparinux 2.5 mg SC daily
D. Enoxaparin 30 mg SC daily

30

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ADDITIONAL CONSIDERATIONS

32

HEPARIN-INDUCED THROMBOCYTOPENIA

- IgG-mediated adverse drug reaction
- antibodies form → activate platelets → **prothrombotic state**
- splenic macrophages remove platelet complex → thrombocytopenia (platelet count < 150 x 10^9/L)
- UFH > LMWH > fondaparinux

	Score = 2	Score = 1	Score = 0
Thrombocytopenia Compare the highest platelet count within the sequence of declining platelet counts with the lowest count to determine the % of platelet fall. **(Select only 1 option)**	○ > 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 **(Select only 1 option)**	○ 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 in past 31-100 days ○ platelet fall after day 10	○ platelet fall ≤ day 4 without exposure to heparin in past 100 days
Thrombosis (or other clinical sequelae) **(Select only 1 option)**	○ 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** **(Select only 1 option)**	○ 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 72 h 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 (see list) ○ non-necrotizing skin lesions at LMWH injection site (presumes DTH) ○ other

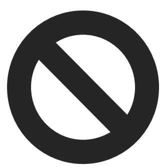
Drugs implicated in drug-induced immune thrombocytopenia (D-ITP)
Relatively Common: glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban); quinine, quinidine, sulfa antibiotics, carbamazepine, vancomycin **Less Common**: actinomycin, amitriptyline, amoxicillin/piperacillin/nafcillin, cephalosporins (cefazolin, ceftazidime, ceftriaxone), celecoxib, ciprofloxacin, esomeprazole, fexofenadine, fentanyl, fucidic acid, furosemide, gold salts, levofloxacin, metronidazole, naproxen, oxaliplatin, phenytoin, propranolol, propoxyphene, ranitidine, rifampin, suramin, trimethoprim. Note: This is a partial list.

4 T'S SCORE

Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published correction appears in Chest. 2015 Dec;148(6):1529. doi:10.1378/chest12-2960.] *Chest*. 2012;141(2 Suppl):e495S-e530S. doi:10.1378/chest11-2303

HEPARIN-INDUCED THROMBOCYTOPENIA

- **stop all heparin products!**
- start non-heparin anticoagulation
- reverse warfarin
  - vitamin K
  - warfarin + low platelets → warfarin-induced limb gangrene + necrosis



KNOWLEDGE CHECK

The following are true about both LMWH and fondaparinux, EXCEPT:

A. Dose adjustment or avoiding use is necessary in patients with impaired renal function
B. Anti-Xa testing is recommended for most patients and should be drawn on Days 2 and 4 of therapy
C. Active major bleeding is a contraindication for use
D. Both are associated with lower risk of HIT development compared to heparin
E. Both are indicated for VTE treatment and prophylaxis

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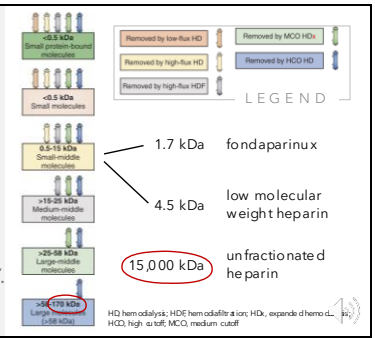
DIALYZABILITY

average molecular weight



HD, hemodialysis; HDF, hemodiafiltration; HDx, expanded chemod...
HCO, high cutoff; MCO, medium cutoff

KNOWLEDGE CHECK

A nurse calls, concerned about their patient on heparin for a new blood clot. The patient is going for hemodialysis today. They are unsure of how dialysis will affect the patient's heparin therapy. You should...

A. Recommend an additional bolus heparin dose after dialysis
B. Contact the provider about changing to LMWH because heparin is contraindicated in dialysis patients
C. Advise that hemodialysis will not affect heparin levels so it is safe to continue therapy without any intervention
D. Instruct the nurse to increase the heparin rate during dialysis

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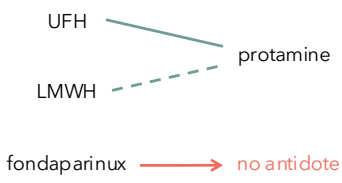
REVERSAL



REVERSAL: PROTAMINE

- combines with heparins to form stable salt complex
- UFH
  - if given in past 2-2.5 hr
  - 1 mg protamine reverses ~100 units heparin (max 50 mg)
- enoxaparin (LMWH)
  - if given in past 8 hr
  - 1 mg protamine reverses 1 mg enoxaparin
  - variable anti-Xa neutralization → less effective
- slow IV push/infusion (max 50 mg over 10 minutes)

PREGNANCY

LMWH = preferred pharmacologic agent

VTE Treatment

- monitor anti-Xa peak
  - 4 hr post-dose
  - controversial (i.e. cost limitations)
- continue for at least 6 weeks postpartum (minimum duration of therapy of 3 months)

KNOWLEDGE CHECK

The following are true regarding low molecular weight heparin, EXCEPT:

A. Protamine will completely reverse LMWH effects
B. Dose adjustments are necessary for CrCl < 30 mL/min
C. Due to longer half-life, once or twice daily dosing is possible
D. LMWH is preferred in pregnant patients
E. All of the above are true

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INDICATIONS

THROMBOPROPHYLAXIS

NON-SURGICAL

Acutely Ill Hospitalized Medical Patients

- increased thrombosis risk: **LMWH, low-dose UFH BID/TID, or fondaparinux** (Grade 1B)
  - patient preference
  - compliance
  - ease of administration
- low thrombosis risk: recommend **against** pharmacologic or mechanical prophylaxis (Grade 1B)
- bleeding or high bleed risk: recommend **against** anticoagulant thromboprophylaxis (Grade 1B)

Critically Ill Patients

- suggest **LMWH or low-dose UFH** thromboprophylaxis over no prophylaxis (Grade 2C)

Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e195S-e226S. doi:10.1378/chest.11-2296

Stevens SM, Woller SC, Baumann Kreuziger L, et al. Antithrombotic Therapy for VTE Disease: Compendium and Review of CHEST Guidelines 2012-2021. *Chest*. 2024;166(2):388-404. doi:10.1016/j.chest.2024.03.003

THROMBOPROPHYLAXIS

SURGICAL

Nonorthopedic

- no major bleed complications
  - moderate VTE risk: **LMWH or low-dose UFH** (Grade 2B) or mechanical prophylaxis (Grade 2C) over no prophylaxis
  - high VTE risk: **LMWH or low-dose UFH** (Grade 1B) with mechanical prophylaxis (Grade 2C) over no prophylaxis
- major bleed complications
  - moderate to high VTE risk: mechanical prophylaxis until can initiate pharmacologic prophylaxis over no prophylaxis (Grade 2C)

Orthopedic

- major surgery*: **LMWH** preferred over low-dose UFH, fondaparinux, apixaban, dabigatran, rivaroxaban, adjusted-dose VKA, or aspirin (Grade 2C/2B)
- knee arthroscopy with no h/o VTE: no thromboprophylaxis rather than prophylaxis (Grade 2B)

*total hip/knee arthroplasty and hip fracture surgery

Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published correction appears in Chest. 2012 May;141(5):1369]. *Chest*. 2012;141(2 Suppl):e227S-e277S. doi:10.1378/chest.11-2297

Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e278S-e325S. doi:10.1378/chest.11-2404

VTE TREATMENT

- high clinical suspicion of acute VTE/PE: treatment with **parenteral anticoagulants** over no treatment while awaiting the results of diagnostic tests (Grade 2C)
- acute VTE in patients treated with VKA therapy
  - recommend **parenteral anticoagulation** as initial treatment (LMWH, fondaparinux, IV or SC UFH) rather than no such initial treatment
  - **LMWH or fondaparinux** recommended over IV or SC UFH
    - cost
    - availability
    - familiarity of use

Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2016;149(2):315-352. doi: 10.1016/j.chest.2015.11.026

ACUTE CORONARY SYNDROME

"Parenteral anticoagulation is recommended for all patients with ACS, irrespective of the initial treatment strategy, to treat the underlying pathophysiologic process (coronary atherothrombosis) and reduce the risk of recurrent MACE"

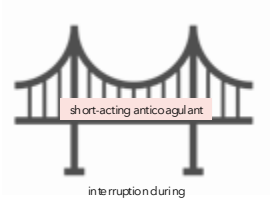
- NSTE-ACS
  - **IV UFH**
  - no early invasive approach: **enoxaparin or fondaparinux** are recommended alternatives
- Anticoagulant Therapy to Support PCI (STEMI and NSTE-ACS)
  - **IV UFH**
  - fondaparinux should NOT be used to support PCI in patients with ACS
- STEMI treated with fibrinolytic therapy
  - no plan for invasive approach: **enoxaparin** preferred (alternative: fondaparinux)

Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-177. doi: 10.1093/eurheartj/ehx393

SPECIFIC SCENARIOS

BRIDGING

VKA therapy



VKA therapy

interruption during
perioperative period

BRIDGING

Suggest <u>Against</u> Heparin Bridging

- DOAC interruption for elective surgery/procedure (Conditional, Very Low)
- receiving VKA therapy for ___ and require interruption for elective surgery/procedure
  - mechanical heart valve (Conditional, Very Low)
  - atrial fibrillation (Strong, Moderate)
  - VTE (Conditional, Very Low)

BRIDGING

BRIDGE Trial

- randomized, double-blind, placebo-controlled trial
- atrial fibrillation (N=1884)
  - intervention: bridging LMWH anticoagulation therapy Q12 hr (n=934)
  - comparator: placebo Q12 hr (n=950)
- noninferior in arterial thromboembolism prevention (RD 0.1% points, 95CI -0.6 to 0.8)
- not bridging decreased major bleeding (RR 0.41, 95 CI 0.20 to 0.78)

ONCOLOGY PATIENTS

Khorana Risk Score for Chemotherapy-Associated VTE

Patient Characteristic	Risk Score
site of primary cancer	very high risk 2 high risk 1
pre-chemotherapy platelet count 350 x 10^9/L or higher	1
hemoglobin level < 10 g/dL or use red cell growth factors	1
pre-chemotherapy leukocyte count higher than 11 x 10^9/L	1
BMI 35 kg/m^2 or higher	1

Total Score

- Low Risk: 0
- Intermediate Risk: 1-2
- High Risk: ≥3

ONCOLOGY PATIENTS

Medical Oncology Patient | VTE Prophylaxis

Inpatient

- dalteparin 5000 units SC daily
- enoxaparin 40 mg SC daily
- fondaparinux 2.5 mg SC daily
- UFH 5000 units SC Q8-12 hr

Post-Discharge

- dalteparin 200 units/kg SC daily x 1 month
  then 150 units/kg SC daily x 2 months
- enoxaparin 1 mg/kg SC daily x 3 months
  then 40 mg SC daily

ONCOLOGY PATIENTS

Surgical Oncology Patient | VTE Prophylaxis

Inpatient

- dalteparin 5000 units SC evening pre-op then 5000 units SC daily
- enoxaparin 40 mg SC 2-12 hr pre-op then once daily
- fondaparinux 2.5 mg SC daily no earlier than 6-8 hr post-op
- UFH 5000 units SC 2 hrs pre-op then 5000 units SC Q8h through post-op day 1

Post-Discharge

- dalteparin 5000 units SC daily x 28 days
- enoxaparin 40 mg SC daily x 28 days

ONCOLOGY PATIENTS

Chemotherapy-Induced Thrombocytopenia

Enoxaparin Dose Modification in the Setting of Thrombocytopenia

Platelet Count	Dose Adjustment	Suggested Dose of Enoxaparin	Alternative Once-Daily Dosing Regimen
>50,000/µL	Full-dose enoxaparin	1 mg/kg twice daily	1.5 mg/kg daily
25,000–50,000/µL	Half-dose enoxaparin	0.5 mg/kg twice daily	—
<25,000/µL	Temporarily hold enoxaparin		

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