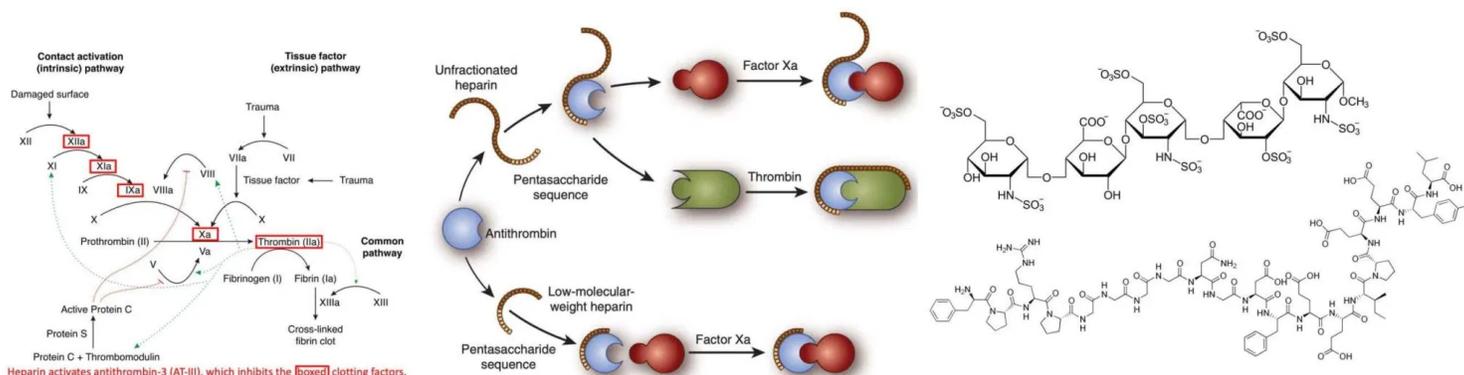


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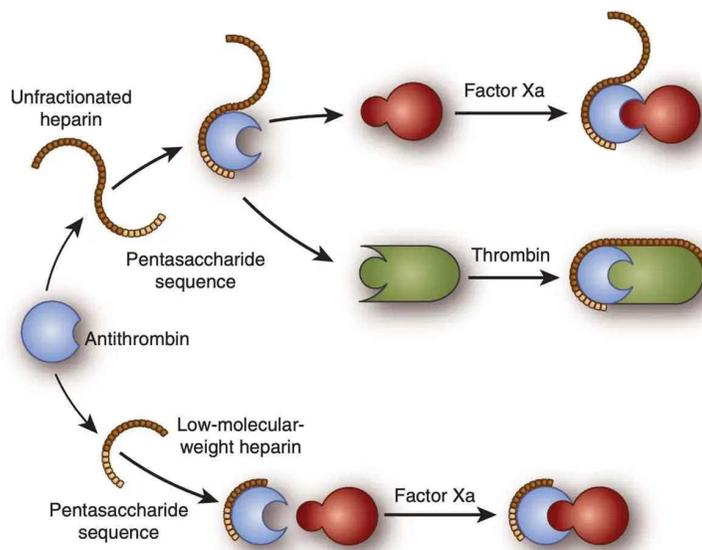
Unfractionated heparin (UFH), LMWH, fondaparinux, argatroban, and bivalirudin

May 24, 2020 by [Josh Farkas](#)



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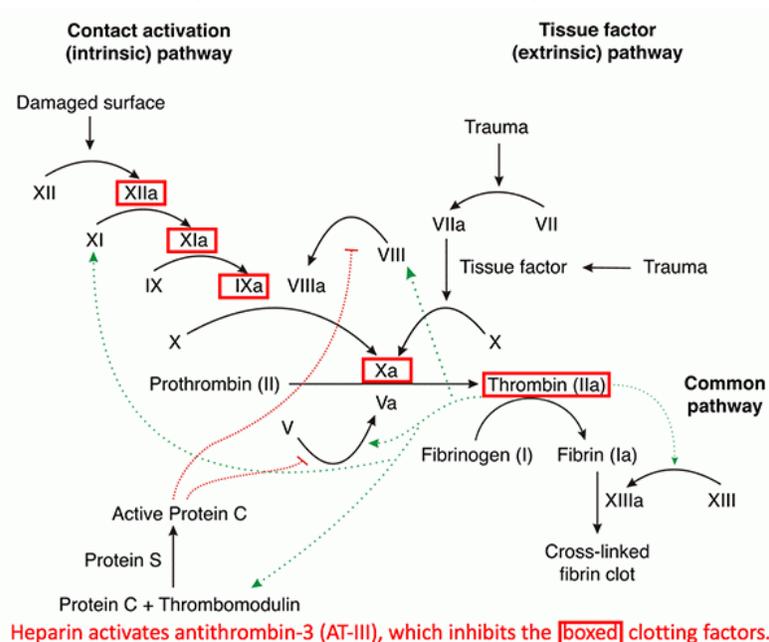
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heparin, low molecular-weight heparin, and fondaparinux

Heparin functions by activating antithrombin-III to bind to serine proteases involved in coagulation, blocking their function (predominantly Factor Xa and Factor IIa a.k.a. thrombin). Low molecular heparin predominantly facilitates inhibition of Xa, whereas unfractionated heparin inhibits Xa and thrombin. This reaction *consumes* antithrombin-III (which remains permanently stuck to factor Xa and/or thrombin).

Lai S et al. *Kidney International* 2013

- Unfractionated heparin (UFH) binds to anti-thrombin III (AT-III), which enhances antithrombin's inhibition of several coagulation factors – especially factor Xa and factor IIa (thrombin).
- Low Molecular-Weight Heparin (LMWH) is a heterogeneous collection of heparin molecules with a *lower* average molecular weight compared to unfractionated heparin. Since longer length is necessary to facilitate the interaction between anti-thrombin III and factor IIa, LMWH is less effective at inhibiting factor IIa (acting mostly via inhibition of Xa).
 - LMWH preparations have differences in the distribution of heparin chain lengths. The ratio of anti-Xa activity to anti-IIa activity varies between preparations (between roughly ~2:1 to ~4:1).
- Fondaparinux is essentially a synthetic, short molecule shaped like heparin. It exerts no activity against factor IIa, working purely via inhibition of Xa.
- All of these agents are effective only against fluid-phase clotting factors. In contrast, direct thrombin inhibitors may inhibit both fluid-phase and clot-bound thrombin. This might *theoretically* make direct thrombin inhibitors more potent agents.



<https://io.wp.com/emcrit.org/wp-content/uploads/2018/01/anticoagcasc.gif>

choice of agent

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Parenteral anticoagulants used in acute care medicine

	Unfractionated Heparin (UFH)	Low molecular weight heparin	Fondaparinux	Argatroban	Bivalirudin
Source	Biological	Biological	Synthetic	Synthetic	Synthetic
Molecular weight	~15,000 Heterogeneous mixture	~5,000 Heterogeneous mixture	1,727	508	2,180
Biological targets	Factor Xa & IIa (thrombin) Some anti-platelet effect	Factor Xa >> Factor IIa (~4:1 to 2:1 ratio)	Factor Xa	Direct thrombin inhibitor (reversible)	Direct thrombin inhibitor (reversible)
Half-life	~1 hour (may increase at higher doses)	~3-6 hours with normal renal function	17-21 hours with normal renal function	45 minutes (~180 min hepatic dysfunx)	25 minutes
Metabolism/excretion	Reticuloendothelial voodoo	~10-40% Renal	Renal	Hepatic metabolism	~80% serum proteases ~20% excreted by kidneys
Use in renal failure	Fine for renal failure	Contraindicated if GFR <30	Contraindicated if GFR <30	Fine for renal failure (no dose adjustment)	OK, but need dose reduction & careful titration
Monitoring	Anti-Xa level (optimally) PTT (less optimal)	Anti-Xa level 4 hrs post dose	Anti-Xa level 4 hrs post dose	PTT level	PTT level
Antidote?	Protamine Highly effective	Protamine, Partially effective	No antidote Long half-life 😊	No antidote (short half-life)	No antidote (very short half-life)
Risk of HIT	Highest risk (absolute risk usually low; depends on dose & clinical context).	Considerably lower than unfractionated heparin.	No risk	No risk	No risk
Typical role in ICU	Workhorse anticoagulant (especially in patients with renal insufficiency or need for procedures).	Good for patients with adequate renal function, no anticipated procedures & adequate dermal blood perfusion.	Low dose (2.5 mg QD) excellent for prophylaxis and/or acute coronary syndrome. Long half-life makes therapeutic anticoagulation awkward.	- Treatment of HIT. - Treatment of heparin resistance.	- Treatment of HIT. - Anticoagulation for ECMO, cardiothoracic surgery.

From multiple sources including Goodman & Gilman's textbook 13th edition page 589; Burstein et al. 2019.

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UFH vs. LMWH

- LMWH is generally preferable for the following reasons:
 - LMWH is easier to give logistically (doesn't require IV infusion or monitoring).
 - LMWH has a decreased risk of heparin induced thrombocytopenia with thrombosis (HIT).
 - Studies comparing UFH and LMWH generally show that LMWH is more effective and causes less bleeding.
- However, UFH is still needed in the following situations:
 - Renal failure (GFR < 30 ml/min).
 - Need to rapidly stop anticoagulation (e.g., in a patient at risk for bleeding, or pending a procedure).

LMWH vs. Fondaparinux

- LMWH is generally preferable in the ICU because it has a shorter duration of action (half-life of ~4 hours versus ~20 hours). Therapeutic fondaparinux is problematic if the patient starts bleeding or requires an unexpected procedure. Furthermore, fondaparinux has no reversal

agent (unlike LMWH, which can be ~50% reversed with protamine).

- Fondaparinux has the advantage of never causing HIT, so:
 - Fondaparinux can be used in a patient with a history of HIT.
 - Fondaparinux use simplifies the workup for new-onset thrombocytopenia (you don't need to worry about HIT).
- In general ICU practice, fondaparinux is used mostly at a low ("prophylactic") dose of 2.5 mg sq. daily.
 1. May be used for DVT prophylaxis.
 2. This *same dose* is preferred therapy for patients with NSTEMI based on the [OASIS-5 trial](https://www.ncbi.nlm.nih.gov/pubmed/16250000).
(<http://www.nejm.org/doi/pdf/10.1056/NEJMoa055443>)

risk assessment

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Any decision in medicine should ideally be informed by weighing the risks versus benefits. Validated risk scores for hemorrhage exist, but only for outpatients on oral anticoagulation. To date, no such scores exist for inpatients being treated with parenteral anticoagulation. In the absence of a validated risk score, the following factors may warrant special consideration:

- **Bleeding history**, especially:
 - More severe bleeding episodes (e.g., any CNS bleeding)
 - More *recent* bleeding
- **Coagulopathy**, for example:
 - Thrombocytopenia (e.g., <30 billion/L is an absolute contraindication)([Klok 2020](https://www.ncbi.nlm.nih.gov/pubmed/32000000)
(<https://ashpublications.org/blood/article/135/10/724/431044/How-I-assess-and-manage-the-risk-of-bleeding-in>.)
 - Simultaneous use of other anticoagulants (e.g., anti-platelet agents)
 - Renal failure (uremia causes platelet dysfunction)
 - Liver disease
- **Vasculopathy**, for example:
 - Older age
 - Chronic uncontrolled hypertension
- **CNS disease** (e.g., prior intracranial hemorrhage, vascular malformation, active malignancy)

dosing & monitoring of unfractionated heparin

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pharmacology of UFH

- UFH is a heterogeneous mixture of different length strands of heparin. It sticks to endothelial cells, macrophages, and various heparin-binding proteins. This makes its pharmacokinetics unpredictable, requiring monitoring.
- UFH generally has a half-life of about an hour, so it may be shut off 4-6 hours before a surgical procedure.

monitoring UFH infusions: PTT vs. anti-Xa levels

- Heparin infusion may be monitored either with PTT or anti-Xa activity.
- Physiology of anti-Xa versus PTT:
 - PTT is a more *integrative* test, depending on several coagulation factors. This could theoretically make PTT a better reflection of the entire coagulation cascade. However, this also makes it more challenging to achieve stable PTT levels over time.
 - Anti-Xa levels depend on fewer factors (essentially the heparin concentration and anti-thrombin III levels) – which makes it less variable.
- Advantages of using anti-Xa levels:
 - (1) Anti-Xa levels may provide a more accurate measurement of the physiologic effect of heparin.
 - (2) Anti-Xa levels tend to be more stable over time, thus leading to fewer dose adjustments.
 - (3) Anti-Xa levels are not affected by lupus anticoagulant (which may cause aberrantly elevated PTT values).
 - (4) Patients with acute inflammation or pregnancy may have elevated factor VIII levels, which may tend to decrease the PTT. Anti-Xa monitoring may be preferred in this situation.

- Advantages of PTT levels:
 - Theoretically, PTT levels could provide a more holistic view of coagulation, which in some situations could be a more accurate measurement of the true biological clotting tendency (e.g., following thrombolysis).
- Overall, most hospitals seem to be moving towards monitoring heparin infusions based on Xa levels, rather than PTT values. There is no patient-centered evidence that one monitoring system is superior to the other.

portable heparin protocol

- It's best to use your hospital's heparin protocol.
 - Various protocols differ slightly. If using PTT, hospitals may adjust their protocol based on the PTT reagent used in their lab.
- The below protocol isn't recommended for daily use. Rather, it's merely intended as a rough guide to the significance of various PTT and Xa levels.

portable heparin infusion protocol for DVT/PE

PTT level	Anti-Xa level	Dose change (U/kg/hr)	Additional action
PTT <25 sec (<1.2 x normal)	<0.1	+4	Rebolus 80 IU/kg
PTT 35-45 sec (1.2-1.5 x normal)	0.1-0.3	+2	Rebolus 40 IU/kg
PTT 46-70 sec (1.5-2.3 x normal)	0.3-0.7	0	None: Perfect
	0.7-0.8	-1	None
PTT 71-90 sec (2.3-3 x normal)	0.8-1	-2	None
PTT >90 sec (>3 x normal)	>1	-3	Hold infusion for 1 hour

To begin infusion: Bolus with 80 IU/kg heparin and start the infusion at 18 U/kg/hr.
If weight >130 kg, use *adjusted body weight* (basically the average of ideal & actual weights)

<https://iz.wp.com/emcrit.org/wp-content/uploads/2018/01/porthept.gif>

heparin resistance

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definition

- Heparin resistance is generally defined as either requiring >35,000 IU/day heparin to achieve therapeutic anticoagulation or being unable to achieve therapeutic anticoagulation ([Durrani et al 2018](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5998275/) (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5998275/>)).
- Consider evaluating for heparin resistance if the infusion is increasing above ~25 units/kg/hr.

differentiation from pseudo-heparin resistance

- Definition of pseudo-heparin resistance: elevation of factor VIII and/or fibrinogen decreases the PTT, making it difficult to achieve a target PTT ([Downie 2019](https://www.ncbi.nlm.nih.gov/pubmed/31076959/) (<https://www.ncbi.nlm.nih.gov/pubmed/31076959/>)).
 - Elevated levels of factor VIII and/or fibrinogen are usually due to systemic inflammation. Other causes include pregnancy, malignancy, liver disease, and renal disease ([Kennedy et al. 2013](https://www.ncbi.nlm.nih.gov/pubmed/23737512/) (<https://www.ncbi.nlm.nih.gov/pubmed/23737512/>)).
- The PTT makes it *appear* that the patient isn't therapeutically anticoagulated, but in fact the patient is experiencing clinical anticoagulation! This is potentially dangerous, because persistent up-titration of heparin in attempts to increase the PTT could actually lead to iatrogenic hemorrhage due to excessively high heparin concentration.
- Diagnosis of pseudo-heparin resistance:
 - The key to the diagnosis is measuring the anti-Xa activity (a more accurate measurement of heparin effect which *won't* be affected by factor VIII and/or fibrinogen).
 - Factor VIII and fibrinogen levels may also be measured directly, to provide some indirect support to the diagnosis (although these tests often take a while to return).
- Management:
 - Pseudo-heparin resistance is fundamentally a *monitoring failure*. Management involves avoiding the use of PTT to titrate the heparin infusion, for example:
 - (1) If anti-Xa monitoring is available, this should be used to titrate the heparin infusion.
 - (2) Another alternative could be to transition to therapeutic low molecular molecular-weight heparin if that is an option (e.g., if renal function is adequate and no procedures are anticipated).

- As many hospitals are shifting towards the routine use of anti-Xa levels for all monitoring of heparin infusions, the entity of pseudo-heparin resistance may disappear. Unfortunately, a similar phenomenon can occur with direct thrombin inhibitors – which may be even harder to diagnose (more on this [below](#) ([#direct_thrombin_inhibitors_\(DTIs\)](#))).

causes of heparin resistance

- [1] Pseudo-heparin resistance** (see above; due to increases in factor VIII and/or fibrinogen)
- [2] Heparin concentration is genuinely low**
 - Increases in heparin binding to leukocytes, endothelial cells, and acute-phase proteins (e.g., platelet factor 4). This usually results from systemic inflammation.
 - Increased heparin clearance (e.g., due to splenomegaly).
- [3] Antithrombin-III deficiency**, which is most commonly due to:
 - Disseminated intravascular coagulation (DIC) or acute thrombosis
 - Liver disease (mostly cirrhosis)
 - Nephrotic syndrome
 - ECMO or hemodialysis
 - Surgery or trauma (anti-thrombin III levels often nadir ~3 days postoperatively)([Durrani et al 2018](#) (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5998275/>)).
 - Pregnancy (especially with preeclampsia)
 - Heparin itself can reduce anti-thrombin levels* ([Marciniak et al 1977](#) (<https://europepmc.org/article/MED/71399>)).

investigation & management of heparin resistance				
Cause of heparin resistance	anti-Xa level	PTT level	Antithrombin-III level	Treatment
Pseudo-heparin resistance (Increased levels of factor VIII and fibrinogen due to inflammation)	Therapeutic	Low	Normal or moderately low	Dose heparin based on Xa level -or- Transition to low molecular-weight heparin
Genuinely low heparin concentration - Increased heparin clearance - Increased heparin-binding proteins	Sub-therapeutic	Sub-therapeutic	Normal or moderately low	Increase heparin dose -or- Transition to direct thrombin inhibitor
Antithrombin-III deficiency	Sub-therapeutic	Sub-therapeutic	Severely reduced (e.g. <40-50%)	May give antithrombin-III -or- Transition to direct thrombin inhibitor

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evaluation: heparin resistance panel

- In practice, critically ill patients may often have *several* factors contributing to heparin resistance. Thus, for the sake of efficiency it may make sense to obtain the following panel of studies simultaneously:
 - PTT level (if that was previously being used to titrate the heparin infusion)
 - anti-Xa level
 - Factor VIII level & Fibrinogen level
 - Anti-thrombin III level

management step #0: the basics

- If therapeutic anticoagulation is *achievable*, then no intervention is necessary (although some investigation may be prudent to exclude pseudo-heparin resistance).

management step #1: titrate based on anti-Xa levels

- If previously titrating heparin infusion against PTT, check an anti-Xa level and ensure that this correlates with the PTT level.
- Titration of heparin infusion to target an Xa level is generally superior to targeting PTT in the context of heparin resistance ([Levine 1994](#) (<https://www.ncbi.nlm.nih.gov/pubmed/8267489>)).

management step #2a: if Antithrombin-III level is adequate (>40-50%) & anti-Xa levels are sub-therapeutic

- (1) May consider increasing the heparin infusion
 - The exact maximal rate of heparin infusion is unclear. One case report describes the successful use of >50,000 units/day of heparin ([Durrani et al 2018](#) (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5998275/>)).
- (2) Transition to a direct thrombin inhibitor (e.g., argatroban or bivalirudin).
 - This avoids the entire issue of heparin resistance.

management step #2b: if antithrombin-III level is low (<40-50%) & anti-Xa levels are sub-therapeutic

- There are two general treatment options in this situation:
 - (i) Administration of antithrombin-III concentrates along with ongoing administration of heparin infusion.
 - (ii) Transition to a direct thrombin inhibitor (e.g., argatroban or bivalirudin).
- There is no high-quality evidence regarding optimal management here.
- Transition to a direct thrombin inhibitor might be superior, for the following reasons:
 - (1) Evidentiary support for the use of direct thrombin inhibitors in the ICU is greater than for the use of antithrombin-III concentrates. For example, many studies describe the use of argatroban infusions among ICU patients, including specifically patients with heparin resistance ([Bachler et al. 2020 \(https://pubmed.ncbi.nlm.nih.gov/32244368/\)](https://pubmed.ncbi.nlm.nih.gov/32244368/)). Alternatively, the use of antithrombin-III concentrate supplementation seems to be limited to case studies. As such, the safety of antithrombin-III is difficult to evaluate.
 - (2) Simultaneous dosing with antithrombin-III and heparin is complex and potentially dangerous. The two drugs interact in a synergistic fashion, so they must be combined with considerable caution and sophistication. In contrast, transitioning to argatroban monotherapy is straightforward and easily achieved with standard ICU protocols.
 - (3) Antithrombin-III is extremely expensive ([Salas et al. 2013 \(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3875262/\)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3875262/)).
 - (4) Many critically ill patients may have multi-factorial heparin resistance (e.g., low anti-thrombin III levels, elevated factor VIII, and increased heparin metabolism). Administration of antithrombin-III won't fully resolve this situation.
 - (5) Heparin itself may be a contributor to low antithrombin-III levels. Thus, continuing heparin may theoretically perpetuate an iatrogenic cycle of heparin use, antithrombin-III reduction, and antithrombin-III repletion.

various LMWH agents and dosing[\(back to contents\) \(#top\)](#)**several LMWH formulations are available (including enoxaparin, dalteparin, and nadroparin)**

- The greatest experience exists with enoxaparin, especially in terms of monitoring anti-Xa levels.
 - Thus, enoxaparin is a preferred agent – especially in patients with unusual weight or pharmacokinetics.
- However, enoxaparin doses may be roughly correlated into dalteparin doses as follows below.
- Dosing with tinzaparin and nadroparin is less clear, as different formulations may have variable amounts of anti-Xa activity.

understanding dosing differences between enoxaparin and dalteparin

- 1 mg enoxaparin has 100 units of anti-factor Xa activity (e.g., 40 mg enoxaparin = 4,000 units of anti-Xa).
- 1 mg of dalteparin has 156 units of anti-factor Xa activity. Dalteparin is typically measured in terms of anti-Xa units, rather than in milligrams.
- *So: (dalteparin dose measured in units)/100 is roughly the equivalent enoxaparin dose in mg.* For example, 5000 units of dalteparin is roughly equivalent to 50 mg of enoxaparin.
 - However, the ratio of anti-Xa vs. anti-IIa may vary between different medications, so it cannot be assumed that the two drugs are interchangeable.

enoxaparin dosing for full anticoagulation[\(back to contents\) \(#top\)](#)**full therapeutic dosing**

- Generally, enoxaparin is dosed uniformly (1 mg/kg q12 hours for GFR>30).
- Recently, some authors have suggested dosing enoxaparin in a more finely graded fashion as shown below for patients with borderline renal function ([Shaikh 2017 \(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5358682/pdf/ptj4204245.pdf\)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5358682/pdf/ptj4204245.pdf)). This dosing scheme has yet to gain widespread acceptance, but it might be a consideration in very select situations (with close monitoring of anti-Xa levels).
 - GFR > 50 ml/min: 1 mg/kg q12hr
 - GFR 40-50 ml/min: 0.6 mg/kg q12hr
 - GFR 30-40 ml/min: 0.5 mg/kg q12hr
 - GFR 20-30 ml/min: May consider 0.4 mg/kg q12hr with Xa monitoring

monitoring anti-Xa level

- Indications
 - Borderline renal function
 - Unusual weight (<50 kg or >150 kg)
 - Pregnancy
 - Unexpected bleeding
 - Before emergent procedure
- Check anti-Xa level 4 hours after administering the dose (peak blood level) and adjust as shown below.
 - LMWH has a greater effect on anti-Xa and less effect on thrombin (factor IIa) compared to UFH. This means that LMWH doesn't strongly affect the PTT, and cannot be monitored by measuring the PTT level.

adjustment of enoxaparin based on anti-Xa level (q12hr dosing, targeting full anticoagulation)

Anti-Xa level 4 hours after dose	Management
<0.4	Increase dose by 25%, repeat
0.4-0.6	Increase dose by 10%, repeat
0.6-1	No change
1.1-1.5	Decrease by 20%, repeat
1.6-2	Hold next dose 3 hours, decrease 30%
>2	Hold enoxaparin Check Xa level q12hr When Xa < 0.6, consider restart with 40% decreased dose Follow renal & liver function carefully* Consider transition to heparin infusion

*Enoxaparin metabolism partially occurs in the liver, where it is desulfated and/or depolymerized into smaller molecules with less anticoagulant activity.

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enoxaparin dosing for DVT prophylaxis

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#1) patients who are *not* critically ill

- For very low-weight patients: 30 mg sq. daily
- Most patients with average weight: 40 mg sq. daily
- For patients with morbid obesity: may consider 0.5 mg/kg sq. daily

#2) enoxaparin for DVT prophylaxis in critical illness

- Increased dosing of enoxaparin may be beneficial for critically ill patients for several reasons:
 - i) Patients are generally at increased risk of DVT (compared to less ill patients).
 - ii) Inflammation triggers increased levels of acute-phase reactant proteins, which may reduce the effectiveness of heparin.
- Numerous recent studies seem to be converging on a dose of **0.5 mg/kg enoxaparin BID** ([Parikh 2015](#) (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5990203/>), [Bethea A et al 2019](#) (<https://pubmed.ncbi.nlm.nih.gov/30954541/>), [Walker CK et al 2017](#) (<https://pubmed.ncbi.nlm.nih.gov/28228055/>), [Pannucci CJ et al 2018](#) (<https://pubmed.ncbi.nlm.nih.gov/29649055/>)). This dose has the following advantages:
 - i) Twice-daily dosing avoids sub-therapeutic trough levels (it's possible that the trough levels are the primary determinant of efficacy).
 - ii) Unusual weight has been shown to be a primary predictor of inappropriate dosing. Correcting the dose for weight increases the likelihood of obtaining target drug levels.
 - iii) Many protocols involve a variety of arbitrary cutoffs and tiers based on weight and body mass index. Using a single formula is simpler to apply and more closely mirrors the pharmacokinetics of enoxaparin (which is linear).
- For patients with very unusual weight or borderline renal function, consider obtaining an anti-Xa level to monitor the heparin effect. This is typically done after the third dose, but could probably be done sooner (unless renal function is really awful, the trough heparin levels will be low and won't contribute substantially to the following peak level).

monitoring Xa level for prophylactic enoxaparin

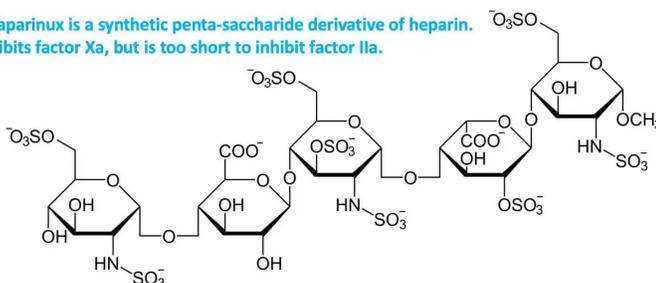
- Indications:

- Pregnancy
- Borderline renal function (note that GFR <30 ml/min is a contraindication to enoxaparin)
- Morbid obesity
- Anti-Xa assay should be done 4 hours after dose, to obtain a peak level.
- Target anti-Xa level ([Pannucci CJ et al 2018 \(https://pubmed.ncbi.nlm.nih.gov/29649055/\)](https://pubmed.ncbi.nlm.nih.gov/29649055/)):
 - For once-daily prophylactic enoxaparin, the target anti-Xa level is 0.3-0.5 IU/ml.
 - For twice-daily prophylactic enoxaparin, the target anti-Xa level is 0.2-0.4 IU/ml.

fondaparinux

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Fondaparinux is a synthetic penta-saccharide derivative of heparin. It inhibits factor Xa, but is too short to inhibit factor IIa.



basics of fondaparinux

- Fondaparinux is essentially a synthetic derivative of LMWH.
 - It is provided in relatively fixed doses, usually q24hrs.
 - Fondaparinux is contraindicated in patients with renal dysfunction (GFR < 30 ml/min).
 - It works via enhancing anti-thrombin's inhibition of factor Xa.
- Advantages of fondaparinux over LMWH
 - Doesn't cause HIT
 - Fondaparinux can be used in patients with suspicion for HIT.
 - Use of fondaparinux can help avoid unnecessary workup and empiric therapy for possible HIT.
 - Use of 2.5 mg fondaparinux can *double* as DVT prophylaxis and treatment for acute coronary syndrome.
- Disadvantages of fondaparinux compared to LMWH
 - Fondaparinux may be more expensive.
 - Fondaparinux has a very long half-life at 17-21 hours. This can be problematic if the patient needs an urgent procedure or develops bleeding.
 - Enoxaparin can be about 50% reversed by protamine, but no reversal agent exists for fondaparinux.
 - Dosing algorithms using anti-Xa levels are better established for LMWH than for fondaparinux.

contraindications to fondaparinux

- Renal dysfunction (GFR < 30 ml/min).
- Weight < 50 kg.
- Possible procedure in near-term.

dosing

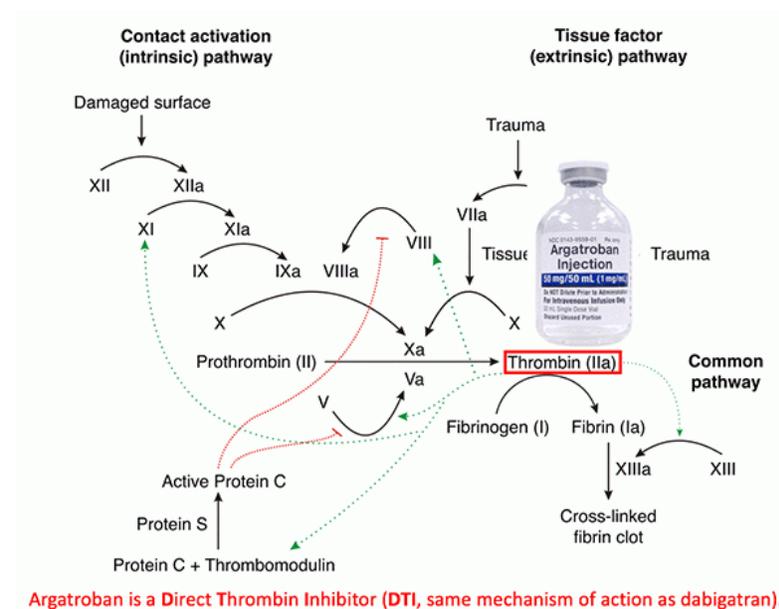
- DVT prophylaxis: 2.5 mg sq. q24 hours.
- Full therapeutic anticoagulation:
 - Weight <50 kg: 5 mg q24 hr.
 - Weight 50-100 kg: 7.5 mg q24 hr.
 - Weight >100 kg: 10 mg q24 hr.
- [Medscape monograph \(https://reference.medscape.com/drug/arixtra-fondaparinux-342172\)](https://reference.medscape.com/drug/arixtra-fondaparinux-342172), on fondaparinux.

monitoring

- Overall this is very similar to monitoring for LMWH.
- Monitoring generally isn't necessary, but may be indicated in specific situations (e.g., weight <50 kg or >150 kg, pregnancy, or borderline renal function).
- An anti-Xa level may be obtained three hours after a dose of fondaparinux. Target ranges are roughly ~0.2-0.5 IU/ml for prophylaxis or ~0.5-1.5 IU/ml for a therapeutic dose.
 - However, a specific calibration curve should be used for fondaparinux – if doubt exists about which test and cutoff values to use, discuss with the laboratory. Many hospitals will lack a fondaparinux-calibrated anti-Xa level assay.

direct thrombin inhibitors (DTIs)

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basic properties

- These act via direct inhibition of thrombin (factor IIa). This has numerous physiologic effects as shown above (e.g., inhibits activation of factors V, VIII, and XI).
- They are active against both fluid-phase and clot-bound thrombin (unlike heparin, which acts only on fluid-phase thrombin).
- These prolong the INR, PTT, and the thrombin time (TT) (because they impair the final common pathway of clot formation).
 - PTT prolongation is generally used to titrate the dose of a direct thrombin inhibitor.
 - INR prolongation is problematic, as this can make it difficult to transition to warfarin.
 - Assays for clotting factors and fibrinogen may be falsely prolonged (causing the lab to register falsely low values).

advantages of direct thrombin inhibitors compared to heparin

1. They avoid the issue of heparin-induced thrombocytopenia (or any concerns about this possibility).
2. They are not dependent on anti-thrombin III levels
3. Pharmacokinetics are generally more predictable than those of heparin (especially bivalirudin, which doesn't bind to plasma proteins).
4. Bivalirudin's short half-life (25 minutes) may make it easier to stop, compared to a heparin infusion (with half-life close to 45 minutes).

disadvantages compared to heparin

1. Less widespread experience and less universally available.
2. Lack of any reversal agent. This could be problematic for patients with hepatic dysfunction on argatroban – wherein the half-life may be considerable.

selection of different agents

- Argatroban has traditionally been used more in the ICU (especially as a front-line agent for patients with HIT or suspected HIT).

- Bivalirudin has traditionally been used more in the cardiac catheterization laboratory. More recently, bivalirudin has been used increasingly in ICUs as an anticoagulant for ECMO.
- Properties of the two agents are compared here:

	Argatroban	Bivalirudin
Half-life	45 minutes ~180 minutes (hepatic impairment)	25 minutes with normal renal function
Metabolism/excretion	Hepatic metabolism	Largely metabolized by serum proteases 20% excreted by kidneys
Protein binding	20% albumin 34% alpha-acid glycoprotein	None
Dose reduction for	Multi-organ failure Hepatic dysfunction especially	Renal dysfunction

From multiple sources including Burstein et al. 2019

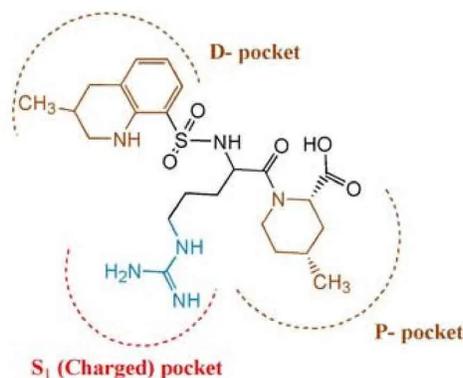
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direct thrombin inhibitor pseudo-resistance

- True resistance doesn't seem to occur with direct thrombin inhibitors (because unlike heparin, their pharmacology is more predictable and their efficacy doesn't depend on anti-thrombin III).
- Pseudo-resistance can occur with both argatroban and bivalirudin ([Kennedy et al. 2013](https://www.ncbi.nlm.nih.gov/pubmed/23737512) (<https://www.ncbi.nlm.nih.gov/pubmed/23737512>); [Poyant et al. 2019](https://www.ncbi.nlm.nih.gov/pubmed/31694454) (<https://www.ncbi.nlm.nih.gov/pubmed/31694454>), [Walker et al 2019](https://www.ncbi.nlm.nih.gov/pubmed/29538017) (<https://www.ncbi.nlm.nih.gov/pubmed/29538017>), [Cardinale et al 2016](https://www.ncbi.nlm.nih.gov/pubmed/28057952) (<https://www.ncbi.nlm.nih.gov/pubmed/28057952>)).
 - This is essentially the same as pseudo-heparin resistance (discussed above).
 - PTT values are aberrantly low due to excessive levels of factor VIII and/or fibrinogen (usually due to inflammation). This creates a dangerous situation where it falsely appears that the patient is resistant. Ongoing up-titration of the direct thrombin inhibitor in efforts to increase the PTT can cause hemorrhage.
- Pseudo-resistance may be suspected if:
 - An unusually high dose of direct thrombin inhibitor is required, or if it is impossible to achieve a therapeutic PTT.
 - A baseline *reduction* in PTT might also support pseudo-resistance.
- Diagnostic evaluation:
 - In the case of argatroban, drug levels may be checked if this test is available (unfortunately, many hospitals may lack this).
 - Thrombin time may be a better measurement of direct thrombin effect than PTT ([Beiderlinden et al. 2018](https://www.ncbi.nlm.nih.gov/pubmed/29426286) (<https://www.ncbi.nlm.nih.gov/pubmed/29426286>)). If the thrombin time is considerably elevated, this may support a diagnosis of pseudo-resistance.
 - Marked elevation of factor VIII also supports the diagnosis of pseudo-resistance.
- Management
 - If argatroban levels are available with a rapid turn-around time, then argatroban could be continued with a transition towards monitoring based on argatroban levels (rather than PTT). Unfortunately, this currently isn't an option in most hospitals.
 - An alternative form of anticoagulation is generally needed, one that doesn't rely on PTT for dose titration.

argatroban

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Argatroban was designed to bind to the catalytic site of thrombin, thereby inhibiting it.

Sinauridze El et al 2011

basics

- Argatroban is a small molecule which directly inhibits thrombin (factor IIa)(figure above).
- Argatroban is cleared by the liver with a ~45-minute half-life. In patients with normal hepatic function, coagulation will normalize about 2-4 hours after stopping the infusion. The half-life may extend to ~3 hours in patients with hepatic dysfunction. Argatroban may be used in patients with liver dysfunction, but lower doses should be used and it may be harder to rapidly discontinue anticoagulation.

dosing & monitoring

- For ICU patients with multi-organ failure (and *especially* with hepatic dysfunction) a low starting dose is safest (~0.3 ug/kg/min). In patients with otherwise intact organ function, a higher starting dose may be considered (~1.5 ug/kg/min).
 - Use caution in patients with hepatic dysfunction (e.g. serum bilirubin >1.5 mg/dL)([Sedhai et al 2020](#) (<https://www.ncbi.nlm.nih.gov/books/NBK555971/>)).
- Titration is based on the PTT value, with a goal PTT of ~1.5-2.5 times normal (table below).
- Make sure to obtain a baseline PTT before starting the argatroban infusion (and possibly a thrombin time as well)([Beiderlinden et al. 2018](#) (<https://www.ncbi.nlm.nih.gov/pubmed/29426286>)).
 - If the PTT is elevated at baseline and this is unrecognized, it may lead to sub-therapeutic argatroban dosing (“PTT confounding”).
 - If the PTT is reduced at baseline, this could lead to problems with argatroban pseudo-resistance (discussed below).
 - The optimal target PTT might be 1.5-3 times the baseline value ([Sedhai et al 2020](#) (<https://www.ncbi.nlm.nih.gov/books/NBK555971/>)).

However, sources disagree about whether to target PTT to the *patient's* baseline or to the *laboratory* baseline.
- [Medscape monograph](#) (<https://reference.medscape.com/drug/acova-argatroban-342145>) on argatroban.

adjustment of argatroban infusion based on PTT

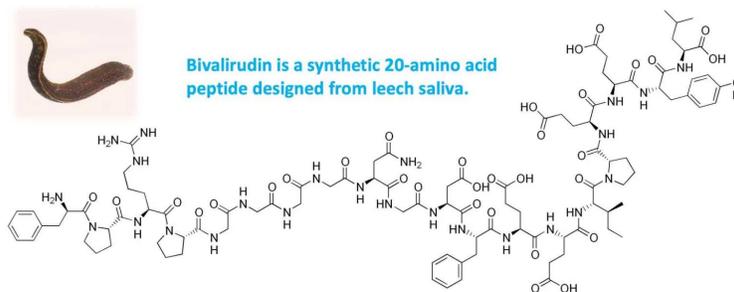
PTT level*	Normal end organ function	Impaired end organ function
<35 seconds	Increase by 0.5 mcg/kg/min	Increase by 0.2 mcg/kg/min
35-49 seconds	Increase by 0.25 mcg/kg/min	Increase by 0.1 mcg/kg/min
50-74 seconds	No change	
75-90 seconds	Decrease by 0.25 mcg/kg/min	Decrease by 0.1 mcg/kg/min
91-120 seconds	Decrease by 0.5 mcg/kg/min	Decrease by 0.2 mcg/kg/min
>120 seconds	Stop infusion, Repeat PTT STAT	

*PTT levels should be checked q3hours. If the PTT is within therapeutic range for two checks, this may be stretched out to q6hr.

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bivalirudin

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basics

- Bivalirudin is a synthetic 20-amino acid long peptide designed to mimic the active site of hirudin, an anticoagulant produced by the medicinal leech *Hirudo medicinalis*. Along with argatroban, it is an intravenous direct thrombin inhibitor.
- Given its peptide structure, bivalirudin is partially metabolized by serum proteases. Additionally, ~20% of its clearance is due to renal excretion (Bohman et al. 2019 (<https://www.ncbi.nlm.nih.gov/pubmed/30299300>)). Dose adjustment is necessary in renal insufficiency.
 - Cleavage by serum proteases may help achieve stable serum levels in the face of fluctuating organ function. However, this can also lead to pockets of low bivalirudin levels in regions of low-flow, stagnant blood, which may lead to thrombus formation (which is mostly an issue with ECMO and cardiac surgery).

dosing & monitoring

- The initial infusion rate may vary depending on renal function (see table below). Maintenance infusion rates typically range from ~0.05 mg/kg/hr to 0.25 mg/kg/hr (Burstein et al. 2019 (<https://www.ncbi.nlm.nih.gov/pubmed/31750086>)).
- Use of a loading bolus may be important for some applications (e.g., emergency percutaneous coronary intervention or cardiothoracic surgery). However, for use as a maintenance anticoagulant in the ICU there is no clear requirement for a loading bolus.
- Doses >0.5 mg/kg/hr should be avoided; the requirement for such high doses may suggest pseudo-resistance (see *pseudo-resistance* in the section on [direct thrombin inhibitors \(#direct_thrombin_inhibitors_\(DTIs\)\)](#) (Walker et al 2019 (<https://www.ncbi.nlm.nih.gov/pubmed/29538017>)).
- Protocols:
 - When available, local protocols should be utilized.
 - A protocol from Yale is shown below (Cardinale et al. 2016 (<https://www.ncbi.nlm.nih.gov/pubmed/28057952>)). An identical protocol is used by the University of Washington ([here](http://depts.washington.edu/anticoag/home/content/bivalirudin-initial-dosing) (<http://depts.washington.edu/anticoag/home/content/bivalirudin-initial-dosing>), and [here](http://depts.washington.edu/anticoag/home/sites/default/files/Bivalirudin%20dosing%20algorithm_0.pdf) (http://depts.washington.edu/anticoag/home/sites/default/files/Bivalirudin%20dosing%20algorithm_0.pdf)).
 - Titration is based on the PTT value, with a goal PTT of ~1.5-2.5 times normal (table below)

Yale-New Haven Hospital Nurse-Driven Bivalirudin Dose Adjustment Protocol

Bivalirudin renal dose adjustment for treatment of heparin-induced thrombocytopenia (HIT)

Renal function	Initial rate
Creatinine clearance > 60 mL/min	0.15 mg/kg/h
Creatinine clearance 30 – 60 mL/min	0.08 mg/kg/h
Creatinine clearance < 30 mL/min	0.05 mg/kg/h
Hemodialysis (HD)	0.02 mg/kg/h
Continuous veno-venous hemofiltration (CVVH)	0.06 mg/kg/h

Monitoring and dose adjustments

PTT*	Dosage adjustment	Monitoring
<60	Increase rate by 20%	PTT every 2 hours until therapeutic
60–80	No change	PTT every 2 hours until 2 consecutive results are therapeutic then draw PTT daily
>80	Hold infusion for 1 hour, then decrease rate by 50%	PTT 2 hours after restarting

* Round partial thromboplastin time (PTT) to nearest whole number.

Source: Yale-New Haven Hospital Anticoagulation Management Program. Revised April 2015.

Cardinale M et al. Hosp Pharm 2016; 51:022

podcast

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<https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/apps.40518.14127333176902609.7be7b901-15fe-4c27-863c-7c0dbfc26c5c.5c278f58-912b-4af9-88f8-a65fff2da477.jpg>

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questions & discussion

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To keep this page small and fast, questions & discussion about this post can be found on another page [here \(https://emcrit.org/pulmcrit/parenteral-anticoagulants/\)](https://emcrit.org/pulmcrit/parenteral-anticoagulants/).



<https://i0.wp.com/emcrit.org/wp-content/uploads/2016/11/pitfalls2.gif>

- Don't give enoxaparin or (especially) fondaparinux to a patient who may need a procedure soon (especially lumbar puncture).
- Avoid antithrombin administration among patients with heparin resistance and borderline anti-thrombin-III levels (such patients often have multi-factorial heparin resistance, so anti-thrombin III won't work well).
- Beware of pseudo-heparin, pseudo-argatroban, and pseudo-bivalirudin resistance!
- Be careful of patients on multiple anticoagulants, or patients with multiple risks for bleeding (you can often get away with a single anti-clotting agent, but risk of bleeding multiples with additional agents).
- When in doubt, don't hesitate to seek help (especially from critical care pharmacists).

Going further:

- [Mythbusting enoxaparin 40 mg daily for DVT prophylaxis in critical illness \(https://emcrit.org/pulmcrit/40-enoxaparin/\)](https://emcrit.org/pulmcrit/40-enoxaparin/) (PulmCrit)

Image credits: [anticoagulation cascade \(https://en.wikipedia.org/wiki/Coagulation\)](https://en.wikipedia.org/wiki/Coagulation)

The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.

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