Anticoagulants:
A Review from a Pharmacist Perspective

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I DO NOT have a financial relationship with an ineligible company.

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Learning Objectives

Title: Anticoagulation Management

Speaker: Rebecca Lemus, PharmD

Learning Objectives:

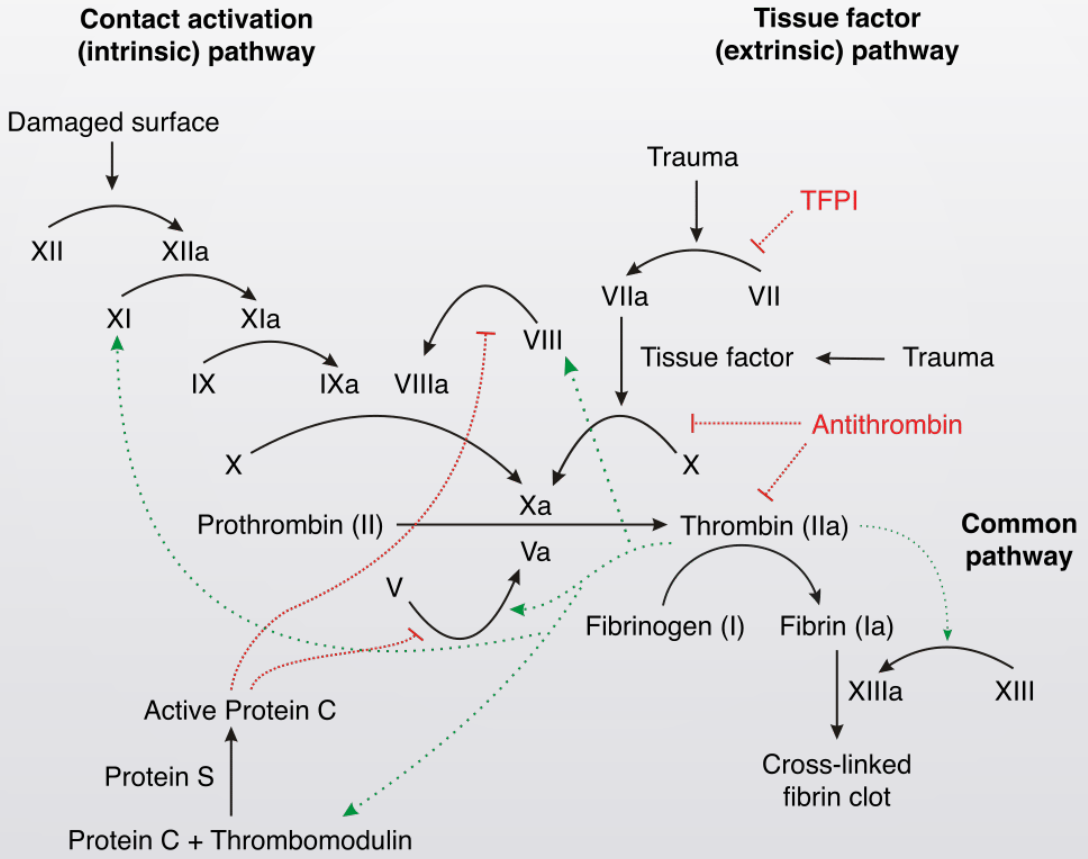
1. Describe the therapeutic role and use of anticoagulants
2. Explain appropriate dosing and adjustment considerations
3. Discuss methods of reversal and potential complications
4. Identify appropriate management and discontinuation of anticoagulants
5. Recognize special considerations
6. Demonstrate awareness of practice updates and current literature

Intrinsic Pathway versus Extrinsic Pathway

Intrinsic Pathway	Extrinsic Pathway
Multiple cascades of protein interactions activated by a trauma *inside blood vessels*	Multiple cascades of protein interactions activated by *damaged external surfaces*
Activated by internal trauma	Activated by external trauma
Factors involved: VIII, IX, XI, and XII	Factor involved: VII
Activation requirements: Ionized calcium	Activation requirements: Thromboplastin Calcium
Slower onset	Rapid onset
Activated clothing between 15 and 20 minutes	Activated clotting between 2 to 6 minutes

Need to cite: https://pediaa.com/difference-between-intrinsic-and-extrinsic-pathways-in-blood-clotting/#google_vignette

Intrinsic and Extrinsic Pathways

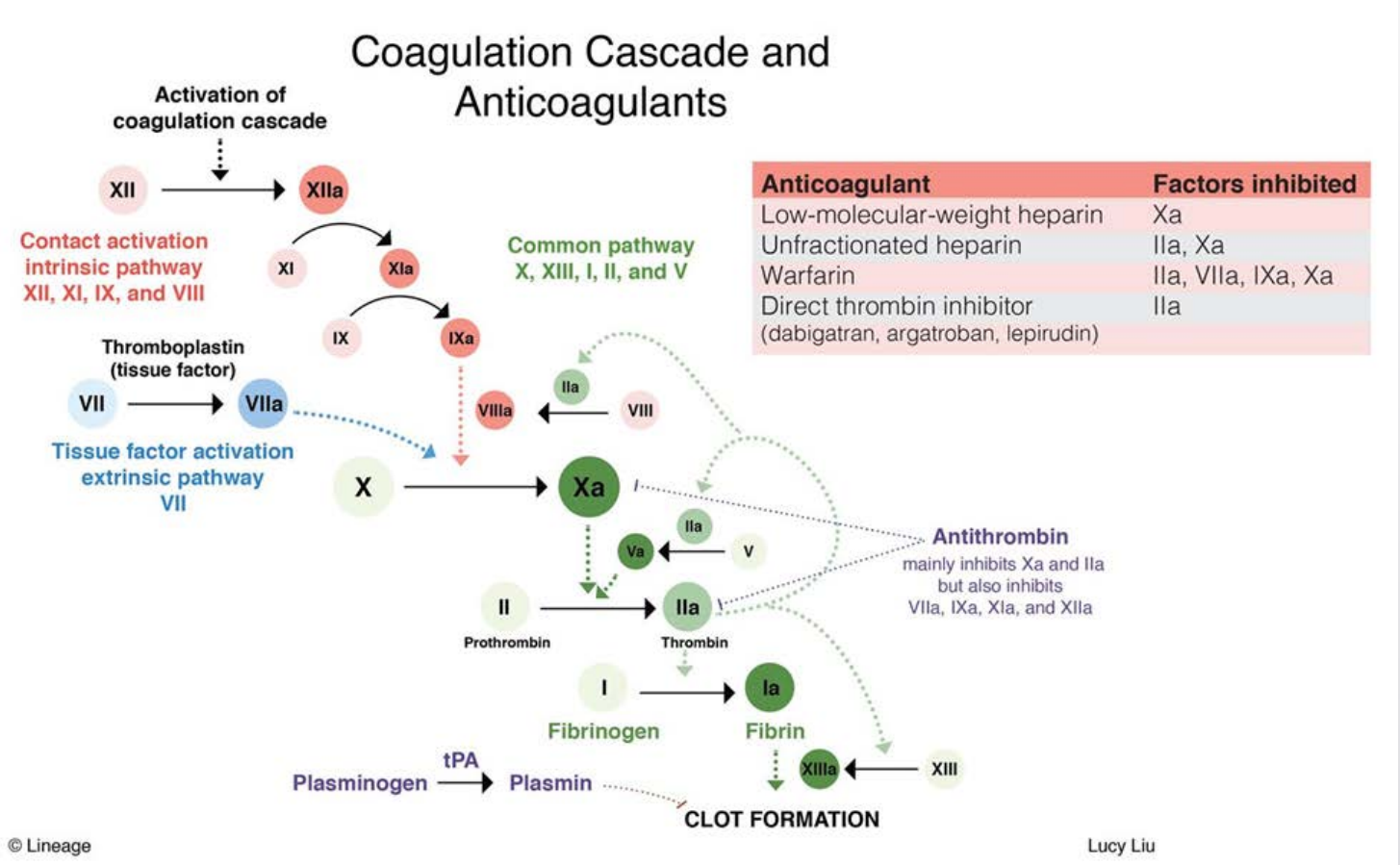


Need to cite: https://teachmephysiology.com/immune-system/haematology/coagulation/

Anticoagulants

- Low-molecular-weight heparin: dalteparin, enoxaparin
- Unfractionated heparin
- Vitamin K antagonist: warfarin
- Direct-Acting Oral Anticoagulants (DOACs): apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban
- Direct thrombin inhibitors: argatroban, bivalrudin, dabigatran
- Fibrinolytic (thrombolytic): alteplase, reteplase, tenecteplase

Anticoagulant Targets



Need to cite: https://step1.medbullets.com/hematology/111030/anticoagulants

Intrinsic & Extrinsic Pathways and Evaluations

- Prothrombin Time (PT): evaluates coagulation factors VII, X, V, II, and I (fibrinogen); extrinsic pathway; evaluates ability to clot
  - International normalized ratio (INR): ensures that results from a PT test are the same from one lab to another
- Activated Partial Thromboplastin Time (aPTT): evaluates coagulation factors XII, XI, IX, VIII, X, V, II (prothrombin) and I (fibrinogen); intrinsic pathway; determines if blood-thinning therapy is effective

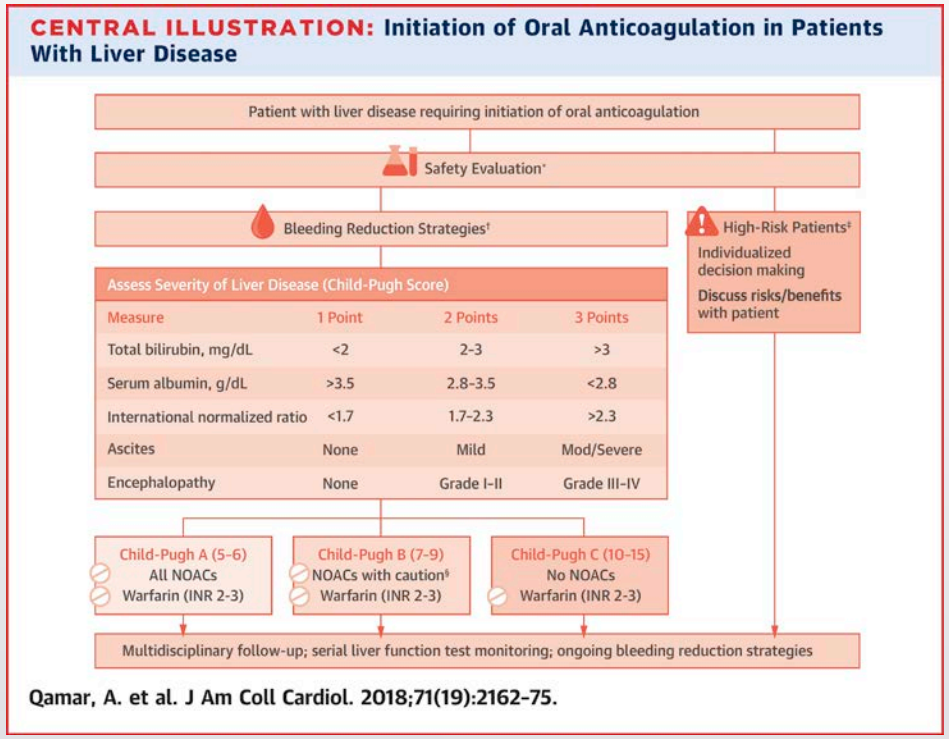
aPTT	PT	Pathway Affected/Interpretations
Increased	Normal	Intrinsic pathway
Increased	Increased	Common pathway or Multiple pathways
Normal	Increased	Extrinsic pathway or a rare condition

Need to cite: https://vn98.wordpress.com/2018/02/13/coagulation-cascade/
https://labpedia.net/coagulation-part-4-partial-thromboplastin-time-ptt-and-aptt/

Special Considerations Selecting Anticoagulation

- Hepatic dysfunction
- Renal dysfunction
- Pending procedures
- Pregnancy/Breastfeeding
- Patient values/adherence/preference
  - Monitoring requirements
  - Diet

Special Consideration: Hepatic Dysfunction

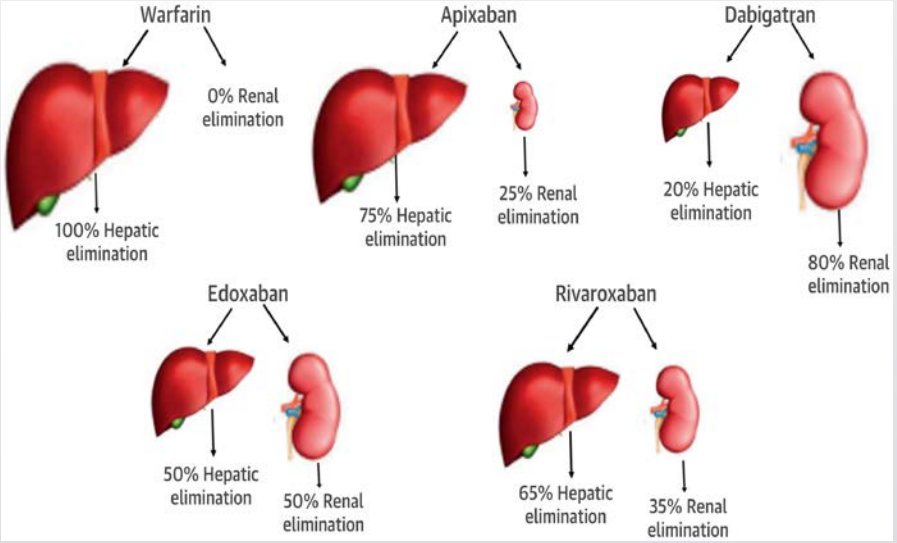


- VTE and bleeding events are increased in patients with liver disease compared with the general population
  - Antithrombin levels ~10-23% lower in patient with cirrhosis versus general population
  - Assumption made that patients are “auto-anticoagulated”
- Warfarin has traditionally been the OAC of choice for treatment and prevention of thrombotic complications in liver disease
  - No specific guidelines available for impaired liver function – complicated by elevated INR at baseline
- LMWH can be used in patient with cirrhosis but renal function is often overestimated in patient with decompensated cirrhosis – allowing bioaccumulation

Qamar, A, Vaduganathan, M, Greenberger, N. et al. Oral Anticoagulation in Patients With Liver Disease. J Am Coll Cardiol. 2018 May, 71 (19) 2162–2175.
Rodriguez-Castro KI, Simioni P, Burra P, Senzolo M. Anticoagulation for the treatment of thrombotic complications in patients with cirrhosis. Liver Int. 2012;32(10):1465-1476.

Special Consideration: Hepatic Dysfunction

- Randomized trials of DOACs routinely exclude patients with liver disease
  - Evidence regarding safety and efficacy predominately consists of PK studies, case reports, or small observational studies
- Keep in mind that all DOACs undergo some degree of hepatic metabolism
  - All are contraindicated in severe liver disease



Special Considerations: Renal Dysfunction

eGFR (mL/min)	UFH	LMWHs	Warfarin	Direct oral anticoagulants
>90	Yes	Yes	Yes	Yes
60-89	Yes	Yes	Yes	Yes
30-59	Yes	Yes	Yes	Rivaroxaban dose adjustment
15-29	Yes	Dose adjustments may be needed; bioaccumulation possible	Yes	Dabigatran contraindicated
		Enoxaparin use with caution		Apixaban and Rivaroxaban - use with caution
<15	Yes	Use contraindicated outside selected patients with appropriate monitoring	Yes	Rivaroxaban and dabigatran contraindicated

Need to cite: https://ashpublications.org/hematology/article/2016/1/188/21057/Thrombosis-and-anticoagulation-in-the-setting-of

Special Considerations: Renal Adjustments in DOACs

Reversal Agents

Reversal Agents: Potential Complications

PERIOPERATIVE BRIDGING

High Risk = Bridging advised

Moderate risk = case by case

Low risk = not advised

Which patients on warfarin should receive heparin bridging before surgery?

High risk for thromboembolism: bridging advised	Intermediate risk for thromboembolism: bridging on a case-by-case basis	Low risk for thromboembolism: bridging not advised
• Known hypercoagulable state as documented by a thromboembolic event and one of the following: Protein C deficiency Protein S deficiency Antithrombin III deficiency Homozygous factor V Leiden mutation Antiphospholipid-antibody syndrome • Hypercoagulable state suggested by recurrent (two or more) arterial or idiopathic venous thromboembolic events (not including primary atherosclerotic events, such as stroke or myocardial infarction due to intrinsic cerebrovascular or coronary disease) • Venous or arterial thromboembolism within the preceding 1-3 months • Rheumatic atrial fibrillation • Acute intracardiac thrombus visualized by echocardiogram • Atrial fibrillation plus mechanical heart valve in any position • Older mechanical valve model (single-disk or ball-in-cage) in mitral position • Recently placed mechanical valve (<3 mo) • Atrial fibrillation with history of cardioembolism	• Cerebrovascular disease with multiple (2 or more) strokes or transient ischemic attacks without risk factors for cardiac embolism • Newer mechanical valve model (eg, St. Jude) in mitral position • Older mechanical valve model in aortic position • Atrial fibrillation without a history of cardiac embolism but with multiple risks for cardiac embolism (eg, ejection fraction <40%, diabetes, hypertension, nonrheumatic valvular heart disease, transmural myocardial infarction within preceding month) • Venous thromboembolism >3-6 months ago*	• One remote venous thromboembolism (>6 mo ago)* • Intrinsic cerebrovascular disease (eg, carotid atherosclerosis) without recurrent strokes or transient ischemic attacks • Atrial fibrillation without multiple risks for cardiac embolism • Newer model prosthetic valve in aortic position

* For patients with a history of venous thromboembolism undergoing major surgery, consideration can be given to postoperative bridging therapy only (without preoperative bridging).

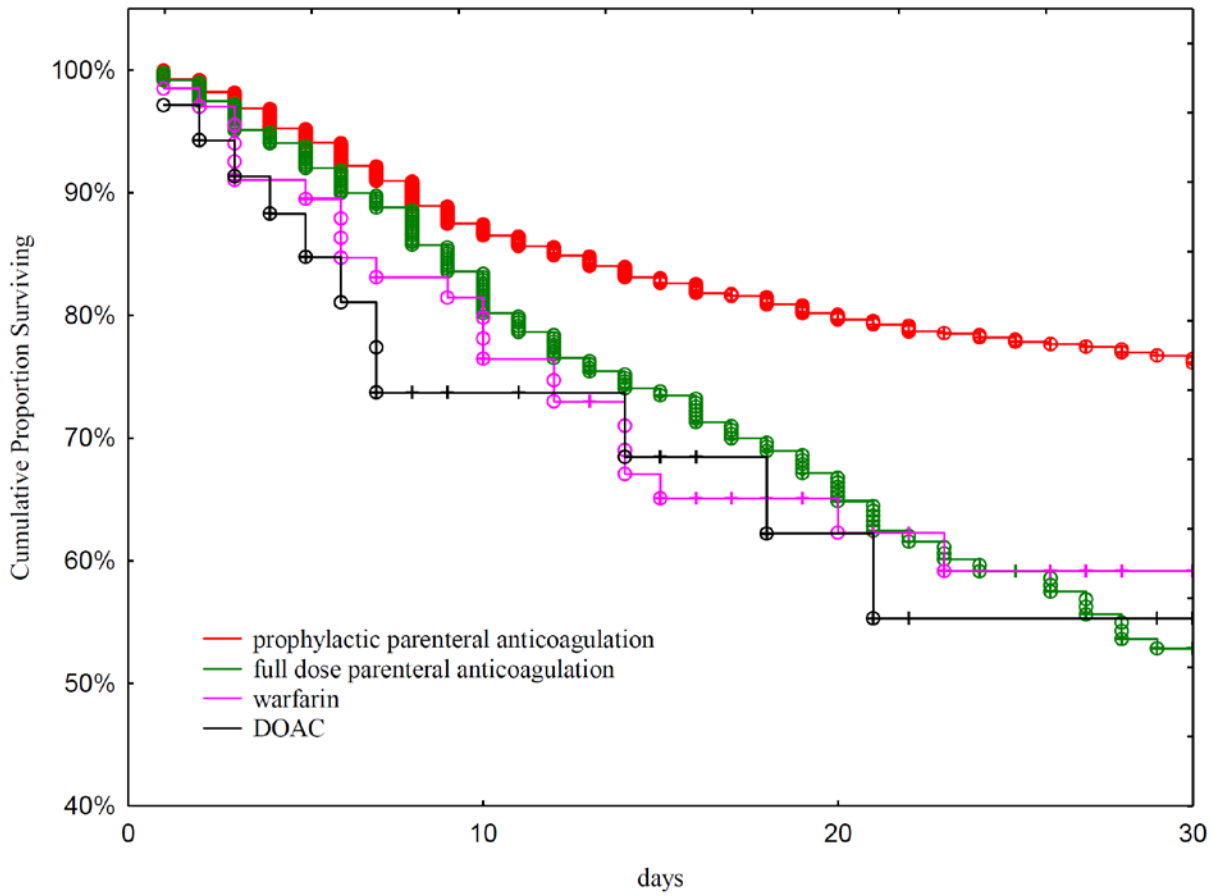
American College of Chest Physicians Evidence-Based Clinical Practice Guidelines 8th, 9th ed.

Douketis, James D., et al. "Perioperative bridging anticoagulation in patients with atrial fibrillation." *New England Journal of Medicine* 373.9 (2015): 823-833.

Remember COVID ?

5838 patients; standard prophylactic dosing fared best

Most benefit with invasive ventilation (53% vs 64%; $p = 0.05$)



Santoro, Francesco, et al. "Anticoagulation therapy in patients with coronavirus disease 2019: Results from a multicenter international prospective registry (health outcome predictive evaluation for corona virus disease 2019 [HOPE-COVID19])." *Critical Care Medicine* 49.6 (2021): e624-e633.

Barnes, Geoffrey D., et al. "Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum." *Journal of thrombosis and thrombolysis* 50 (2020): 72-81.

Cosmi, B., Giannella, M., Fornaro, G. *et al.* Intermediate dose enoxaparin in hospitalized patients with moderate-severe COVID-19: a pilot phase II single-arm study, INHIXACOVID19. *BMC Infect Dis* **23**, 718 (2023). https://doi.org/10.1186/s12879-023-08297-7

1933

Rats

1933 = sweet clover disease, coumarin

1940/1 = synthesis, patent of Compound 42; dicoumarol

1948 = Warfarin sodium, rat poison

1954 = Coumadin® approved for human use

1955 = Ike, MI

SUPERWARFARINS

Brodifacoum (1977) T ½ = 20-130 DAYS !

P450 inhibition + synthetic cannabinoids

FDA STATEMENT July 19, 2018

Statement from FDA warning about significant health risks of contaminated illegal synthetic cannabinoid products that are being encountered by FDA

Reversal : Vitamin K 15-600mg/d x 30 – 200 days

King, Nathan, and Minh-Ha Tran. "Long-acting anticoagulant rodenticide (superwarfarin) poisoning: a review of its historical development, epidemiology, and clinical management." *Transfusion medicine reviews* 29.4 (2015): 250-258.

Tran, Minh-Ha, and Nathan C. King. "Epidemiology and symptomatology of long acting anticoagulant rodenticide poisoning." *J Epidemiol Res* 2.2 (2015): 1.

Spahr, Joseph E., J. Scott Maul, and George M. Rodgers. "Superwarfarin poisoning: a report of two cases and review of the literature." *American journal of hematology* 82.7 (2007): 656-660.

Padua Prediction Score

Items	Score
Active cancer (metastases and/or chemoradiotherapy in the previous 6 months)	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Bedrest for ≥3 days	3
Thrombophilia	3
Recent (≤1 month) trauma and/or surgery	2
Elderly age (≥70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥30 kg/m^2)	1
Ongoing hormonal treatment	1

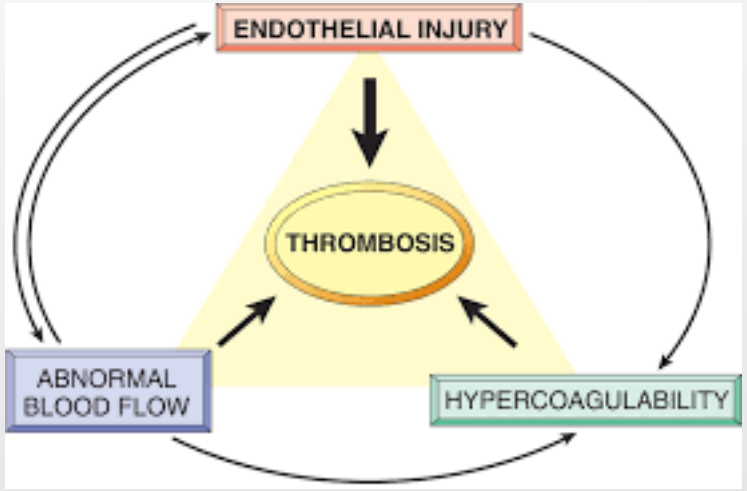
High risk of VTE: ≥4 points. VTE: Venous thromboembolism; BMI: Body mass index.

VTE

100,000 people die each year of VTE.

PE accounting for 10% of inpatient mortality

Pharmacologic prophylaxis has been proven to reduce PE risk by 57%



Skeik, Nedaa, and Emily Westergard. "Recommendations for VTE prophylaxis in medically ill patients." *Annals of vascular diseases* 13.1 (2020): 38-44.

Anticoagulation after stroke /w A.fib

? Some recommendations suggest initiation of anticoagulation at 1, 3, 6, or 12 days after a transient ischemic attack or after a minor, moderate, or severe ischemic stroke, respectively (the “1-3-6-12–day rule”)

2013 participants

Any DOAC

Early: < 48 hours after a minor or moderate stroke or on day 6 or 7 after a major stroke)

Vs Later: day 3 or 4 after a minor stroke, day 6 or 7 after a moderate stroke, or day 12, 13, or 14 after a major stroke).

recurrent ischemic stroke at 90 days were 1.9% (early) 3.1% (later)

(odds ratio, 0.60; 95% CI, 0.33 to 1.06).

Symptomatic intracranial hemorrhage 0.2% in both groups (odds ratio, 1.00; 95% CI, 0.15 to 6.45).

Fischer, Urs, et al. "Early versus later anticoagulation for stroke with atrial fibrillation." *New England Journal of Medicine* 388.26 (2023): 2411-2421.

Anticoagulation after stroke /w A.fib

- Initiating NOAC treatment within 4 days after ischemic stroke was noninferior to initiation of NOAC between days 5 and 10.
- No patient experienced symptomatic intracerebral hemorrhage in any study group, and rates of ischemic stroke and death were numerically lower in patients randomized to early initiation of NOAC.

Oldgren, Jonas, et al. "Early versus delayed non–vitamin k antagonist oral anticoagulant therapy after acute ischemic stroke in atrial fibrillation (TIMING): a registry-based randomized controlled noninferiority study." *Circulation* 146.14 (2022): 1056-1066.

FRAIL – AF

662 patients ≥75 years of age plus a Groningen Frailty Indicator score ≥3

12 months

Primary endpoint: bleeding

The hazard ratio for our primary outcome was 1.69 (95% CI, 1.23–2.32). The hazard ratio for thromboembolic events was 1.26 (95% CI, 0.60–2.61).

Switching international normalized ratio–guided VKA treatment to an NOAC in frail older patients with atrial fibrillation was associated with more bleeding complications compared with continuing VKA treatment, without an associated reduction in thromboembolic complications.

Joosten, Linda PT, et al. "Safety of Switching From a Vitamin K Antagonist to a Non–Vitamin K Antagonist Oral Anticoagulant in Frail Older Patients With Atrial Fibrillation: Results of the FRAIL-AF Randomized Controlled Trial." *Circulation* 149.4 (2024): 279-289.

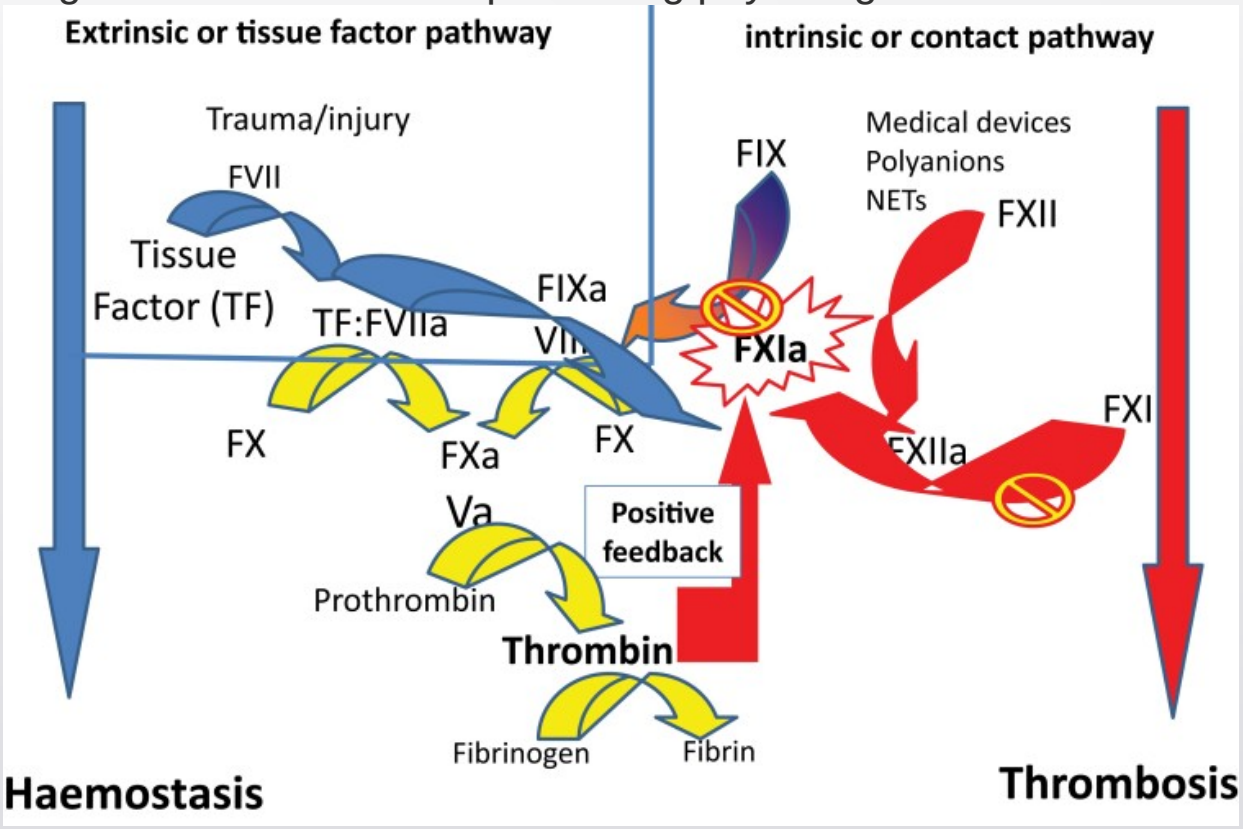
Factor XI/XIa (FXI) inhibitors

FXII and FXI are not strictly necessary for the formation of a stable clot

Hence the rationale to inhibit FXI/FXIa to block pathological thrombosis while preserving physiological haemostasis

Hemophilia C = Factor XI deficiency

incidence and severity of bleeding induced by FXI insufficiency are low



CTEPH

DOAC vs WARFARIN

927 patients

The 1-, 2-, and 3-year rates of composite morbidity and mortality outcome were comparable between the DOAC and warfarin groups (2.6%, 3.1%, and 4.2% vs 3.0%, 4.8%, and 5.9%, respectively; $P = .52$).

The 1-, 2-, and 3-year rates of clinically relevant bleeding were significantly lower in DOACs than in the warfarin group (0.8%, 2.4%, and 2.4% vs 2.5%, 4.8%, and 6.4%, respectively; $P = 0.036$).

DOACs =warfarin in preventing morbidity and mortality events, with a lower risk of clinically relevant bleeding (hazard ratio: 0.35; 95% CI: 0.13, 0.91; $P = .032$)

Hosokawa, Kazuya, et al. "Long-term outcome of chronic thromboembolic pulmonary hypertension using direct oral anticoagulants and warfarin: a Japanese prospective cohort study." *Journal of Thrombosis and Haemostasis* 21.8 (2023): 2151-2162.

SSPE

292 patients , from 2011-2021

- **Inclusion criteria:** Newly diagnosed isolated subsegmental PE
  - 1 or more intraluminal filling defects on CTA with no proximal involvement
- **Exclusion criteria:**
  - Active cancer
  - DVT
  - History of venous thromboembolism
  - Requirement for O2 therapy (to maintain SpO2 >92%)
  - Other indications for long-term anticoagulation
  - Pregnancy
  - Anticoagulated before enrollment
  - Hospitalized at the time subsegmental PE was diagnosed.

Total Patients with Subsegmental PE Analyzed	266 (100%)
Total Patients with VTE recurrence	8 (3.1%; 95% CI, 1.6% - 6.1%)
VTE Recurrence: PE	4 (1.5%)
VTE Recurrence: DVT	4 (1.5%)
Cumulative Incidence of recurrent VTE	
Single Subsegmental PE	2.1% (CI, 0.8% - 5.5%)
≤65 years of age	1.8% (CI, 0.6% - 5.4%)
>65 years of age	2.3% (CI, 2.3% - 12.7%)
Multiple Subsegmental PE	5.7% (CI, 2.2% - 14.4%)

No patients had a fatal recurrent pulmonary embolism.

- **Patients with isolated subsegmental pulmonary embolism (PE):** Rule out proximal deep venous thrombosis (e.g., with ultrasonography). If risk for recurrent VTE is low, surveillance is recommended over anticoagulation. If risk for recurrent VTE is high, anticoagulation is recommended. (*Weak recommendation, low-certainty evidence*) CHEST

Le Gal, Gregoire, et al. "Risk for recurrent venous thromboembolism in patients with subsegmental pulmonary embolism managed without anticoagulation: a multicenter prospective cohort study." *Annals of Internal Medicine* 175.1 (2022): 29-35.

Dahan, Ariel, et al. "Subsegmental pulmonary embolism and anticoagulant therapy: the impact of clinical context." *Internal Medicine Journal* 53.8 (2023): 1435-1443.

Enoxaparin Review

Therapeutic = 1.5mg/kg/day or 1mg/kg/bid = equivalent (P = 0.26 VTE recurrence, P=0.66 bleeding)

Prophylactic enoxaparin = 40mg/day vs. 30mg q12h. OR = 0.73 (0.71–0.76) VTE and 1.14 (1.10–1.21) bleeding , consider in THR / TKR / high risk trauma

- Dose adjustment for GFR < 30mL/min
- BMI ≥ 40 kg/m2
  - 0.75 mg/kg bid (therapeutic dosing, Anti-Xa 0.6-1.0 units/mL)
  - 0.5 mg/kg or 40mg BID (prophylactic dosing, Anti-Xa *0.2-0.5 IU/mL*).
- Anti-Xa levels should be checked at their peak at 4 hours after dosing
- Prophylaxis <45kg or <18.5 kg/m2 = consider 30mg/d

Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother. 2009;43(6):1064-83.

Niu, Jingrong, et al. "Once-daily vs. twice-daily dosing of enoxaparin for the management of venous thromboembolism: A systematic review and meta-analysis." *Experimental and Therapeutic Medicine* 20.4 (2020): 3084-3095.

Lalama JT, Feeney ME, Vandiver JW, et al. Assessing an enoxaparin dosing in morbidly obese patients. J Thromb Thrombolysis. 2015; 39:516-521

Boyd, R. A., L. DiCarlo, and J. W. Mandema. "Direct oral anticoagulants vs. enoxaparin for prevention of venous thromboembolism following orthopedic surgery: a dose–response meta-analysis." *Clinical and Translational Science* 10.4 (2017): 260-270.

Hakeam, Hakeam A., et al. "Anti-factor Xa levels in low-weight surgical patients receiving enoxaparin for venous thromboembolism prophylaxis: a prospective cohort study." *Clinical and Applied Thrombosis/Hemostasis* 26 (2020): 1076029620931194.
Martin, Annalise M., et al. "Optimal enoxaparin dosing strategies for venous thromboembolism prophylaxis and treatment of high body weight patients." *Thrombosis Research* 207 (2021): 116-122.

LV THROMBUS

84 patients over 3.0 ± 1.4 years,

VKA vs DOAC rates of stroke (2% vs. 0%, *P* = 0.55)

thromboemboli (2% vs. 0%, *P* = 0.55)

bleeding (10% vs. 0%, *P* = 0.13).

rate of resolution of thrombus (76% vs. 65% *P* = 0.33).

Rehospitalization (50% vs. 45%: *P* = 0.53)

all-cause mortality (10% vs. 14%; *P* = 0.61)

Iqbal, Hansa, et al. "Direct oral anticoagulants compared to vitamin K antagonist for the management of left ventricular thrombus." *ESC heart failure* 7.5 (2020): 2032-2041.

LV thrombus

DOAC vs VKA

LVT resolution (RR = 1.00, 95% CI 0.95–1.05, *P* = 0.99).

DOACs reduced risk of stroke (RR = 0.74, 95% CI 0.57–0.96, *P* = 0.021)

all-cause mortality (RR = 0.70, 95% CI 0.57–0.86, *P* = 0.001)

bleeding (RR = 0.75, 95% CI 0.61–0.92, *P* = 0.006)

major bleeding (RR = 0.67, 95% CI 0.52–0.85, *P* = 0.001)

systemic embolism (RR = 0.81, 95% CI 0.54–1.22, *P* = 0.32)

stroke/systemic embolism (RR = 0.85, 95% CI 0.72–1.00, *P* = 0.056)

intracranial hemorrhage (RR = 0.59, 95% CI 0.23–1.54, *P* = 0.28)

adverse cardiovascular events (RR = 0.99, 95% CI 0.63–1.56, *P* = 0.92)

Hu, Tong, et al. "Comparative effectiveness and safety of DOACs vs. VKAs in treatment of left ventricular thrombus-a meta-analysis update." *Thrombosis Journal* 22.1 (2024): 23.

UFH vs. LMWH

The decision between UFH and LMWH for prevention of thromboembolism usually depends on the patient's renal function or risk of bleeding complications

Meta analysis of 13 RCTs (9,619 patients)

No prophylaxis, placebo, or compression stockings only vs. LMWH

reduced the incidence of DVT (OR, 0.59 [95% credible interval [CrI], 0.33-0.90]; high certainty)

unfractionated heparin (UFH) may reduce the incidence of DVT (OR, 0.82 [95% CrI, 0.47-1.37]; low certainty).

LMWH reduces DVT compared with UFH (OR, 0.72 [95% CrI, 0.46-0.98]; moderate certainty)

Compressive devices may reduce risk of DVT (OR, 0.85 [95% CrI, 0.50-1.50])

Combination therapy (compression + chemical) showed unclear effect on DVT compared with either therapy alone (very low certainty).

Fernando, Shannon M., et al. "VTE prophylaxis in critically ill adults: a systematic review and network meta-analysis." *Chest* 161.2 (2022): 418-428.

Same prevalence of DVT (RR 1.05; 95% CI 0.67–1.64, p = 0.85) and PE (RR 0.76; 95% CI, 0.44–1.30, p = 0.31).

Hospital and intensive care unit stay was similar between the two groups.

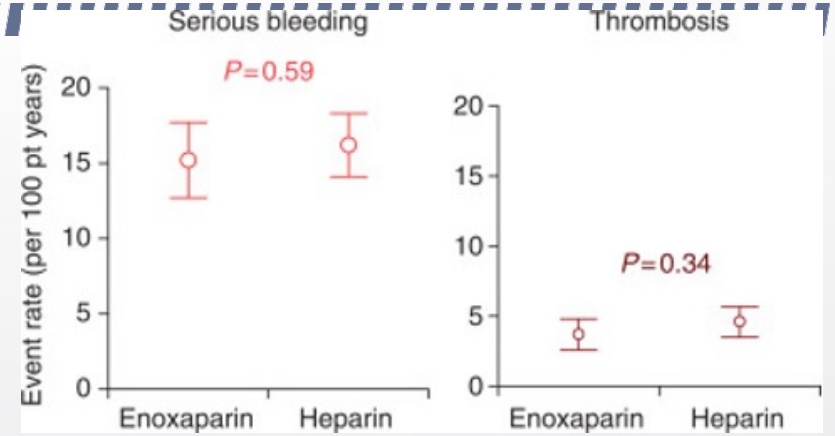
? Higher mortality with UFH (HR 2.04; 95% CI, 1.13–3.70; p = 0.019)

The use of UFH as VTE prophylaxis in ICU patients was associated with a similar prevalence of DVT and PE compared with enoxaparin, and the site and degree of occlusion were similar. However, a higher mortality rate was seen in the UFH group.

Samuel, Sophie, et al. "Unfractionated heparin versus enoxaparin for venous thromboembolism prophylaxis in intensive care units: a propensity score adjusted analysis." *Journal of Thrombosis and Thrombolysis* 55.4 (2023): 617-625.

Samuel, Sophie, et al. "Enoxaparin may be associated with lower rates of mortality than unfractionated heparin in neurocritical and surgical patients." *Journal of Thrombosis and Thrombolysis* 55.3 (2023): 439-448.

RENAL FAILURE / LMWH



7721 dialysis patients

enoxaparin or heparin at doses for thromboprophylaxis

15.2 (95% confidence interval (CI) 12.7–18.2) events per 100 patient-years LMWH

16.2 (95% CI 14.0–18.7) events per 100 patient-years UFH

SAME

enoxaparin no more bleeding vs heparin (risk ratio, 0.98; 95% CI 0.78–1.23)

VTE risk same (risk ratio, 0.77; 95% CI 0.49–1.22).

Thus, in dialysis patients, daily enoxaparin for thromboprophylaxis was not associated with increased serious bleeding or less effective compared to subcutaneous heparin.
standard-dose enoxaparin for normal renal function (31–60 mg per day, *n*=1422) had a standardized bleeding rate of 17.6 events per 100 patient-years (12.6–24.4), whereas patients with a dose reduction for moderate CKD (30 mg per day, *n*=1569) had a standardized bleeding rate of 16.3 events per 100 patient-years (11.7–22.8).

bleeding rates for standard vs CKD dosing were not statistically different (*P*=0.71)

from each other, nor was the cumulative dose of enoxaparin different in patients who had a bleeding event versus those who did not (5499 vs. 4967 mg; *P*=0.13).

In comparison with heparin, the RR for bleeding with low-dose enoxaparin was 0.95 (95% CI 0.71–1.28). The RR for standard-dose enoxaparin was 1.02 (95% CI 0.76–1.38).

The HR was 0.96 (95% CI 0.68–1.35) for bleeding with standard-dose enoxaparin for non-CKD patients and it was 0.89 (95% CI 0.64–1.25) for bleeding with renal dose enoxaparin when compared with heparin.
For thrombosis, the event rates were also not statistically different by dose of enoxaparin (*P*=0.42): 3.0 events per 100 patient-years (1.5–6.3) with standard-dose enoxaparin for non-CKD patients, 2.3 events per 100 patient-years (1.1–4.7) with renal dose enoxaparin, and 3.3 events per 100 patient-years (1.9–5.8) with heparin.

Chan, Kevin E., Ravi I. Thadhani, and Franklin W. Maddux. "No difference in bleeding risk between subcutaneous enoxaparin and heparin for thromboprophylaxis in end-stage renal disease." *Kidney International* 84.3 (2013): 555-561.

HIT (T)

Type I HIT =non-immunological response, direct interaction between heparin and platelets causing platelet aggregation, clumping and sequestration.

HIT type II is immune mediated and associated with a risk of thrombosis

Autoantibodies against platelet factor 4 (PF4) + heparin complex

IgG, PF4 and heparin binds and activates platelets leading to thrombosis

Prevalence of HIT type II is reported to be 0.5–5%

Develops 5–10 days after the initial heparin exposure

- At the time of diagnosis, 50% of patients will already have a thrombosis.
- If not anticoagulated, half of the remaining patients will develop either a venous arterial thrombosis within the next 30 days.
- Overall, there is a 12-15x risk of thrombosis (arterial or venous) compared to patients without HIT

PF4 / serotonin release assay (SRA)

4T score : sensitivity of 98.4%

Alhanshani, Ahmad A. "Heparin Induced Thrombocytopenia–Pathophysiology, Diagnosis and Treatment: A Narrative Review." *International Journal of General Medicine* (2023): 3947-3953.

4 T

Variable	Score		
	2	1	0
Acute **T**hrombocytopenia	Platelet count decrease of >50% and nadir ≥ 20,000/mm3	Platelet count decrease of 30-50% or nadir 10,000-19,000/mm3	Platelet count decrease of <30% or nadir of ≤10,000/ mm3
Timing of onset	Day 5-10 or day 1 if recent heparin exposure	> Day 10 or unclear exposure	≤ Day 4 with no recent heparin exposure
Thrombosis	New thrombosis of anaphylactoid reaction after heparin bolus	Progressive or recurrent thrombosis	None
Other cause of **T**hrombocytopenia	None	Possible	Definite
Total score	High risk (6-8)	Intermediate risk (4-5)	Low risk (0-3)
Probability of HIT	64%	14%	<1%
* adapted from Cuker et al Blood 2012			

HIT treatment

No warfarin, to minimise the risk of microvascular thrombosis and consequent skin necrosis. Reverse if indicated.

4 extremity dopplers should be performed due to a higher rate of thrombosis with HIT. This will change the anticoagulation plan if positive.

CHEST guidelines support the use of bivalirudin, assign low evidence rating to treatment of HIT with fondaparinux

Bivalirudin has a short half-life of 25 min

Titrate to aPTT

Prophylactic fondaparinux doses seem to be effective if no indication for full anticoagulation exists.
2.5 mg SC once daily

Treatment dosing

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

American College of Chest Physicians (ACCP)

Fondaparinux has similar effectiveness and safety as argatroban and danaparoid in patients with suspected HIT.

Reduced thromboembolism (6 studies, OR 0.28, 95% CI 0.06-1.20, P 0.09, i^2 45%)

Lessen primary endpoint events (7 studies, OR 0.26, 95% CI 0.10-0.67, P 0.006, i^2 66%).

Lower rate of bleeding (7 studies, OR 0.78, 95% CI 0.50-1.21, P 0.27, i^2 0%).

Thrombocytopenia less common (4 studies, OR 0.16, 95% IC 0.05-0.57, P 0.004, i^2 0%).

Survival benefit (6 studies, OR 0.26, 95% IC 0.08-0.90, P 0.03, i^2 54%).

Kang, Matthew, et al. "Fondaparinux for the treatment of suspected heparin-induced thrombocytopenia: a propensity score–matched study." *Blood, The Journal of the American Society of Hematology* 125.6 (2015): 924-929.

Sousa, JosÃ© P., et al. "Fondaparinux: A Low-hanging Fruit in Heparin-induced Thrombocytopenia." *Circulation* 142.Suppl_3 (2020): A15944-A15944.

Heparin BID vs. TID

King, Christopher S., et al. "Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: A metaanalysis." *Chest* 131.2 (2007): 507-516.

Metaanalysis, 7,978 patients

VTE risk BID vs TID $p = 0.87$

TID heparin showed a trend toward lower PE ($p = 0.09$) and DVT ($p = 0.05$).

The risk for major bleeding was significantly increased with TID heparin (events per 1000 patient days, BID, 0.35; vs TID, 0.96; $p < 0.001$).

*Conclusions:*BID heparin dosing causes fewer major bleeding episodes, while TID dosing appears to offer somewhat better efficacy in preventing clinically relevant VTE events. Practitioners should use underlying risk for VTE and bleeding to individualize pharmacologic prevention.

Updates