Brigham and Women's Hospital
Founding Member, Mass General Brigham

Hypercoagulable States and New Anticoagulants

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  - Research Focus: Clinical investigation in AL Amyloidosis

Disclosures

Pedro G. Vianna, M.D.

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Employee	Brigham and Women's Hospital

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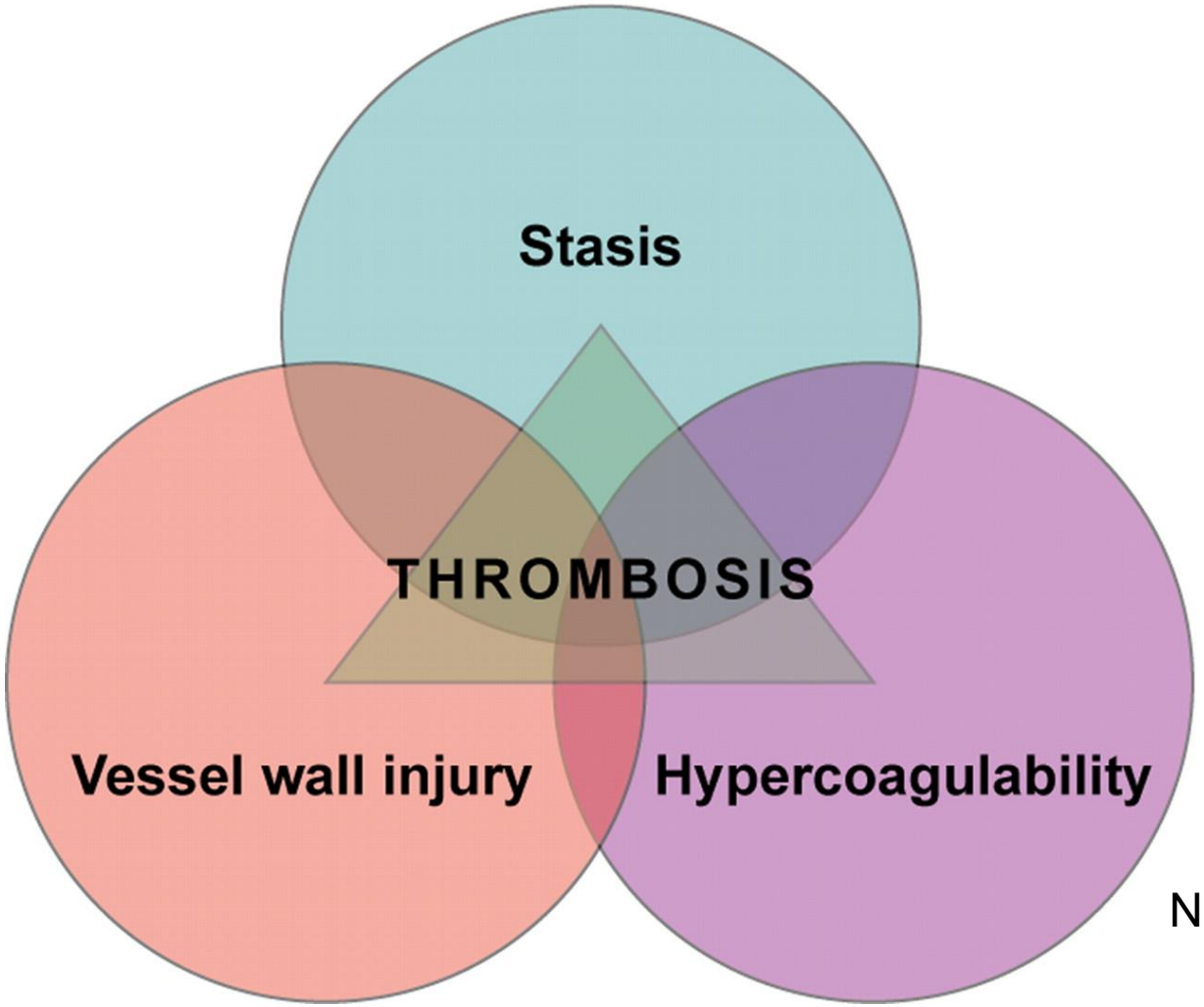
Key Learning Objectives

- Review the risk factors for thrombosis and discuss the components and indications for thrombophilia testing

- Review commonly used anticoagulants and their mechanisms of action and outline an approach to anticoagulation reversal

Virchow's triad



Not just inherited factors

Kyrle P A , Eichinger S Blood 2009;114:1138-1139

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Venous Thromboembolism

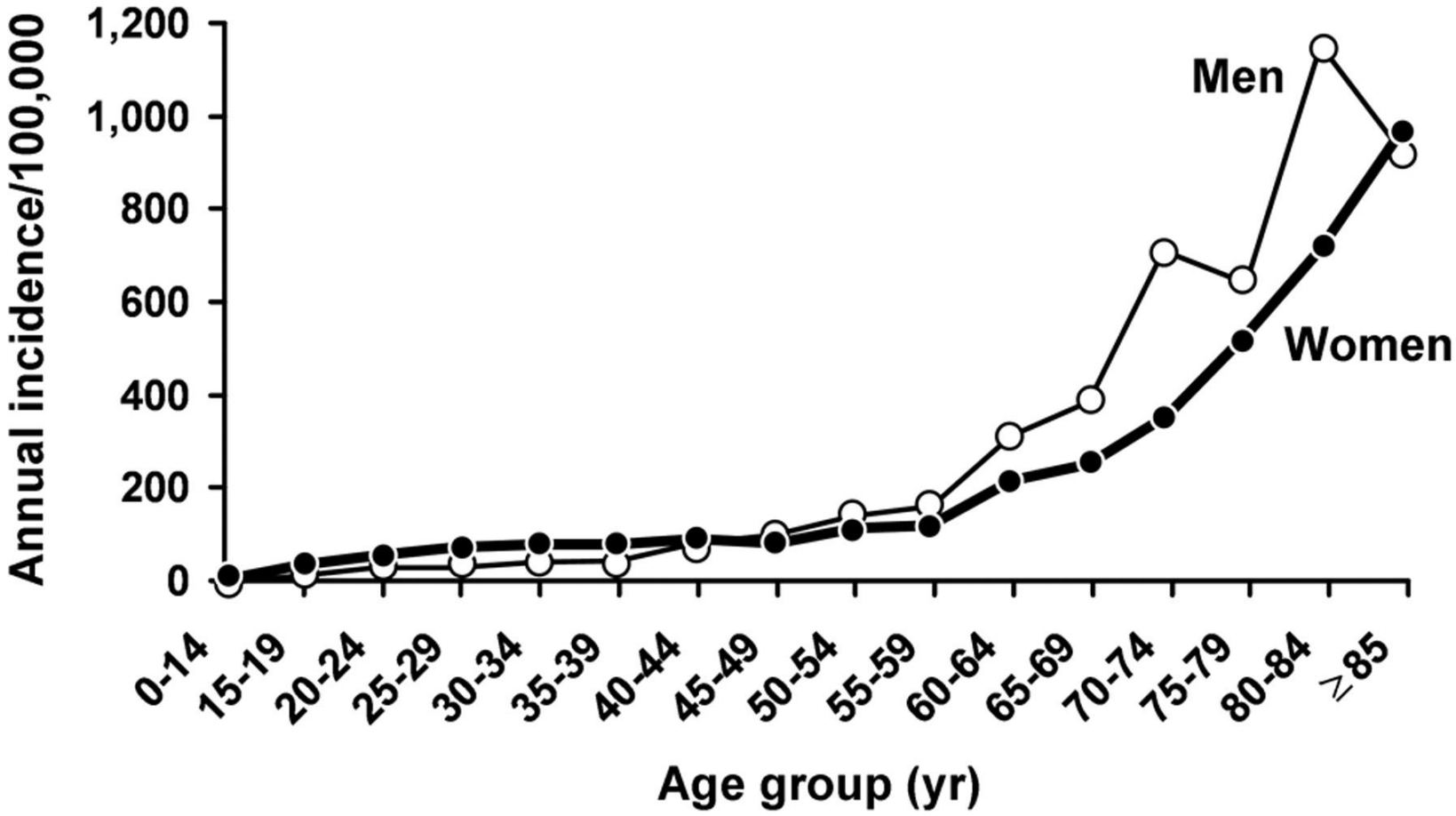
Risks for hypercoagulable states

- Inherited
- Acquired: more common
  - 35% US adults are obese, OR of 2.3 for VTE
  - <10% have an inherited thrombophilia
- Mixed: all are additive or synergistic

"Provoked" vs "Unprovoked"

- Clear precipitating factor vs idiopathic or unidentified risk factor
- Transient vs persistent provoking factor
- Unprovoked = idiopathic

Annual Incidence of Venous Thromboembolism by Age and Sex



Heit J A Hematology 2007;2007:127-135

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Acquired Risk Factors for VTE

TRANSIENT/PROVOKED

Surgery
Trauma
Acute Medical Illness
Immobilization
Estrogen
- OCP, HRT

Pregnancy
HIT
Prolonged Air Travel

PERSISTENT

Obesity
Increasing Age
Chronic Medical Illness
- Cancer/Therapies
  - Thalidomide
  - Tamoxifen
- IBD
- Nephrotic syndrome
- MPN/PNH
- Sickle cell disease

IDIOPATHIC/UNPROVOKED

???

Strength of Acquired Risk Factors

Weak risk factors (OR < 2)
Bed rest >3 days
Diabetes mellitus
Arterial hypertension
Immobility due to sitting (e.g. prolonged car or air travel)
Increasing age
Laparoscopic surgery (e.g. cholecystectomy)
Obesity
Pregnancy
Varicose veins

Strong risk factors (OR > 10)
Fracture of lower limb
Hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months)
Hip or knee replacement
Major trauma
Myocardial infarction (within previous 3 months)
Previous VTE
Spinal cord injury

Moderate risk factors (OR 2–9)
Arthroscopic knee surgery
Autoimmune diseases
Blood transfusion
Central venous lines
Intravenous catheters and leads
Chemotherapy
Congestive heart failure or respiratory failure
Erythropoiesis-stimulating agents
Hormone replacement therapy (depends on formulation)
In vitro fertilization
Oral contraceptive therapy
Post-partum period
Infection (specifically pneumonia, urinary tract infection, and HIV)
Inflammatory bowel disease
Cancer (highest risk in metastatic disease)
Paralytic stroke
Superficial vein thrombosis
Thrombophilia

[Konstantinides SV , et al. *EurHeart J*. 2019 Nov 1 ;40(42):3453-3455]

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Acquired Deficiencies

ANTITHROMBIN

Pregnancy
Liver Disease
DIC
Nephrotic Syndrome
Major Surgery
Acute Thrombosis

Treatment with:
Heparin
Estrogen

PROTEIN C

Liver Disease
DIC

Acute Thrombosis

Treatment with:
Warfarin

PROTEIN S

Pregnancy
Liver Disease
DIC

Inflammation
Acute Thrombosis

Treatment with:
Warfarin
Estrogen

Inherited Thrombophilias

- Mutations create coagulation imbalance
- Increased procoagulant activity
  - Factor V Leiden mutation → Activated Protein C “resistance”
  - Prothrombin gene G20210A mutation → increased prothrombin levels
  - FVL and PTG comprise 50-60% of cases
- Decreased anticoagulant activity
  - Protein C: inactivates factor VIII and factors V
  - Protein S: co-factor for Protein C
  - Antithrombin: inactivates thrombin (Factor IIa) and Factor Xa

Risk of 1st VTE with Thrombophilias

	Relative risk increase for first VTE
No thrombophilia	Reference group
II20210, hetero	3.8 (95% CI 3.0-4.9)
FVL, heterozygous	4.9 (95% CI 4.1-5.9)
II20210, homozygous	Insufficient data
FVL, homozygous	**18** (95% CI 4.1-41)
Hetero II20210 PLUS hetero FVL	**20** (95% CI 11.1-36.1)
Protein S deficiency	**30.6** (95% CI 26.9-55.3)
Protein C deficiency	**24.1** (95% CI 13.7-42.4)
Antithrombin deficiency	**28.2** (95% CI 13.5-58.6)

[Moll S. J Thromb Thrombolys 2015; ;39(3):367-78]

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Risk of Recurrent VTE with Thrombophilias

II20210, hetero: 1.45	(95% CI 0.96-2.21)
FVL, hetero: 1.56	(95% CI 1.14-2.12)

[Segal J et al. JAMA 2009; 301:2472-85]

FVL + II2010: 4.81	(95 % CI 0.50-46.3)
FVL + II2010: 1.0	(95 % CI 0.6-1.9)

[Segal J et al. JAMA 2009; 301:2472-85; meta-analysis]
[Lijfering WM et al. Circulation 2010;121:1706-12]

FVL, homo: 2.65	(95 % CI 1.18-5.97)
FVL, homo: 1.2	(95 % CI 0.5-2.6)

[Segal J et al. JAMA 2009; 301:2472-85; meta-analysis]
[Lijfering WM et al. Circulation 2010;121:1706-12]

II20210, homo: insufficient data

Protein C
Protein S
Antithrombin
} 2.8 (95 % CI 2.0 – 4.0)

[Lijfering WM et al. Circulation 2010;121:1706-12]

[Sokol J et al. JTH 2018;16:680-8]

APLA: 1.41	(95 % CI 0.99-2.00)
ACA: 1.53	(95 % CI 0.76-3.11)
LA: 2.83	(95 % CI 0.83-9.64)

[Garcia D et al. Blood 2013;122:817-824]

APLA syndrome: ~2.0

[Kearon C et al; Chest 2012;141:e419S-494S]

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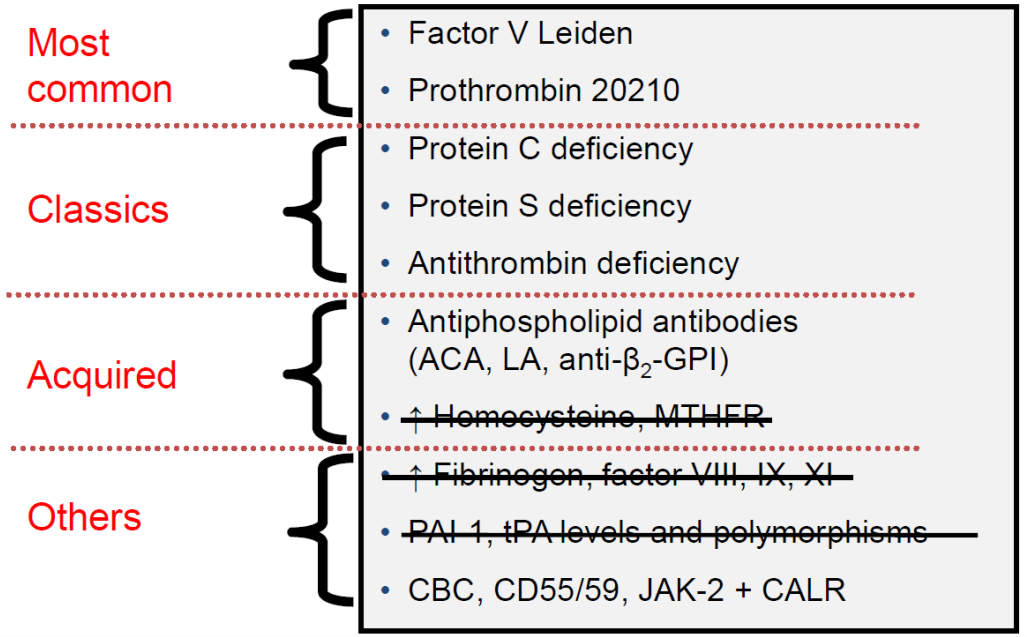
Inherited Thrombophilias

- Extremely rare
  - Dysfibrinogenemia
  - Cystathionine beta synthase deficiency (homocysteinuria)

- What NOT to test:
  - Homocysteine/MTHFR
    - Therapy to lower levels with B complex has no impact on recurrent VTE or MI
  - Factor VIII
  - Factor XIII polymorphisms, Factors IX, XI, and XII
  - PAI-1 4G/5G promoter, PAI-1



NORVIT (NEJM 2006), HOPE2 (NEJM 2006, Ann Intern Med 2007), VITRO (Blood 2007)

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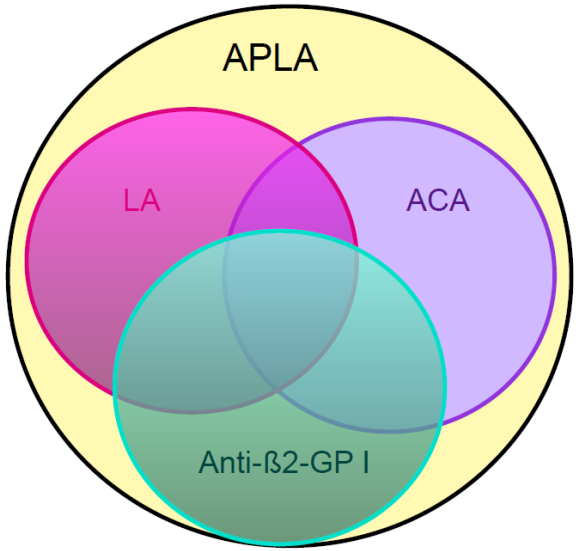
Antiphospholipid Antibodies

- Anticardiolipin
  - IgG and IgM
- Anti-beta-2-glycoprotein I
  - IgG and IgM
- Lupus anticoagulant
  - Screen: functional clotting assays
    - LA-PTT and DRVVT
  - Confirmatory: w/wo added PL
    - Hexagonal phase neutralization



I) Antibody test (ELISA)
- anticardiolipin
- anti-ß2-glycoprotein I
- antiphosphatidylserine
- antiphosphatidylcholine
- antiphosphatidylethanolamine

II) Functional test
- lupus anticoagulant (inhibitor)

[Sapporo criteria: Miyakis S. *J Thromb Haemost*. 2006;4:295-306]
[Devreese KMJ et al. JTH;2018 Apr;16(4):809-813]

Conclusions:

1. LA stronger and more definitive risk factor for thrombosis than ACA.
2. Risk for thrombosis is highest if positive APLA by multiple assays – triple positive.

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Thrombophilia Testing

- Indiscriminate testing in the inpatient setting or ED should be avoided
- Results affected by
  - Medications/anticoagulation: heparin, warfarin, DOACs
  - Acute setting: thrombosis, inflammation, miscarriage
  - Lab quality
- How will it change management?
  - Regardless of thrombophilia status → 3 month minimum

Clinical Clues for Inherited Thrombophilia

- Age of onset <50 years & weak provoking factors
- Recurrent thrombosis
- Positive Family History in 1st Degree Relative
- Unusual location/site

ABNORMALITY	ARTERIAL	VENOUS
Factor V Leiden	-	+
Prothrombin 20210A	-	+
Antithrombin Deficiency	-	+
Protein C Deficiency	-	+
Protein S Deficiency	-	+
Antiphospholipid Antibodies (e.g. LAC, ACL, B2GPI)	+	+

Whom to test for inherited thrombophilia

- YES
  - VTE at age <50 with positive family history in 1st degree relative
  - VTE in unusual locations
    - Cerebral venous thrombosis
    - Portal/mesenteric vein thrombosis (MPN evaluation, PNH)
  - ~~Recurrent pregnancy loss (esp 2nd and 3rd trimester)~~ → NEW DATA SAY DO NOT TEST!
- Controversial
  - VTE associated with OCP/HRT or pregnancy (ASH Thrombophilia Guidelines)
  - Young age with minor provoking risk factor
- NO
  - Age >50 with first spontaneous VTE
  - Active cancer
  - Postoperative
  - Retinal vein thrombosis
  - Arterial thrombosis (except paradoxical emboli)
  - Asymptomatic patients with no family history
  - Women going on OCPs with no family history of VTE

Thrombophilia Testing

- Role of testing not well defined
  - Lack of studies on utility, efficacy/safety of prophylaxis
- When does it change care?
  - Explain etiology
  - Prophylaxis in pregnancy
  - OCP/hormonal therapy
  - Family members
- When does it not change care?
  - Duration of anticoagulation in most PROVOKED VTE cases
  - Antiphospholipid syndrome
  - Malignancy

Proband's thrombophilia	Male Family Member		Female Family Member	
	Sons	Brothers	Daughters	Sisters
Hetero FVL or hetero prothrombin 20210	no	no	no	no
Homo FVL or homo prothrombin 20210	no	reasonable	no	yes
Double hetero	reasonable	reasonable	yes	yes
C, S, AT	reasonable	reasonable	yes	yes

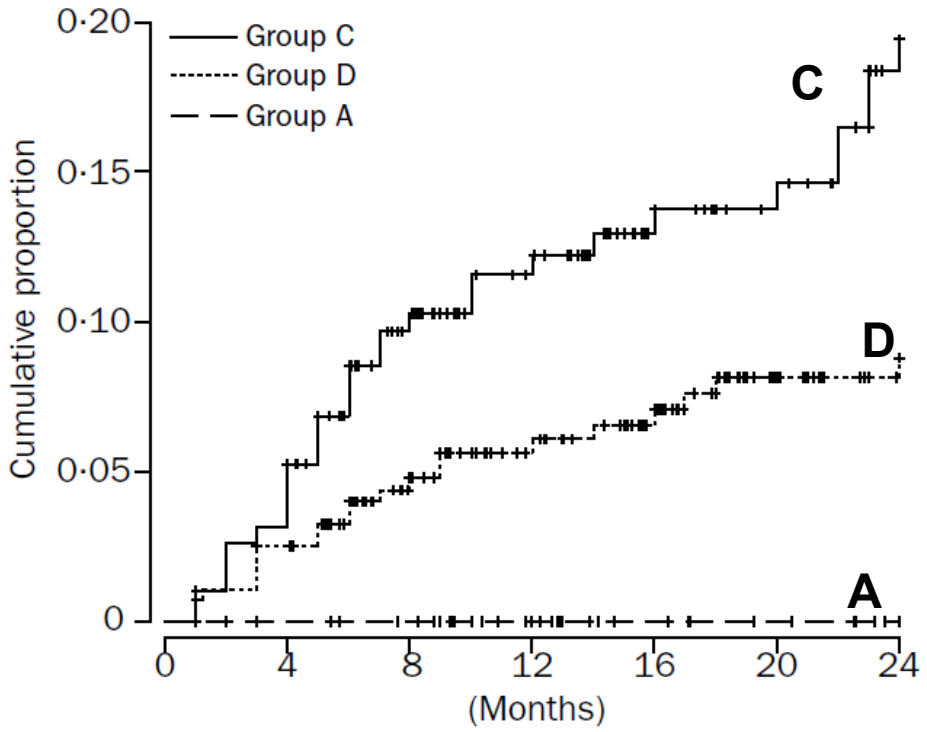
"reasonable" because: consider LMWH with airline travel, cast, non-major surgery; prolonged after major surgeries.

"yes" because: advise against estrogen contraceptives/hormone therapy; give ante- and postpartum anticoagulation.

Duration of Anticoagulation

- What factors impact the decision for extended or indefinite anticoagulation?
- Most significant factor is etiology:
  - Provoked VTE with transient risk factor
  - Idiopathic/Unprovoked VTE
  - Malignancy
  - Antiphospholipid Syndrome
- The presence of an inherited thrombophilia does NOT mandate indefinite duration anticoagulation

VTE Recurrence Risk



Unprovoked

Non-surgical Risks

Postop w/in 6 wks

- Unselected pts who had first VTE episode (n=570) treated with AC for 24-27 weeks
- Prospectively followed for 2 yrs to evaluate cumulative recurrence rate
- 85% tested for inherited thrombophilias
  - No difference in recurrence

In unselected patients who have had a 1st VTE, testing for heritable thrombophilias does not allow prediction of recurrent VTE in the first 2 yrs after AC therapy is stopped. However, assessment of clinical risk factors a/w 1st VTE episode does predict risk of recurrence. Patients with postoperative VTE have a very low rate of recurrence.

Baglin *Lancet* 2003

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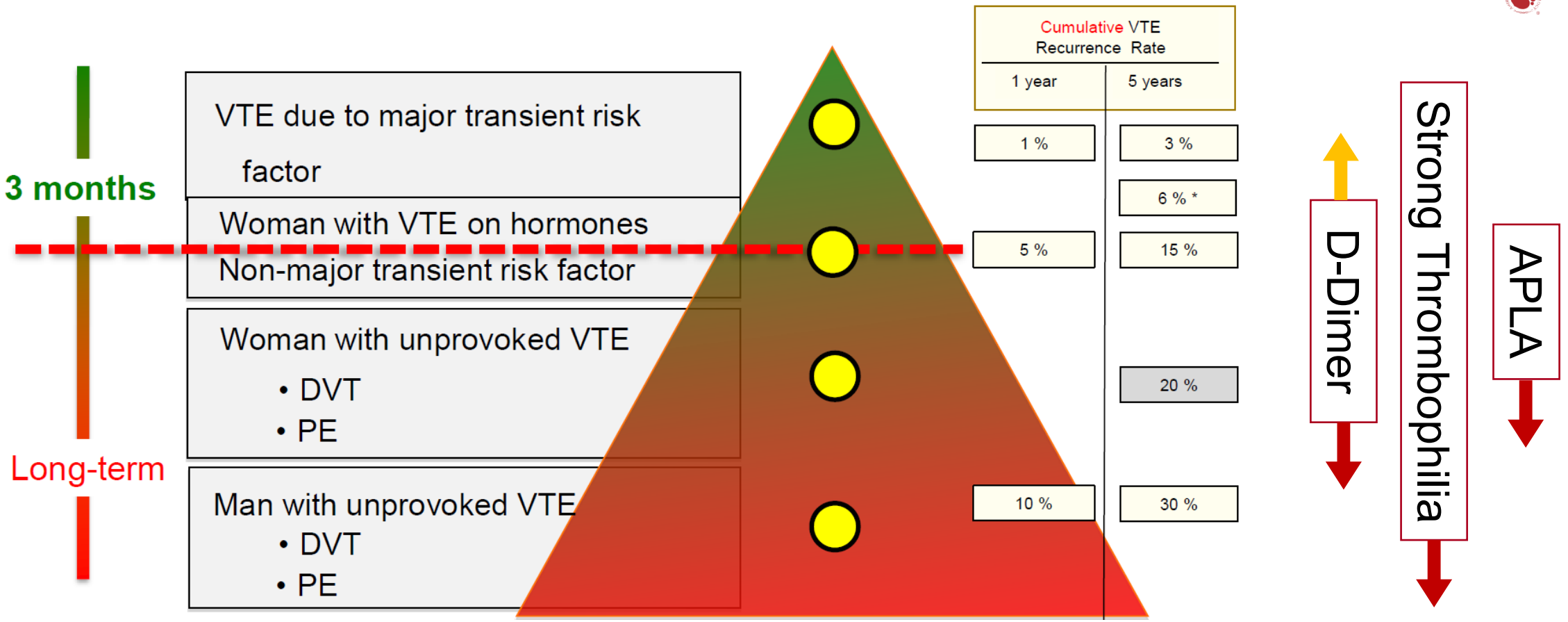
VTE Recurrence Risk

ACCP, AHA, ISTH, BJH
ASH 2021



[Kearon C et al. Blood 2014;123:1794-1801]
[Douketis J et al. BMJ 2011;342:d813]

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Summary: Hypercoagulable States

- The “hypercoagulable state” is a spectrum of risk, with many patients having multiple synergistic risk factors
- Environment and acquired events add to baseline genetic risk and are more common than inherited thrombophilias
- Inherited thrombophilias provide variable baseline risk; testing is easy, whom to test and what to do with results more complex. Published guidelines have been controversial
- Do NOT test 1.) During an acute thrombotic event, 2.) a hospitalized patient, 3.) while a patient is on an anticoagulant, and 4.) if you do not know how to interpret the test or what to do with the results
- Do not overvalue the importance of thrombophilia testing
- Be aware of what influences test results (false pos/neg.)

Anticoagulation

Common Parenteral and Oral Anticoagulants

- Unfractionated heparin
- Low-molecular weight heparin
  - Dalteparin (FRAGMIN®)
  - Enoxaparin (LOVENOX®)
- Synthetic pentasaccharide
  - Fondaparinux (ARIXTRA®)
- Direct Thrombin Inhibitors
  - Argatroban
  - Bivalirudin (ANGIOMAX®)
- Vitamin K Antagonists
  - Warfarin (COUMADIN®, JANTOVEN®)
- Direct Thrombin (FII) Inhibitors
  - Dabigatran (PRADAXA®)
- Factor Xa Inhibitors
  - Rivaro**xa**ban (XARELTO®)
  - Api**xa**ban (ELIQUIS®)
  - Edo**xa**ban (SAVAYSA®)

Warfarin (COUMADIN®, JANTOVEN®)

- Not an anticoagulant on its own
- Start same day
- Initiation: Usually 5mg daily
- Adjustment: 2-3 days to see effect

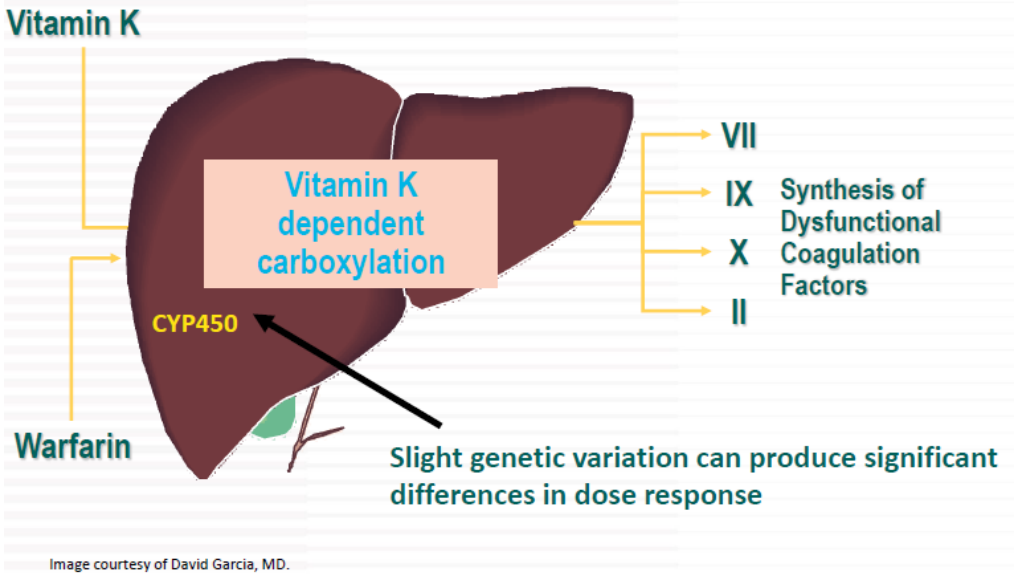
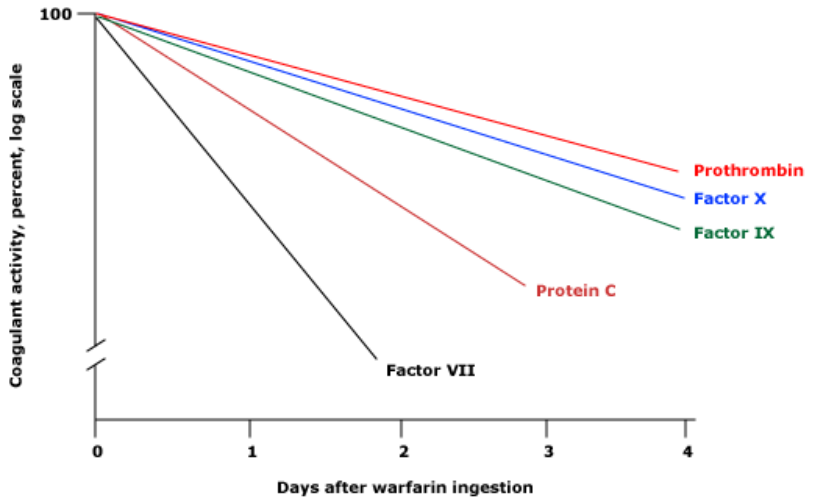


Image courtesy of David Garcia, MD.



Clotting factor	Effect of a factor deficiency	Half life (hours)
Factor VII	Anticoagulant	4-6
Protein C	Procoagulant	8
Factor IX	Anticoagulant	24
Protein S	Procoagulant	30
Factor X	Anticoagulant	48-72
Factor II	Anticoagulant	60

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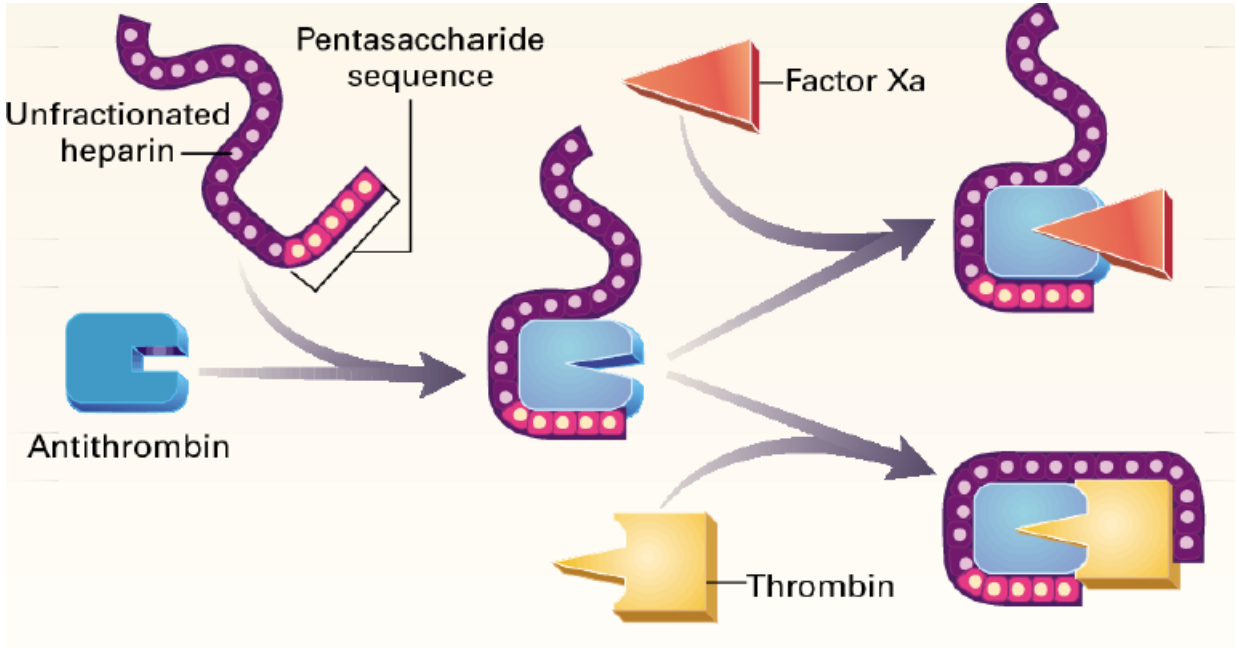
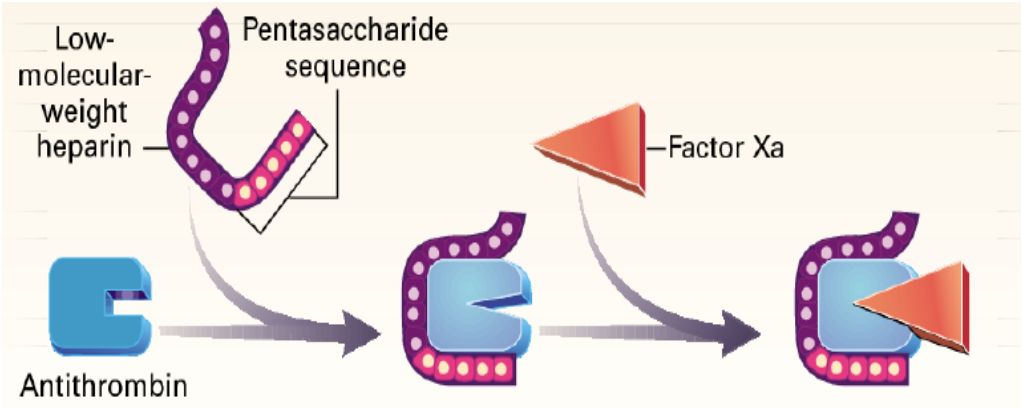
Heparin





Weitz JI. N EnglJ Med 1997;337:688-699.

LMWH/ Fondaparinux Dosing

Agent	Route	Prophylaxis	Therapeutic
Dalteparin	SC	5000 units once daily	Dose in units varies (Once daily)
Enoxaparin	SC	40mg daily	1 mg/kg twice daily
		30mg twice daily	1.5 mg/kg daily (Avoid)
Fondaparinux	SC	2.5mg daily (>50kg)	<50kg: 5mg daily
			50 – 100kg: 7.5mg daily
			>100kg: 10mg daily

Direct Thrombin Inhibitors

Drug	Dosing	Laboratory Monitoring
Arga**troban** **Mechanism:** DTI **Indications:** HIT, including HIT undergoing PCI	**Route:** IV **Half-life:** 40-50 min **Clearance:** Hepatobiliary **Adjust for:** Liver dysfunction, heart failure, anasarca, post-cardiac surgery	aPTT 1.5-3.0 x baseline Drug levels (?anti-IIa level)
Bivaliruidin **Mechanism:** DTI **Indications:** Unstable angina undergoing PTCA, PCI +/- GPIIb/IIIa inhibitor (REPLACE-2), HIT treatment is off-label	**Route:** IV **Half-life:** 25 min **Clearance:** Enzymatic **Adjust for:** Renal or liver dysfunction	APTT 1.5-2.5 x baseline

Blood Adv 2018; 2(22):3360-92

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DOAC Summary

Characteristics	Direct Oral Anticoagulants			
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Mechanism of action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Renal clearance	80%	27%	50%	66% (30% as inactive metabolites)
CYP Metabolism	No	Mostly CYP3A4/5	Minimal	CYP3A4/5, CYP2J2
Impacted by P-glycoprotein transporter system	Yes	Yes	Yes	Yes

DOAC Summary

Characteristics	Direct Oral Anticoagulants			
	Dabigatran	**Apixaban**	**Edoxaban**	**Rivaroxaban**
Bioavailability	3-7%, pH dependent (prodrug)	50%	62%,	66%-100% (increased w/ food for 15-20 mg dose)
Half-life	12-17 hours	8-15 hours	10-14 hours	5-13 hours
Dosing frequency	2x daily	2x daily	Daily	Daily
Administration	Oral, glass of water with meals if dyspepsia occurs	Oral, without regard to food	Oral, without regard to food	Oral, with food, for the 15 mg and 20 mg dose

DOAC Summary

Characteristics	Direct Oral Anticoagulants			
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Parenteral drug run-in	Yes	No	Yes	No
Monitoring*	Renal function	Renal and hepatic function	Renal and hepatic function, weight	Renal and hepatic function
Storage	Store in original package	Room temperature	Room temperature	Room temperature

DOAC Dosing

Agent	Route	Prophylaxis	Therapeutic
Dabigatran	PO	SPAF	VTE: Treat with parental agent days 5-10, then
		CrCl > 30: 150mg BID	CrCl > 30: 150mg BID
		CrCl 15-30: 75mg BID	CrCl <30/dialysis: AVOID
		CrCl<15/dialysis: AVOID	
Agent	**Route**	**Prophylaxis**	**Therapeutic**
Rivaroxaban	PO	Knee: 10mg daily X 10d	15mg BID x 21 days, then 20mg daily
		Hip: 10mg daily X 35d	Extended (> 6 months): 10mg daily
		SPAF: 20mg daily	
Apixaban	PO	Knee: 2.5mg BID X 12d	10mg BID x 7 days, then 5mg BID
		Hip: 2.5mg BID X 35d	Extended (>6 months): 2.5mg BID
		SPAF: 5mg BID	
Edoxaban	PO	SPAF: 60mg daily	Treat with parental agent days 5-10, then
			>60kg: 60mg daily
			≤60kg: 30mg daily

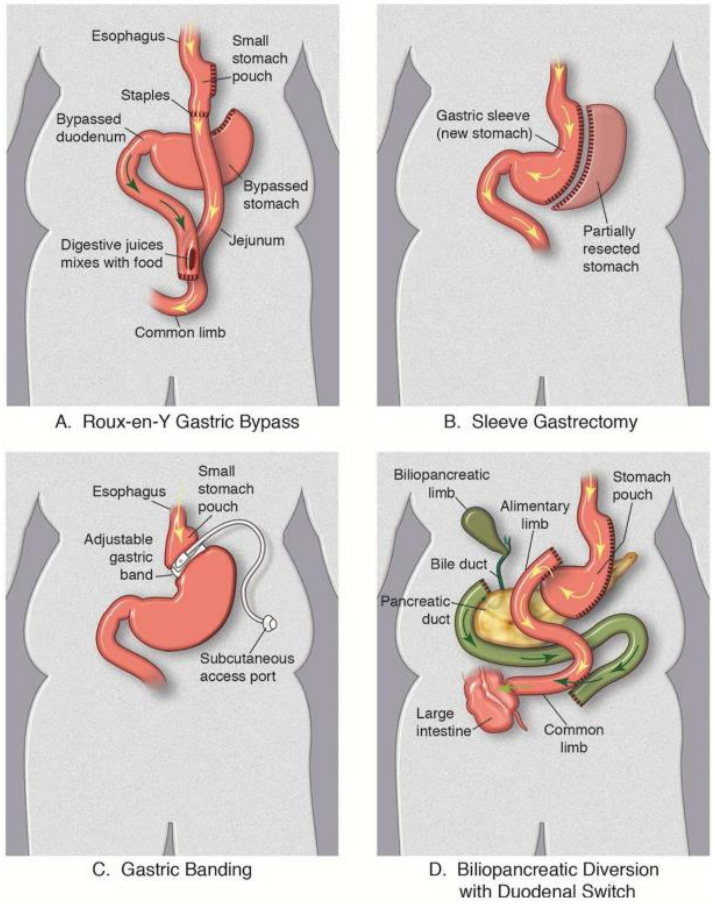
Increasing use in malignancy associated VTE (HOKUSAI VTE Cancer; SELECT-D; ADAM VTE; CARAVAGGIO)

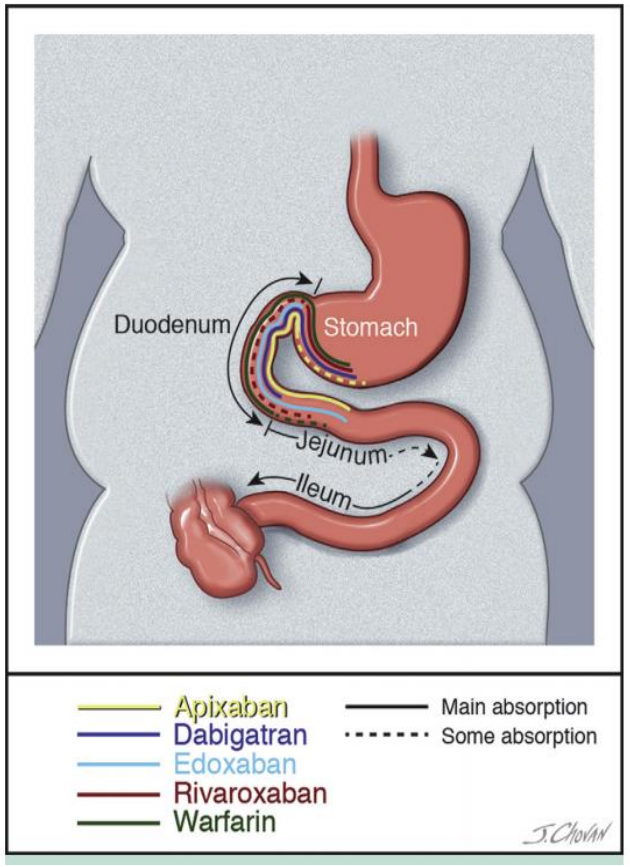
DOACs: Cautions

- **Obesity**: ISTH Guidance - Avoid if weight >120kg or BMI >40
  - Retrospective data showing efficacy up to BMI of 50, more data for rivaroxaban than apixaban, insufficient data for dabigatran, edoxaban
  - Unclear role of DOAC drug levels
- **Mechanical heart valves**: CONTRAINDICATED
- **Antiphospholipid syndrome**: "CONTRAINDICATED"
  - Triple positive: AVOID (TRAPS Trial: Rivaroxaban vs. Warfarin)
  - Single/double positive: Unclear risk/benefit balance
  - ASTRO-APS (Apixaban: increased rates of arterial thrombosis)
- **Bariatric surgery**

Burnett et al. Journal of Thrombosis and Thrombolysis. 2016;41(1):206-32
Martin et al. J of Thromband Haemost. 2021;19(8):1874-1882.

DOACs and Bariatric Surgery





DOAC	Surgical Intervention and Anticipated Effect on Absorption		
	Gastric Banding	Partial/Sleeve Gastrectomy	RYGB
Apixaban	Unlikely affected	Unlikely affected	Possibly reduced
Dabigatran	Possibly reduced	Possibly reduced	Possibly reduced
Edoxaban	Possibly reduced	Possibly reduced	Possibly reduced
Rivaroxaban	Possibly reduced	Possibly reduced	Possibly reduced

DOACs not advised for treatment/prevention of VTE in the "acute setting" after bariatric surgery

- Consider changing to warfarin with reliable INR monitoring or DOAC after at least 4 wks of parenteral treatment
- May be appropriate after at >6-12 months following surgery
- Consider DOAC trough level to monitor drug absorption and bioavailability

J Thromb Haemost. 2021 Aug;19(8):1874-1882
Am J Med. 2017 May;130(5):517-524

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Reversal Strategies

Coagulation Factor Replacement

- Prothombin Concentrate Complex (II, VII*, IX, X, Proteins C/S)
- FEIBA (IIa, VIIa, IXa, Xa), recombinant VIIa, FFP

Specific Antidotes

- Humanized monoclonal antibody fragment against dabigatran
- Inactive factor Xa derivatives

Adjunctive

- Dialysis
- Desmopressin
- Antifibrinolytic Agents

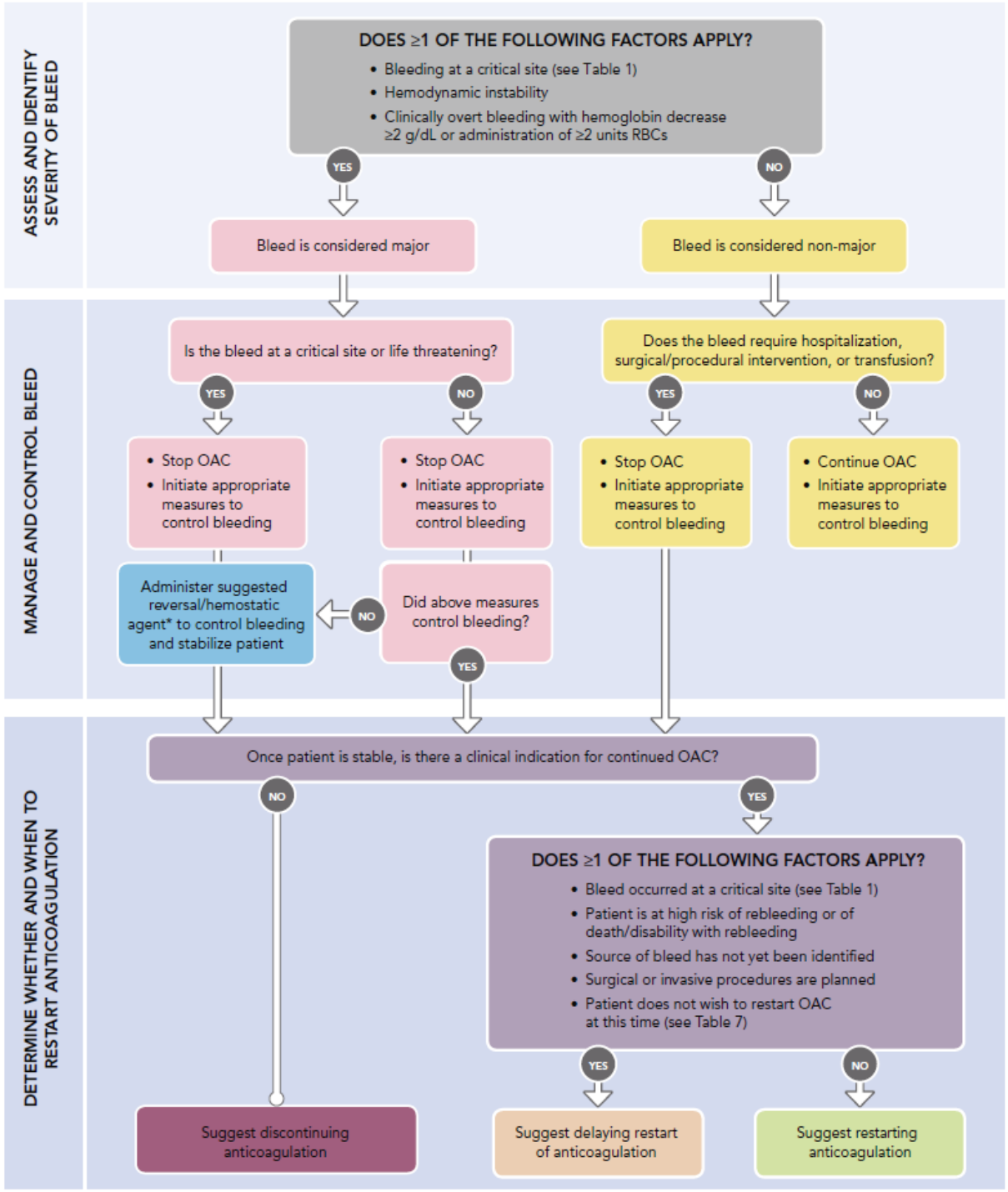
BLOOD, 20 FEBRUARY 2014 • VOLUME 123, NUMBER 8

EXPERT CONSENSUS DECISION PATHWAY

2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

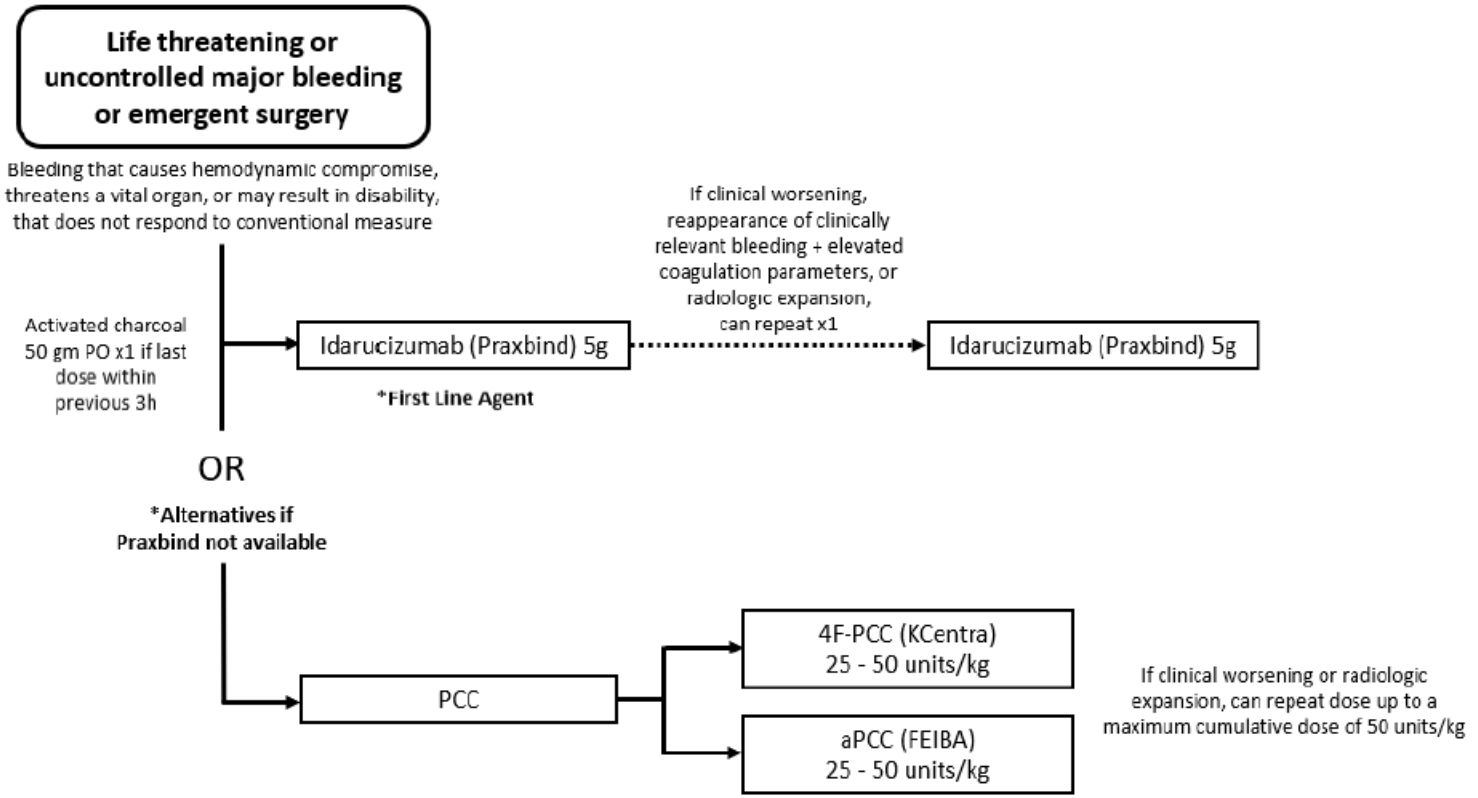
A Report of the American College of Cardiology Solution Set Oversight Committee

- Critical Site Bleeds
  - Intracranial hemorrhage
  - Other CNS bleeding
  - Pericardial tamponade
  - Airway (including posterior epistaxis)
  - Hemothorax, intra-abdominal bleeding, retroperitoneal hematoma
  - Extremity bleeds
- Quantitation of Anticoagulant
  - Apixaban, Rivaroxaban, or Lovenox-specific Anti-Xa levels
  - Dabigatran – thrombin time



J Am Coll Cardiol. 2020 Aug, 76 (5) 594–622

Dabigatran Reversal



Labs:

- aPTT, PT/INR, TT
  - Recheck 12-24h after administration of Idarucizumab (Praxbind)
  - Coagulation parameters may rebound within 12-24 hours following idarucizumab administration as dabigatran redistributes

Notes:

- Consider time of last dose and renal function elimination when determining if reversal is necessary
- Hemodialysis should NOT be considered as part of reversal strategy for ICH
- KCentra/FEIBA dosing based on actual body weight, up to maximum weight 100 kg
- Click here for reversal monitoring parameters

BWH Guidelines for Antithrombic Reversal
https://mgb.ellucid.com/pman/documents/view/24026?

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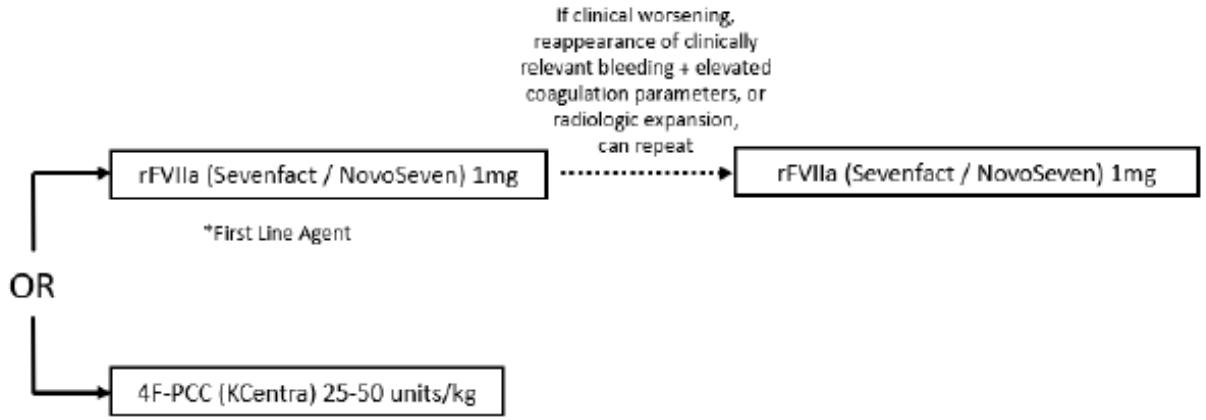
IV Direct Thrombin Inhibitor Reversal

- No agent has been shown to successfully reverse the anticoagulant effects of IV direct thrombin inhibitors
- Due to short half-lives (bivalirudin ~25 min, argatroban ~45 min), agent discontinuation and supportive measures are the mainstay of IV DTI associated bleeding management
- If reversal deemed necessary and appropriate, may consider options below:



BWH Guidelines for Antithrombic Reversal
https://mgb.ellucid.com/pman/documents/view/24026?

Labs:
- Argatroban: aPTT, TT, ACT in certain procedures
- Bivalirudin: aPTT, TT, ACT in certain procedures

Notes:
- rFVIIa: Sevenfact is the BWH preferred option; NovoSeven may also be used
- 4F-PCC (KCentra) dosing based on actual body weight, up to maximum weight 100 kg
- Click here for reversal monitoring parameters

HARVARD MEDICAL SCHOOL

UFH/LMWH Reversal

IV UFH

Protamine dose is dependent on total units of heparin administered within 3 hours preceding reversal, including bolus doses

1. Calculate units of UFH administered <1h before reversal → Protamine 1mg for every 100 units of UFH (Divide total units by 100 for easy math)
2. Calculate units of UFH administered between 1-2h before reversal → Protamine 0.5mg for every 100 units of UFH (Divide total units by 200 for easy math)
3. Calculate units of UFH administered between 2-3h before reversal → Protamine 0.25mg for every 100 units of UFH (Divide total units by 400 for easy math)

Add together for the total protamine dose (max single dose 50mg)

If PTT remains elevated or bleeding continues 4 hours after administration, can consider re-dosing protamine at 0.5mg per 100 units of UFH

Example: Patient has been receiving a heparin infusion at 1500 units/hr without any recent bolus doses.

Total heparin <1h before reversal: 1500 units / 100 = 15mg
Total heparin 1-2h before reversal: 1500 units / 200 = 7.5mg
Total heparin 2-3h before reversal: 1500 units / 400 = 3.75mg

Protamine dose to be administered: 26.25 mg

Labs:

- UFH/LMWH anti-Xa level
- PTT

Notes:

- Test dose of protamine necessary for patients at increased risk for anaphylactic reaction who will receive more than 10mg dose:
  - Previous exposure to protamine
  - Treatment with insulin NPH
  - History of allergy to fish
- Max administration rate: 5mg/min (no more than 50mg over 10 min)
- Click here for reversal monitoring parameters
- For OR procedural areas, refer to BWH protamine monograph in Lexicomp for dosing

***Protamine dose not fully reverse LMWH (~60% of anti-Xa activity neutralized)**

LMWH

Protamine dose is dependent on time of last enoxaparin administration

- Time last dose administered : < 8h ago → Protamine 1mg for every 1mg of enoxaparin
- Time last dose administered : 8-12h ago → Protamine 0.5mg for every 1mg of enoxaparin

Max single protamine dose 50mg

*If time of last dose > 12h and ongoing bleeding, consider protamine 0.5mg for every 1mg of enoxaparin

BWH Guidelines for Antithrombic Reversal
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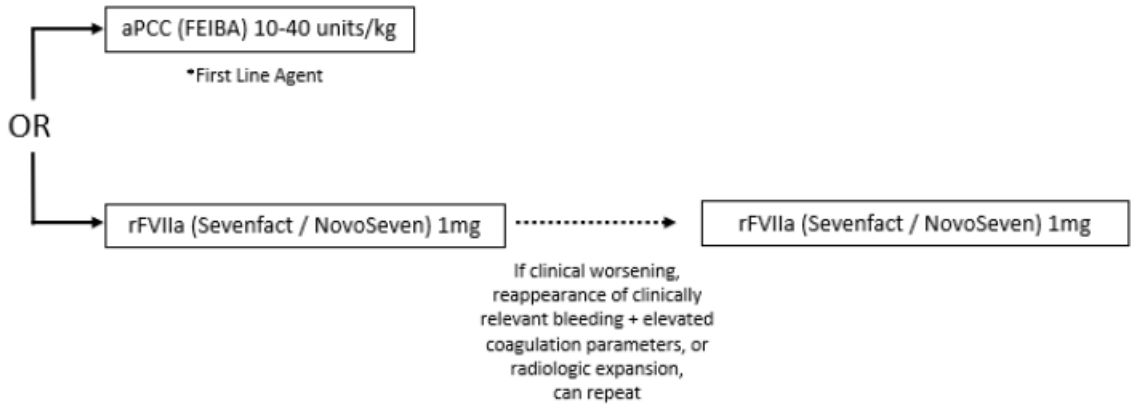
HARVARD MEDICAL SCHOOL

Fondaparinux Reversal

Limited data exists to guide reversal of fondaparinux-associated bleeding



Labs:

- Fondaparinux-calibrated anti-Xa level

Notes:

- rFVIIa: Sevenfact is the BWH preferred option; NovoSeven may also be used
- If rFVIIa and aPCC (FEIBA) are unavailable, consider 4F-PCC (Kcentra) as either a fixed dose of 2000 units or weight-based dose of 25-50 units/kg
- 4F-PCC and aPCC not studied in this population but extrapolated from reversal of oral factor Xa inhibitors; dosing based on actual body weight, up to maximum weight 100 kg
- Click here for reversal monitoring parameters

BWH Guidelines for Antithrombic Reversal
https://mgb.ellucid.com/pman/documents/view/24026?

HARVARD MEDICAL SCHOOL

Warfarin Reversal

Major bleeding

→ IV Vitamin K 5 - 10mg x 1 + 4F-PCC (KCentra)

→ **Weight-based** 4F-PCC (KCentra)

Consider in ICH or patients with INR > 7 or weight > 120kg

Pre-Treatment INR	Reversal Dosing
< 4	4F-PCC (KCentra) 25 units/kg Max: 2500 units
4 – 6	4F-PCC (KCentra) 35 units/kg Max: 3500 units
> 6	4F-PCC (KCentra) 50 units/kg Max 5000 units

→ **Fixed Dose** 4F-PCC (KCentra)

Consider if INR unknown or cases of less severe bleeding

	Pre-Treatment INR	Reversal Dosing
Major bleeding	Any INR	4F-PCC (KCentra) 1000 units
ICH	Any INR	4F-PCC (KCentra) 1500 units

Minor bleeding

Pre-Treatment INR	Reversal Dosing
Any INR	PO Vitamin K 2.5 - 5mg Can repeat vitamin K in 24h if INR remains elevated or continued bleeding

No evidence of bleeding

Pre-Treatment INR	Reversal Dosing
< 4.5	Reversal not recommended unless urgent reversal needed for procedure
4.5 – 10	PO Vitamin K 1 - 2.5mg If bleeding risk factors exist
> 10	PO Vitamin K 2.5 - 5mg

Periprocedural → **See next page**

For patients with confirmed/suspected HIT or contraindication to heparin who require 4F-PCC reversal, may consider aPCC (FEIBA) after consult with HAT/Heme.

Reversal for life-threatening bleed (aPCC):
- INR < 5 consider 1000 units
- INR >/~ 5 consider 1500 units
- Repeat INR after 30 minutes, if INR not at desired goal (i.e. < 1.5) consider additional 500 units

For additional vitamin K dosing considerations please see Appendix

Labs:
- STAT INR (do not wait for result to treat)
- For ICH, repeat INR 30 minutes after 4F-PCC (KCentra) administration to assess need for additional doses

Periprocedural Reversal: See below

Notes:
- 4F-PCC (KCentra) and aPCC (FEIBA) dosing based on actual body weight, up to maximum weight 100 kg
- Additional reversal considerations:
  - Immediate reversal: 4F-PCC (KCentra)
  - Immediate + sustained reversal: 4F-PCC (KCentra) + vitamin K
  - Sustained reversal within 12-24h: vitamin K
- Click here for reversal monitoring parameters
- See additional vitamin K dosing considerations in Appendix
- aPCC (FEIBA) contains activated factor VII which may result in a higher thrombotic risk than 4F-PCC which contains only non-activated clotting factors

BWH Guidelines for Antithrombic Reversal
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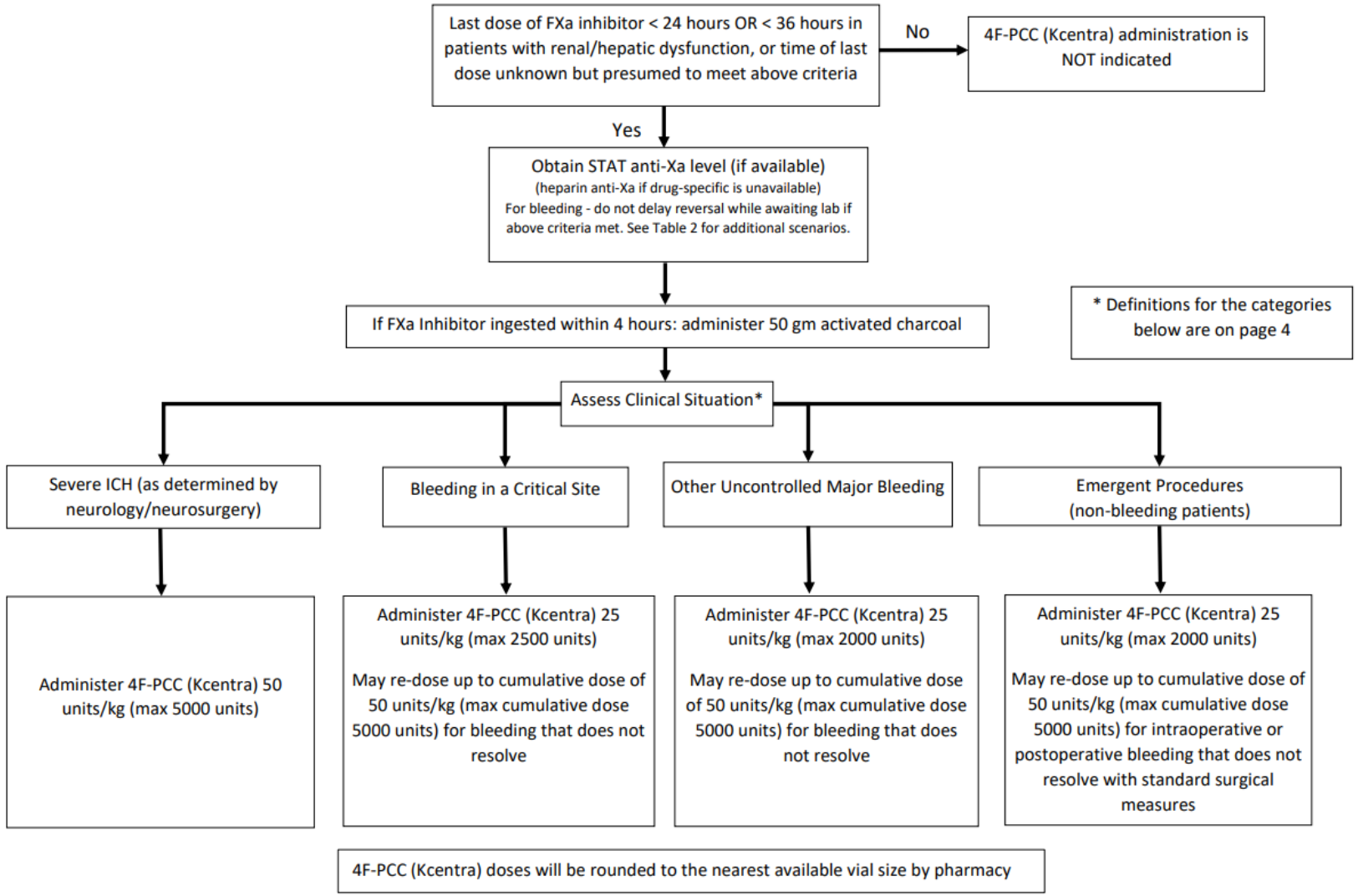
HARVARD MEDICAL SCHOOL

DOAC Reversal



BWH Guidelines for Antithrombic Reversal
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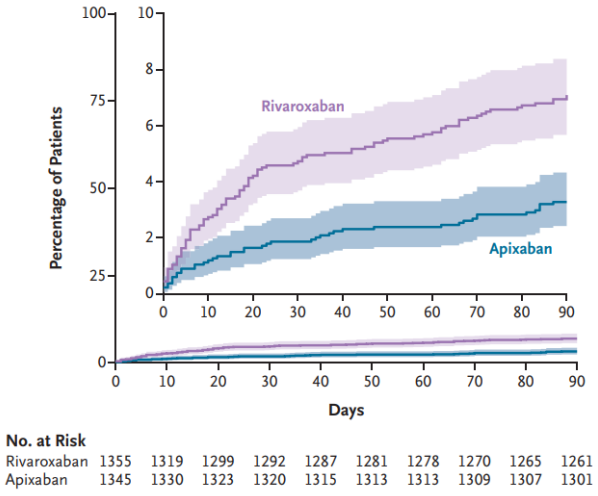
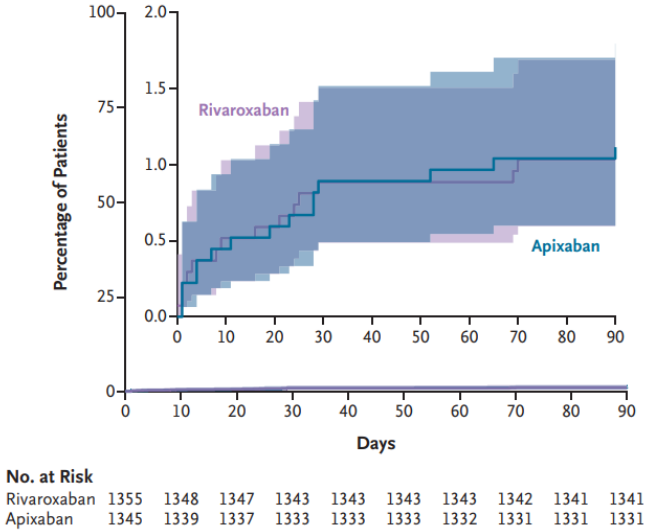
HARVARD MEDICAL SCHOOL

Late-Breaking: COBRRA Trial
Bleeding Risk with Apixaban vs Rivaroxaban in Acute VTE





- Randomized n=2760, prospective, open/blinded endpoint trial compared clinically relevant bleeding events between rivaroxaban and apixaban in acute VTE treatment (3 months)
- Excluded weight >120 kg and cancer-associated VTE
- Primary outcome: Clinically relevant bleeding events and occurred in:
  - 41 of 1346 patients (3.0%) in the apixaban group compared to
  - 91 of 1350 patients (6.7%) in the rivaroxaban group (odds ratio, 0.44; 95% confidence interval (CI), 0.30 to 0.63; P < 0.0001).
- Recurrent symptomatic VTE rates occurred in
  - 13 patients (1.0%) in each treatment group (odds ratio, 1.00; 95% CI 0.46 to 2.17).

In patients with acute symptomatic venous thromboembolism, ***apixaban use led to significantly fewer clinically relevant bleeding events compared to rivaroxaban during 3 months of treatment. There was no difference in recurrent thrombosis or death rates.***

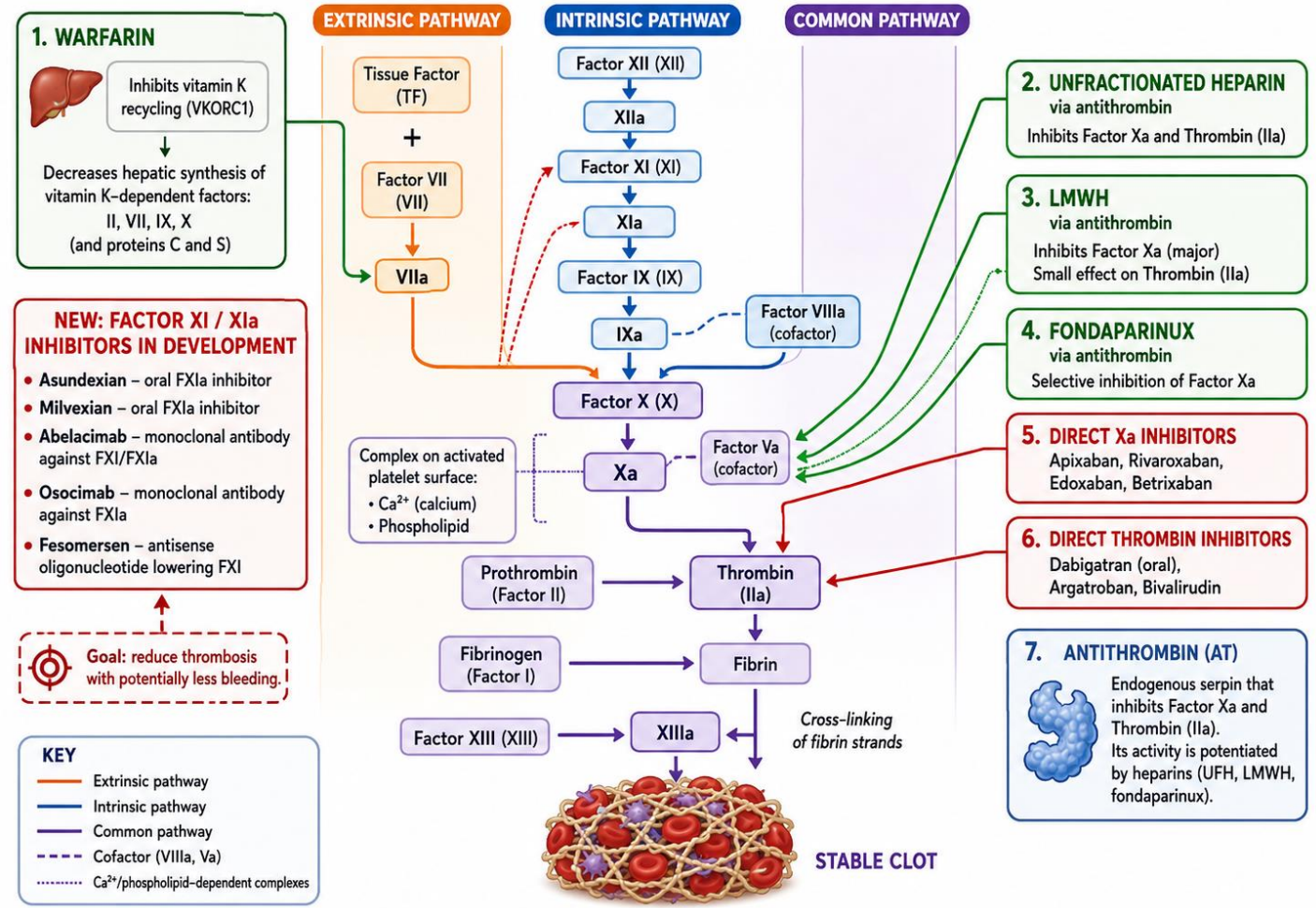
N Engl J Med.2026 Mar 12;394(11):1051-1060

HARVARD MEDICAL SCHOOL

“New” Anticoagulants!

- For many years, “new” anticoagulants meant DOACs (Xa or IIa)

- Major “next generation” anticoagulant class is **factor XI / XIa inhibition**. The idea is to blunt pathologic thrombosis through the intrinsic/contact pathway while preserving enough hemostasis to cause less bleeding than factor Xa or thrombin inhibition



“New” Anticoagulants!

Anticoagulants in pipeline (Not FDA approved)

Agent	Target / type	Route	Current clinical status
Asundexian	FXIa small-molecule inhibitor	Oral daily	Positive phase 3 in secondary prevention after noncardioembolic stroke/TIA; prior AF phase 3 stopped for inferior efficacy vs apixaban
Milvexian	FXIa small-molecule inhibitor	Oral	Phase 3 program ongoing in AF and stroke; ACS phase 3 stopped for futility
Abelacimab	FXI/FXIa monoclonal antibody	Monthly SC/IV lead-in	AF phase 3 ongoing in patients unsuitable for oral anticoagulation; CAT phase 3 program terminated after failure/futility vs apixaban/dalteparin
Osocimab	FXIa monoclonal antibody	Parenteral	Phase 2 data in orthopedic prophylaxis and dialysis; appears discontinued/not in major late-stage development
Fesomersen / IONIS-FXI-LRx	Antisense oligonucleotide lowering FXI synthesis	SC intermittent	Phase 2 data in ESRD/hemodialysis; no major active phase 3 anticoagulation program apparent
Gruticibart / AB023 / xisomab 3G3	Anti-FXI antibody blocking FXI activation by FXIIa	IV/SC investigational	Phase 2/proof-of-concept, including catheter-associated thrombosis/hemodialysis-type settings
Regeneron FXI antibodies	FXI antibodies	Parenteral	Phase 2 proof-of-concept reported in knee arthroplasty; early development
FXIIa inhibitors, e.g. garadacimab	FXIIa antibody	Monthly SC	Approved/developed for hereditary angioedema, not yet an established antithrombotic drug

Summary: Anticoagulation

- Many options for anticoagulation!
- DOACs are first line therapy in most indications
  - Recent randomized trial data suggest apixaban has lower rates of bleeding than rivaroxaban for acute symptomatic VTE
- Need to be careful with renal function and obesity/absorption
- Reversal should be reserved for life threatening bleeding

MOC Reflective Statement

- Review the risk factors for thrombosis and discuss the components and indications for thrombophilia testing
  - Inherited and acquired factors are important
  - Persistence of risk factors drives duration of anticoagulant therapy
  - Thrombophilia testing is over utilized, and you must have a clear change in management in mind before the test is sent

- Review commonly used anticoagulants and their mechanisms of action and outline an approach to anticoagulation reversal
  - Unfractionated and low-molecular weight heparin, synthetic pentasaccharide, parenteral direct thrombin inhibitors
  - Vitamin K antagonists
  - Oral direct thrombin (IIa) and Xa inhibitors are most common
  - Important to address bleeding at life threatening sites
  - Multiple options for anticoagulant reversal
  - Follow-up steps to think about timeline for restarting anticoagulantion in appropriate patients

Question 1

A 58-year-old man presents to the emergency room with diarrhea with bright red blood. He is known to have diverticulosis based on screening colonoscopies and was recently started on apixaban 5 mg twice daily for new onset atrial fibrillation. The last dose of apixaban was 6 hours ago. He is hemodynamically stable, with hemoglobin that is just 1 gm/dL lower than baseline. Treatment should involve:

A. Transfusions with 4 bags of FFP
B. Idarucizumab 5 grams IV bolus
C. IV vitamin K
D. Aggressive supportive care with IV fluids and red cell transfusions if necessary
E. Andexanet alfa according to package insert

Question 2

A 67-year-old man is seen by his PCP for advice about duration of anticoagulation. Two months ago, he had had urgent cholecystectomy with the development of a left calf vein DVT. The surgical team sent a hypercoagulable work up which revealed the patient is heterozygous for a Factor V Leiden mutation. What is the appropriate approach to management?

A. Treatment for 1 additional month
B. Treatment for 3 additional months
C. Lifelong anticoagulation
D. Stop the anticoagulant at this time

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