

# Hypercoagulable States and New Anticoagulants

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Brown University and Rhode Island Hospital

Associate Professor at Harvard Medical School

Clinical Focus: Inherited bleeding disorders

Research Focus: Cost-effectiveness, decision analysis, systems-based hematology



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# Key Learning Objectives

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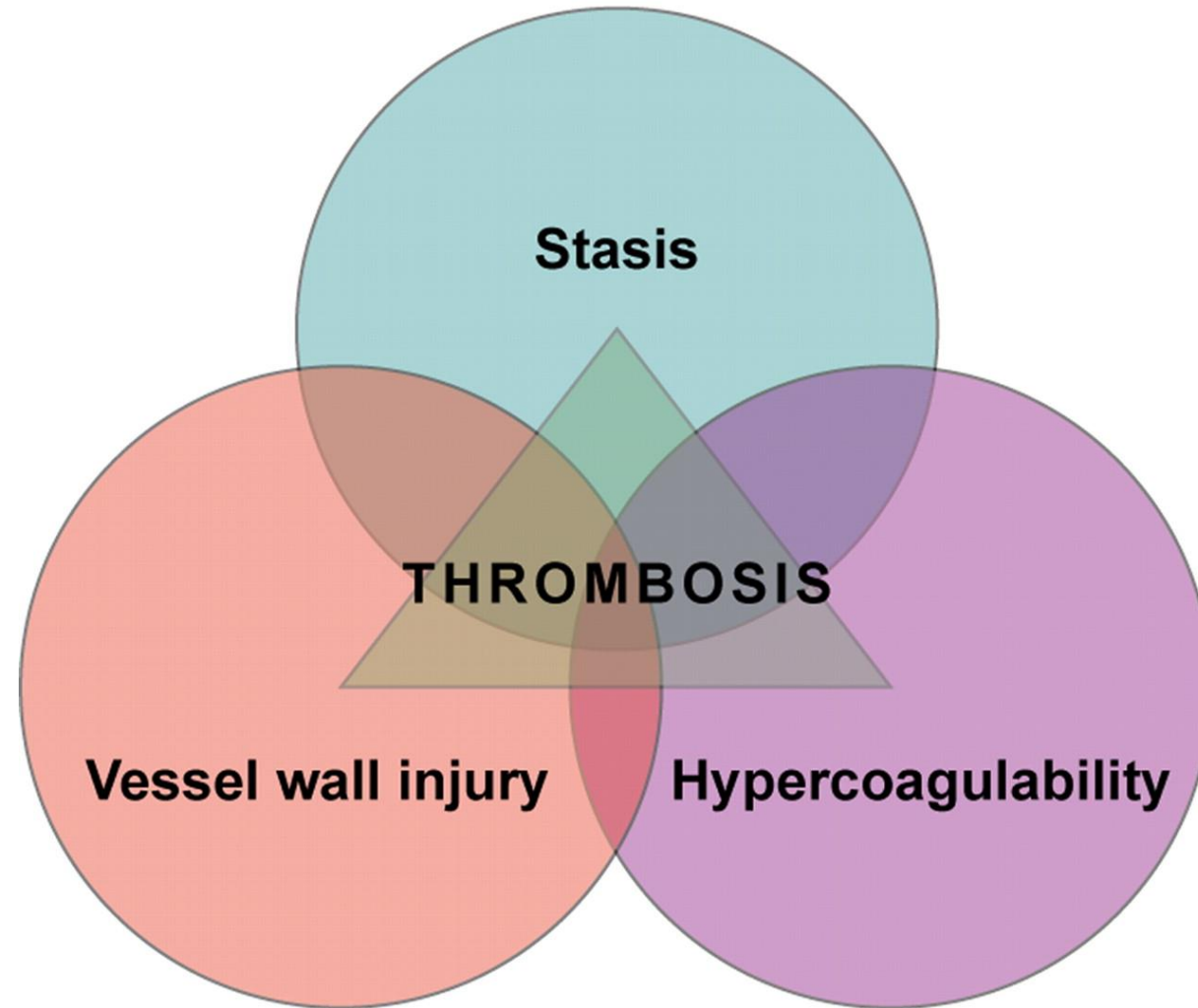
- Review the risk factors for thrombosis and discuss the components and indications for thrombophilia testing
- Review commonly used anticoagulants and their mechanisms of action and outline an approach to anticoagulation reversal

# Disclosures

**Nathan T. Connell, MD, MPH, FACP**

Research Support	None
Honoraria	Octapharma, Pfizer, Sanofi
Advisory Panel/Consultant	Takeda, Genentech, Medzown, Bayer, Sanofi
Stock/Shareholder	Doximity, Medzown
Employee	Brigham and Women's Hospital

# Virchow's triad



Not just inherited  
factors

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# Venous Thromboembolism

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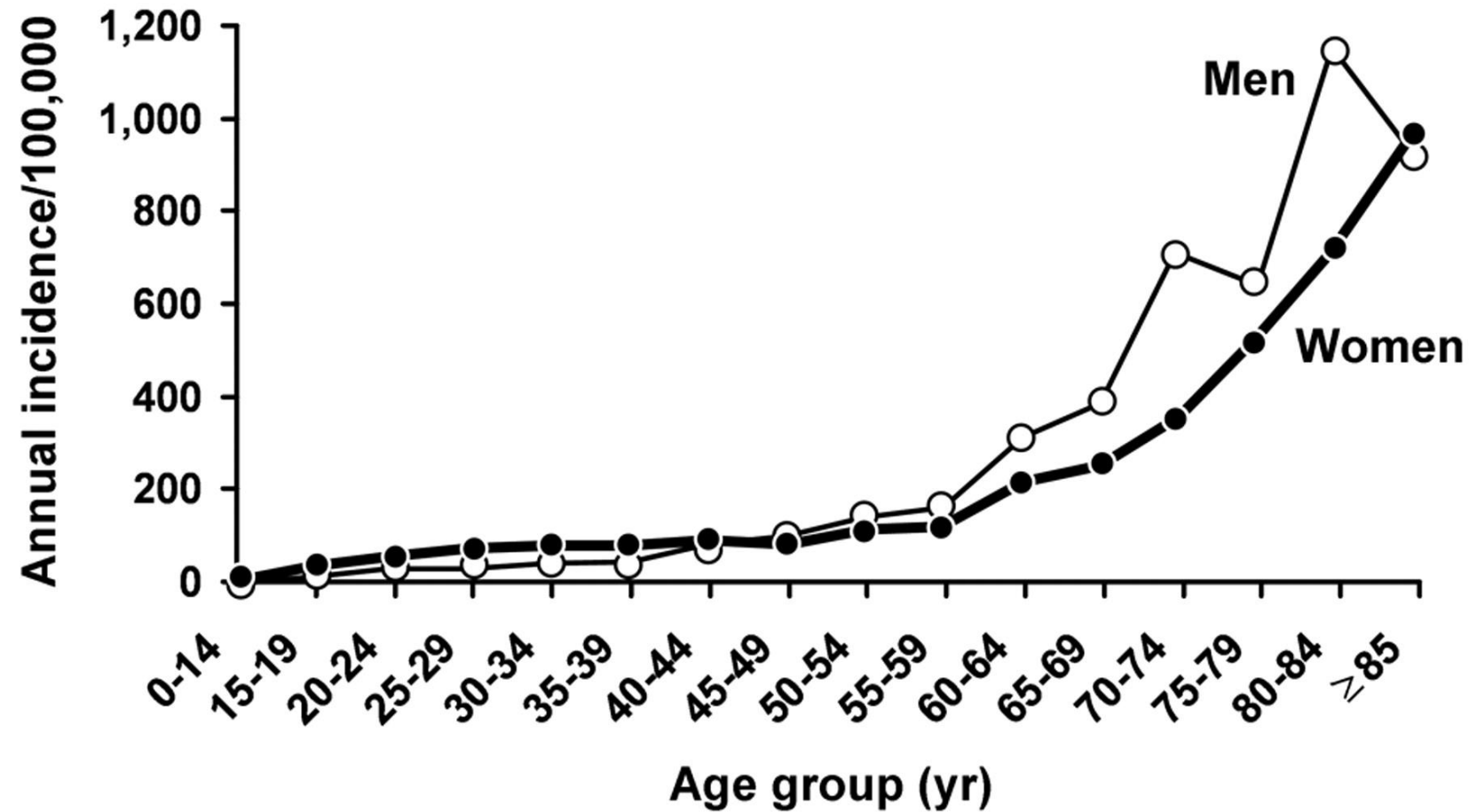
## Risks for hypercoagulable states

- 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.



# 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

???



# 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

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# Inherited Thrombophilias

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- 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

# 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
    - NORVIT (NEJM 2006), HOPE2 (NEJM 2006, Ann Intern Med 2007), VITRO (Blood 2007)
  - Factor VIII
  - Factor XIII polymorphisms, Factors IX, XI, and XII
  - PAI-1 4G/5G promoter, PAI-1

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# Antiphospholipid Antibodies

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- Lupus anticoagulant
  - Screen: functional clotting assays
    - Sensitive aPTT, DRVVT, Kaolin clotting time
  - Confirmatory: remove APLA
    - Platelet neutralization test
    - Hexagonal phase phospholipids
- Anticardiolipin
  - IgG and IgM
- Anti-beta-2-glycoprotein I
  - IgG and IgM

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# Thrombophilia Testing

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- 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
- Recurrent thrombosis
- Positive Family History in 1<sup>st</sup> 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 1<sup>st</sup> degree relative
  - Cerebral venous thrombosis
  - Portal/mesenteric vein thrombosis (MPN evaluation, PNH)
  - ~~Recurrent pregnancy loss (esp 2<sup>nd</sup> and 3<sup>rd</sup> 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

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# Thrombophilia Testing

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- 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



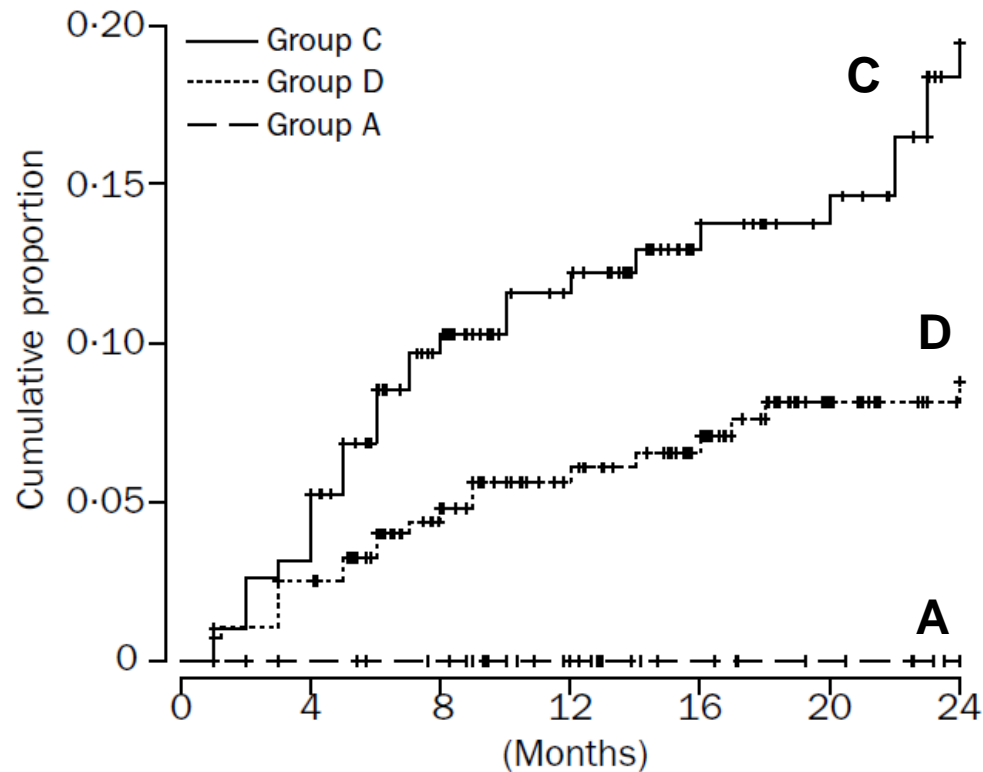
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# Duration of Anticoagulation

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- 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



## Number at risk

Group C	193	184	153	133	110	98	81
Group D	279	269	235	209	185	155	139
Group A	86	82	79	71	61	58	53

A: Postop within 6 weeks

B: Pregnancy VTE (0)

C: Unprovoked

D: Non-surgical risks

n=570 treated 24-27 weeks

Followed 2 years

Tested for thrombophilias  
(no difference in recurrence)

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# Summary: Hypercoagulable States

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- The “hypercoagulable state” is a spectrum of risk, with many patients having multiple additive 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.
- Consult with a specialist can be helpful

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# Anticoagulation

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# Common Parenteral 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
  - Rivaroxaban (XARELTO®)
  - Apixaban (ELIQUIS®)
  - Edoxaban (SAVAYSA®)

# Warfarin (COUMADIN®, JANTOVEN®)

- Not an anticoagulant on its own
- Start same day
- Initiation: Usually 5mg daily
- Adjustment: 3-4 days to see effect

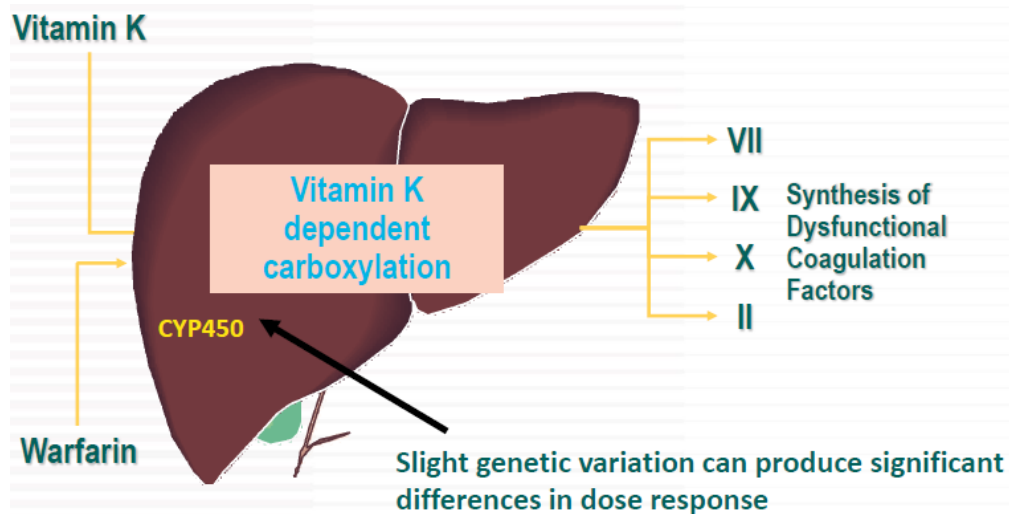
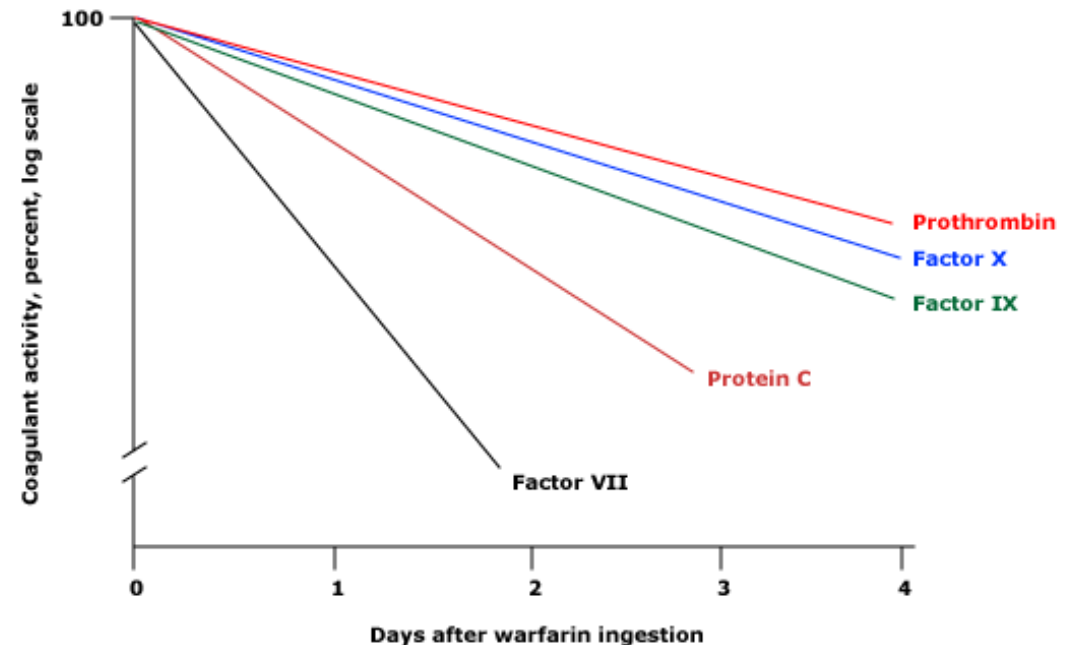
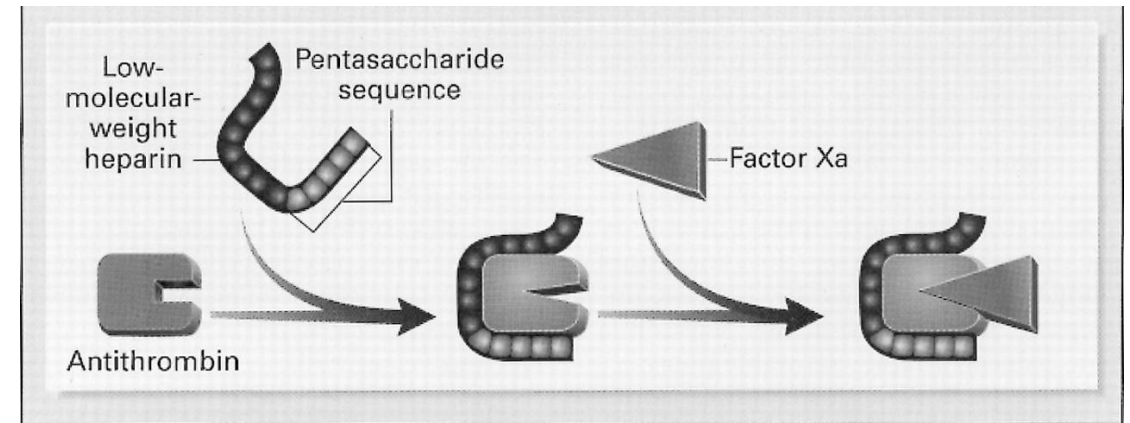
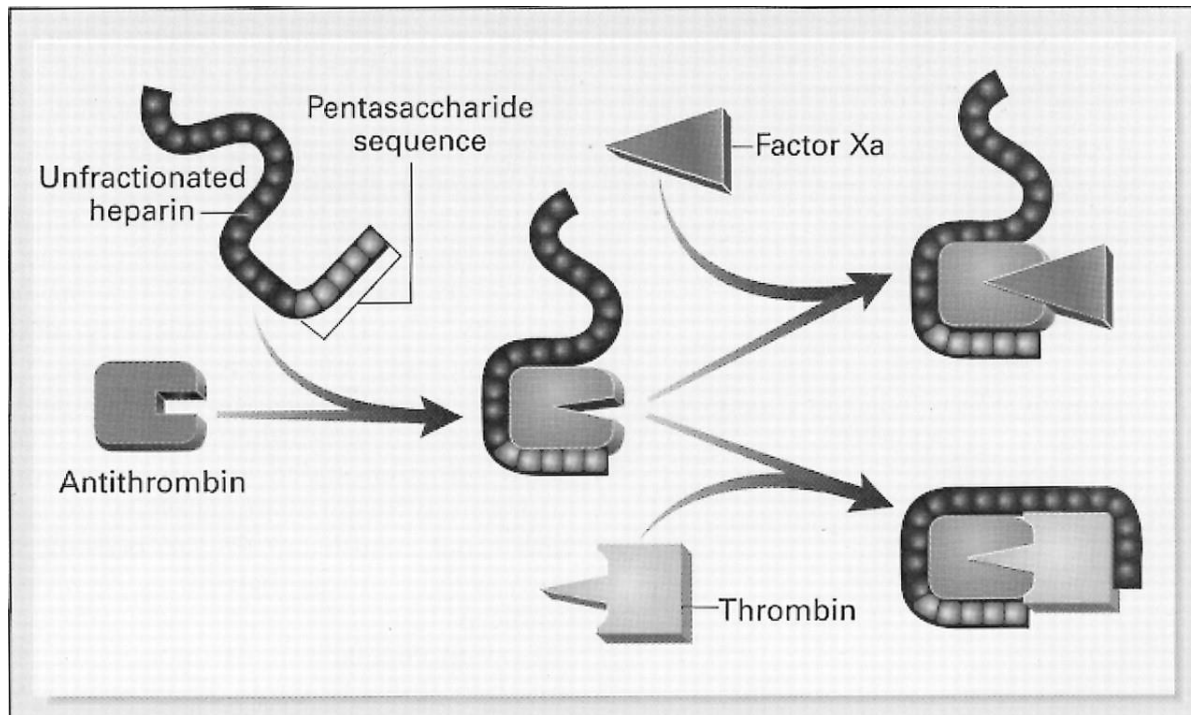


Image courtesy of David Garcia, MD.



# Heparin



# LMWH 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



# DOAC Dosing: Factor II Inhibitor

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	

# DOAC Dosing: Factor Xa Inhibitors

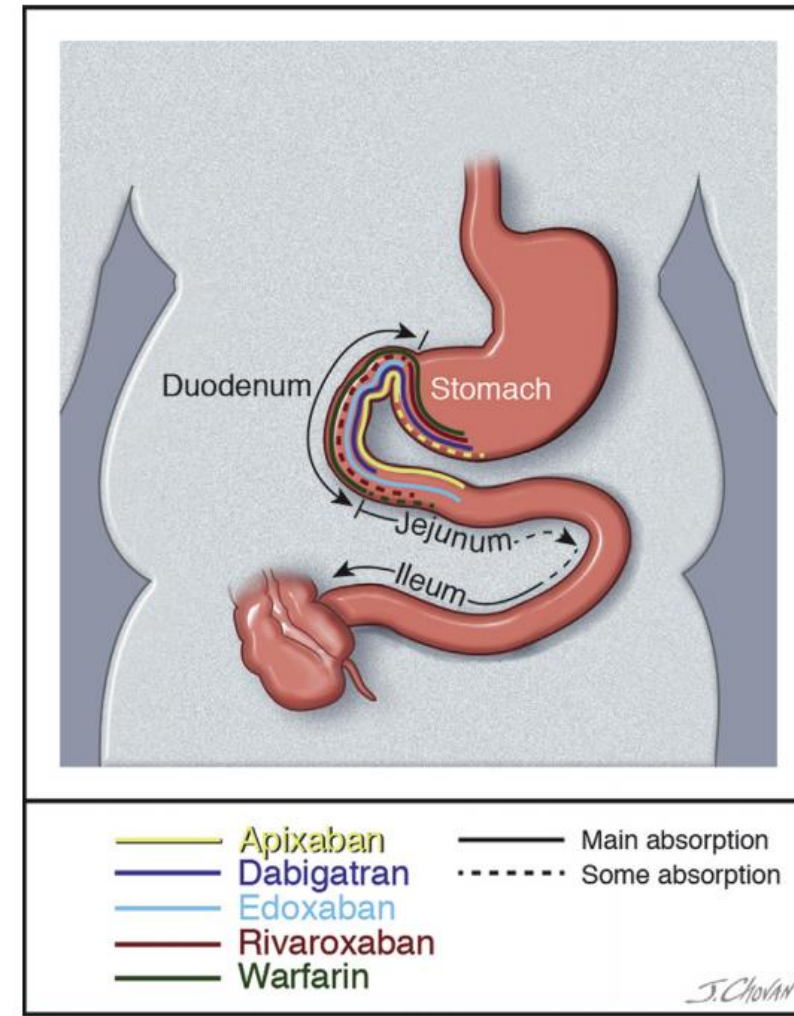
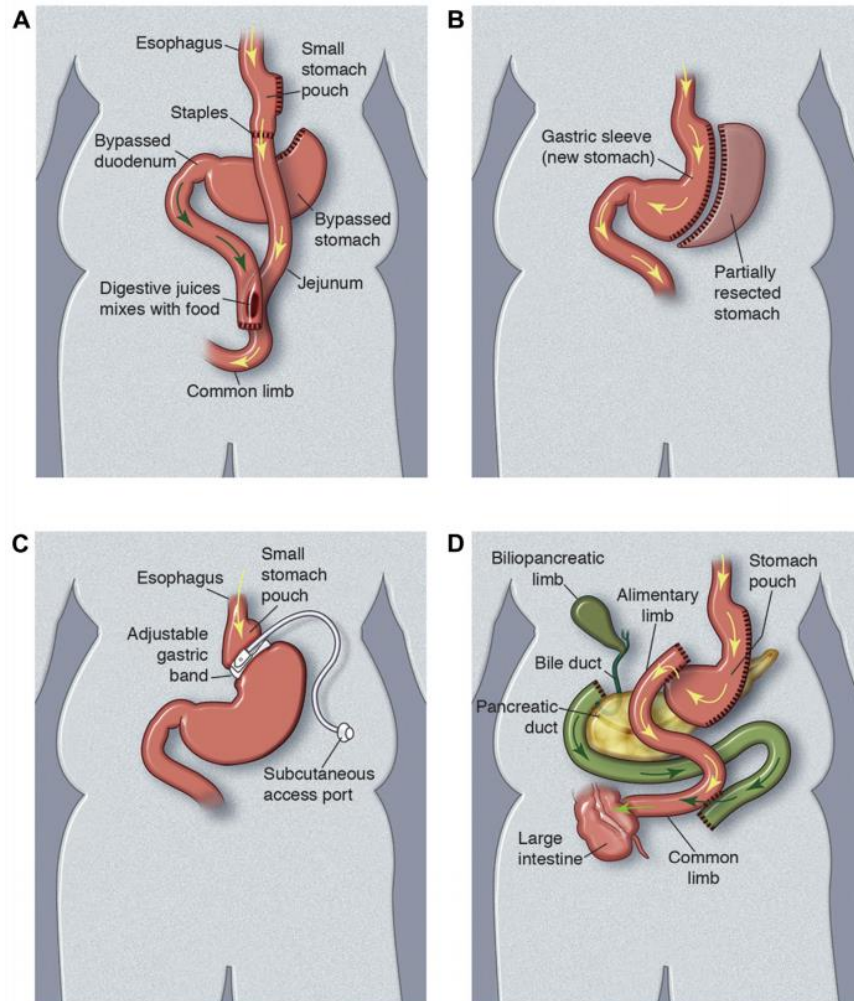
Agent	Route	Prophylaxis	Therapeutic
Rivaroxaban	PO	Knee: 10mg daily X 10d	15mg BID x 21 days, then 20mg daily
		Hip: 10mg daily X 35d	Extended (> 6 months): 10mg daily
		SPAF: 20mg daily	
Apixaban	PO	Knee: 2.5mg BID X 12d	10mg BID x 7 days, then 5mg BID
		Hip: 2.5mg BID X 35d	Extended (>6 months): 2.5mg 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

- ISTH Guidance: Avoid if weight >120kg or BMI >40
  - Retrospective data showing efficacy up to BMI of 50
- Mechanical 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

# DOACs and Bariatric Surgery



# 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

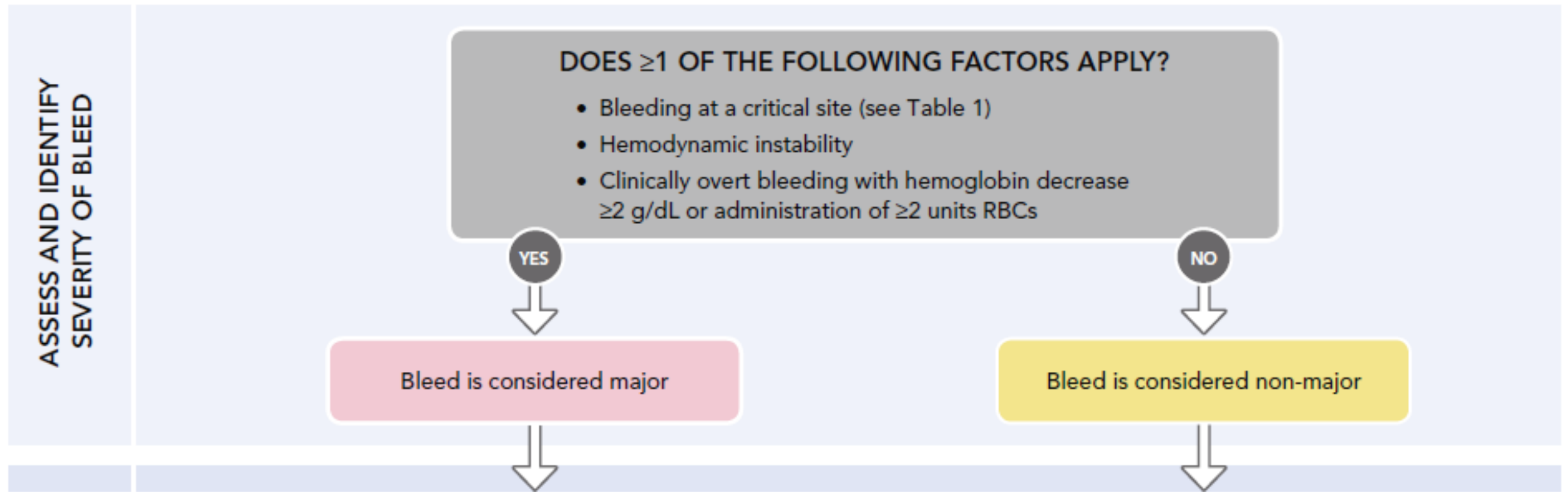
## Adjunctive

- Dialysis
- Desmopressin
- Antifibrinolytic Agents

**EXPERT CONSENSUS DECISION PATHWAY**

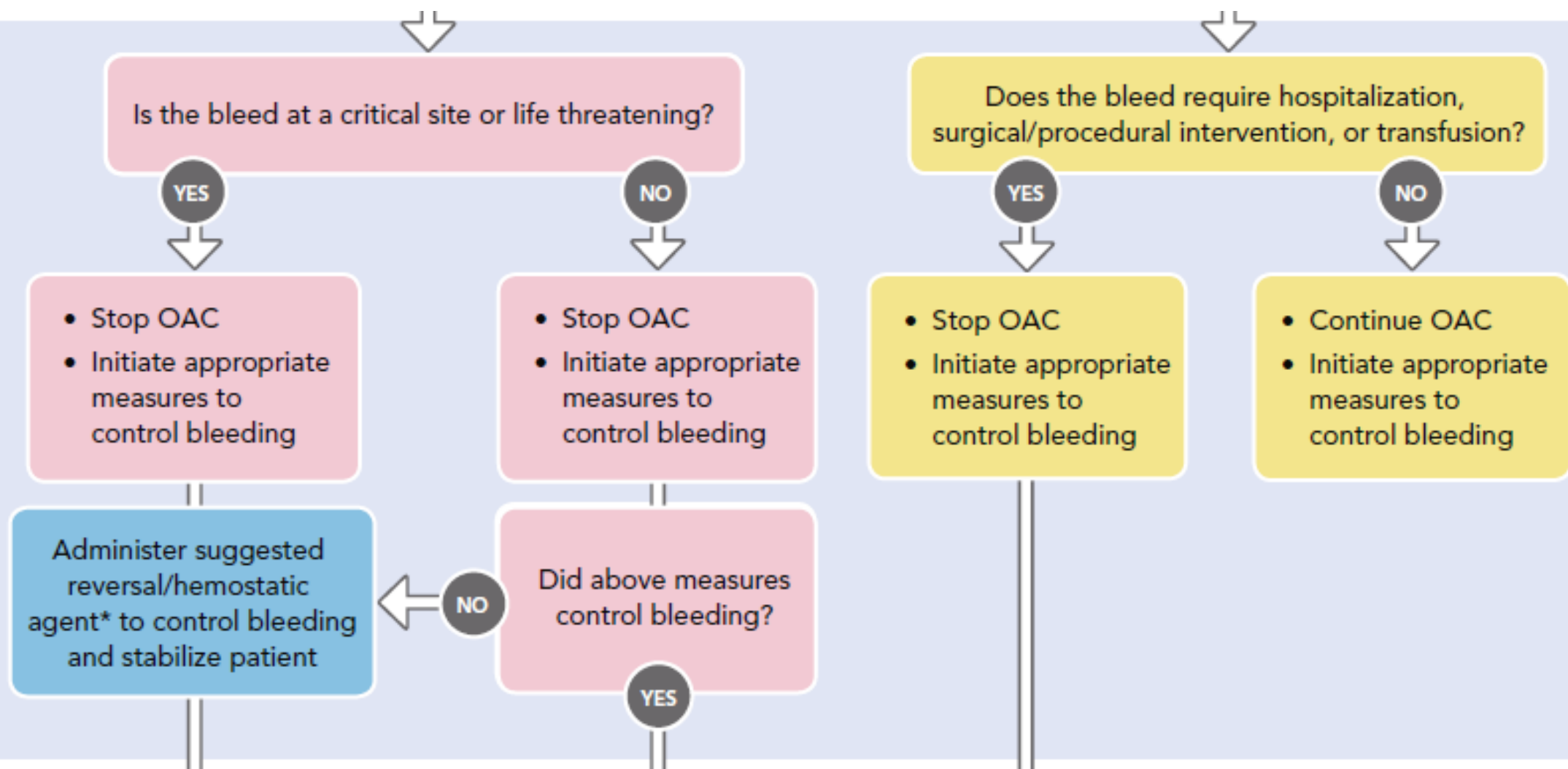
# 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

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



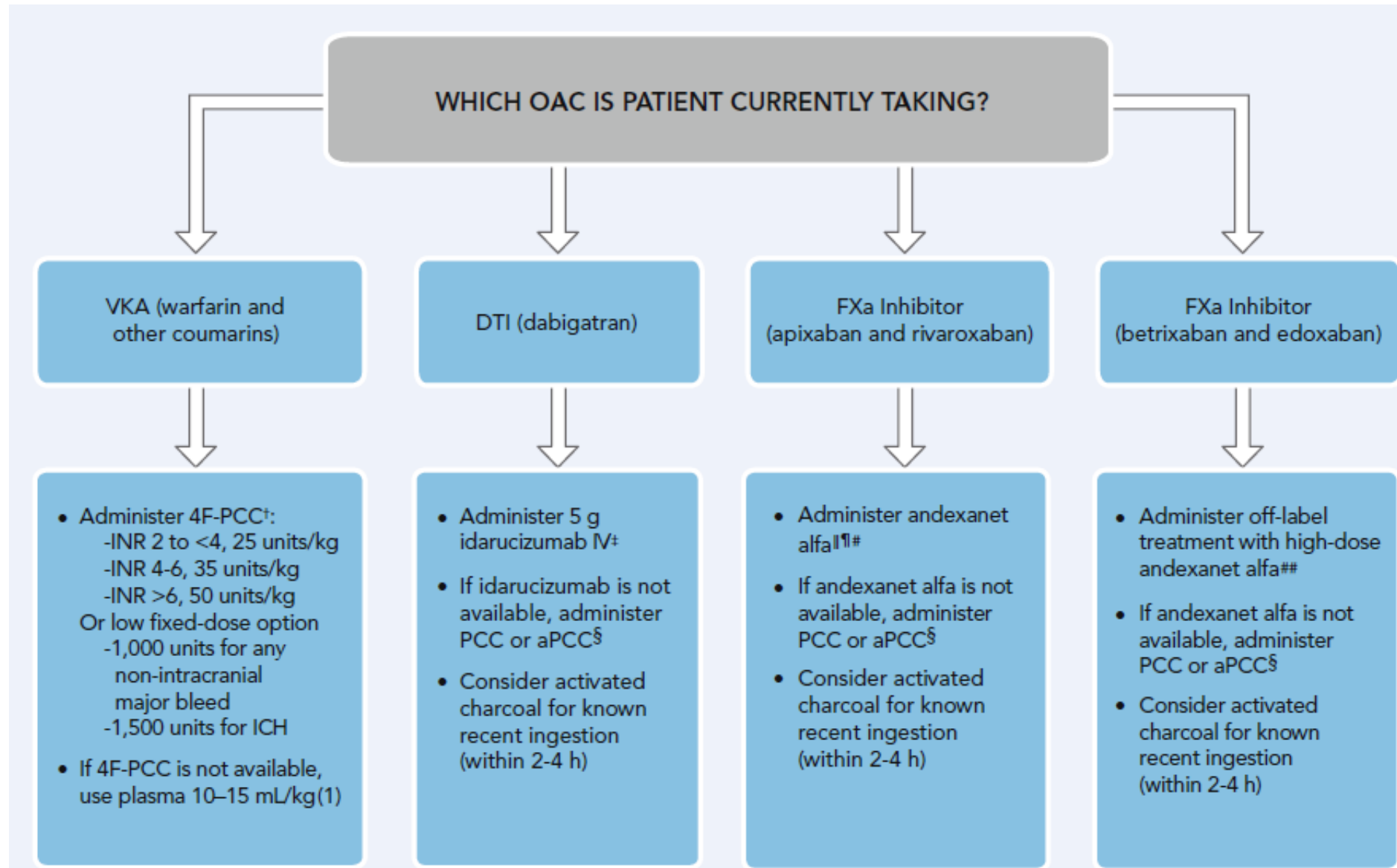


**TABLE 2** Assays Suitable for Quantitation of DOACs

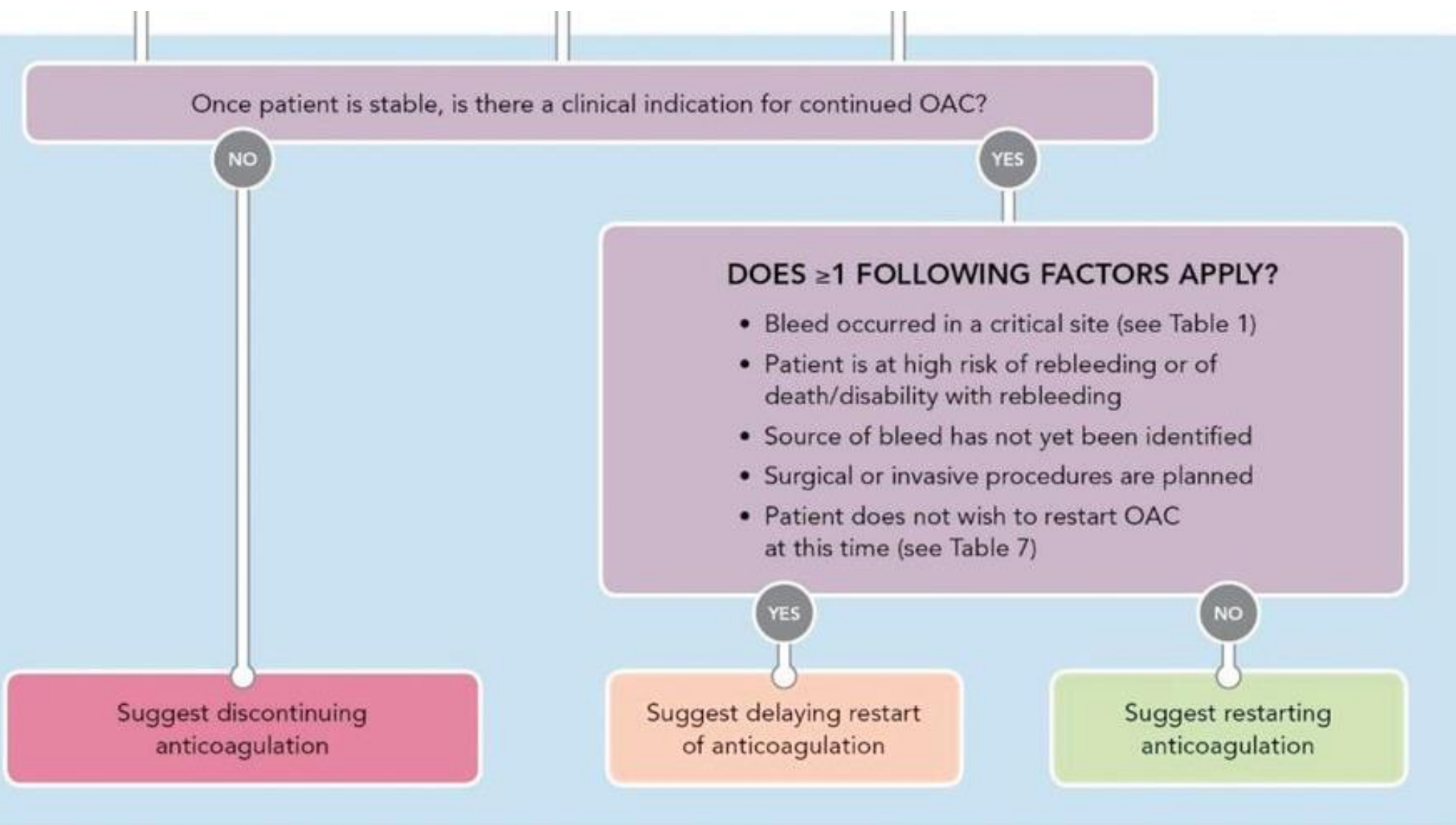
Drug	Suggested Test
Dabigatran	<ul style="list-style-type: none"><li>• Liquid chromatography-tandem mass spectrometry</li><li>• Dilute thrombin time</li><li>• Ecarin clotting time</li><li>• Ecarin chromogenic assay</li></ul>
Apixaban, betrixaban, edoxaban, or rivaroxaban	<ul style="list-style-type: none"><li>• Liquid chromatography-tandem mass spectrometry</li><li>• Anti-FXa*</li></ul>

**TABLE 3** Suggestions for Qualitative Assessment of DOACs When Assays Suitable for Quantitation Are Not Available

Drug	Clinical Objectives			
	Exclude Clinically Relevant* Drug Levels		Determine Whether On-Therapy or Above On-Therapy Levels Are Present	
	Suggested Test	Interpretation	Suggested Test	Interpretation
Dabigatran	TT, aPTT	<ul style="list-style-type: none"> <li>• <b>Normal TT</b> excludes clinically relevant* levels.</li> <li>• <b>Prolonged TT</b> does not discriminate between clinically significant and insignificant levels.</li> <li>• <b>Normal aPTT</b> usually excludes clinically relevant* levels if a sensitive reagent is used.</li> </ul>	aPTT	<ul style="list-style-type: none"> <li>• <b>Prolonged aPTT</b> suggests that on-therapy or above on-therapy levels are present.</li> <li>• <b>Normal aPTT</b> may not exclude on-therapy levels, particularly if a relatively insensitive aPTT reagent is used.</li> </ul>
Apixaban	UFH or LMWH anti-FXa	<ul style="list-style-type: none"> <li>• <b>Normal PT and aPTT</b> do not exclude clinically relevant* levels.</li> <li>• <b>UFH or LMWH anti-FXa below the lower limit of quantitation</b> probably excludes clinically relevant* levels.</li> </ul>	PT	<ul style="list-style-type: none"> <li>• <b>Prolonged PT</b> suggests that on-therapy or above on-therapy levels are present.</li> <li>• <b>Normal PT</b> may not exclude on-therapy or above on-therapy levels, particularly if a relatively insensitive PT reagent is used.</li> </ul>
Betrixaban, edoxaban, or rivaroxaban	UFH or LMWH anti-FXa	<ul style="list-style-type: none"> <li>• <b>Normal PT and aPTT</b> does not exclude clinically relevant* levels.</li> <li>• <b>UFH or LMWH anti-FXa below the lower limit of quantitation</b> probably excludes clinically relevant* levels.</li> </ul>	PT	<ul style="list-style-type: none"> <li>• <b>Prolonged PT</b> suggests that on-therapy or above on-therapy levels are present.</li> <li>• <b>Normal PT</b> may not exclude on-therapy levels, particularly if a relatively insensitive PT reagent is used.</li> </ul>



DETERMINE WHETHER AND WHEN TO  
RESTART ANTICOAGULATION



# Late-Breaking Abstract (ISTH 2025)

- The COBRRA Trial (randomized n=2760, prospective, open/blinded endpoint trial) compared clinically relevant bleeding events between rivaroxaban and apixaban in acute VTE treatment (3 months)
- The primary outcome was independently adjudicated 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.***

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# “New” Anticoagulants!

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- For many years, “new” anticoagulants meant DOACs (Xa or IIa)
- Anticoagulants in pipeline (Not FDA approved)
  - Abelacimab (Factor XI inhibitor)
  - Osocimab, milvexian, and asundexian (Factor XIa inhibitors)
  - Tecarfarin (VKA with different CYP450 profile than warfarin)
  - Garadacimab (Factor XII inhibitor)
  - Novel antisense oligonucleotides therapeutics targeting FXI
  - Novel small molecule therapeutics targeting FXI, FXII, FII

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# Summary: Anticoagulation

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- 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



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# MOC Reflective Statement

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- 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



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# MOC Reflective Statement

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- 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 anticoagulation 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

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## 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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# References

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- Agnelli G, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013 Feb 21;368(8):699-708.
- Agnelli G, et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. *N Engl J Med*. 2020 Apr 23;382(17):1599-1607. doi: 10.1056/NEJMoa1915103.
- Connors JM. Thrombophilia Testing and Venous Thrombosis. *N Engl J Med*. 2017 Sep 21;377(12):1177-1187. doi: 10.1056/NEJMra1700365.
- Martin KA, et al. Oral Anticoagulant Use After Bariatric Surgery: A Literature Review and Clinical Guidance. *Am J Med*. 2017 May;130(5):517-524. doi: 10.1016/j.amjmed.2016.12.033.
- Tomaselli GF, et al. 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. *J Am Coll Cardiol*. 2020 Aug, 76 (5) 594–622.