Brigham and Women's Hospital
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Hypercoagulable States

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

BRIGHAM HEALTH
BRIGHAM AND WOMEN'S
Department of Medicine

Dana-Farber
Cancer Institute

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Postgraduate
Medical Education

Jean M Connors, MD

- Johns Hopkins University School of Medicine
- Medical Residency: BIDMC-East
- Hematology-Oncology Fellowship: BWH
- Transfusion Medicine Fellowship: HMS Program in Transfusion Medicine
- Professor of Medicine: HMS
- Associate Editor: Journal of Thrombosis and Haemostasis
- Research interests: thrombosis and anticoagulation across many clinical settings

DISCLOSURES

Disclosures/Conflicts of Interest

Scientific Ad Boards and Consulting:
- Abbott
- Anthos
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- Pfizer
- Roche
- Sanofi
- Werfen

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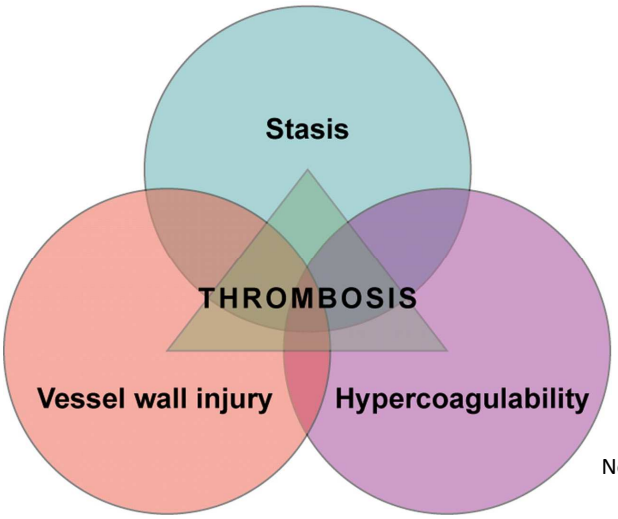
- CSL Behring

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

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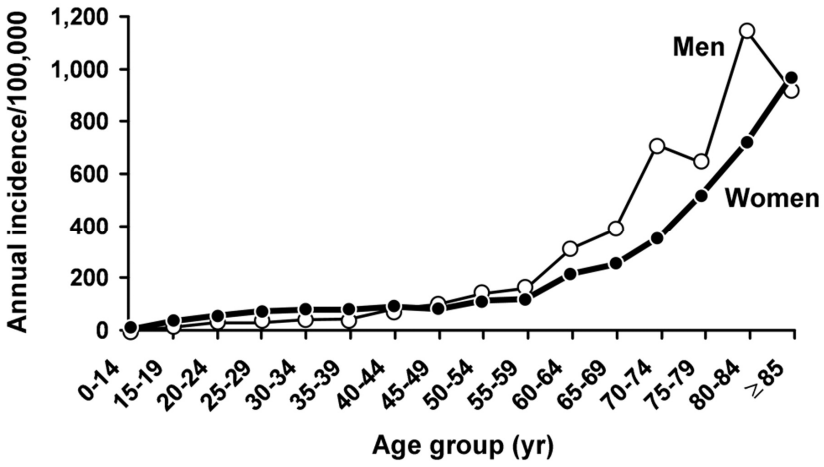
Annual incidence of venous thromboembolism by age and sex.



Heit J A Hematology 2007;2007:127-135

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Acquired Risk Factors for VTE

TRANSIENT/PROVOKED	PERSISTENT	IDIOPATHIC/UNPROVOKED
Surgery Trauma Acute Medical Illness Immobilization Estrogen OCP, HRT Pregnancy HIT Prolonged Air Travel	Obesity Increasing Age Chronic Medical Illness Cancer/Therapies Thalidomide Tamoxifen IBD Nephrotic syndrome MPN/PNH Sickle cell disease	???

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Acquired Deficiencies

ANTITHROMBIN	PROTEIN C	PROTEIN S
Pregnancy		Pregnancy
Liver Disease	Liver Disease	Liver Disease
DIC	DIC	DIC
Nephrotic Syndrome		
Major Surgery		Inflammation
Acute Thrombosis	Acute Thrombosis	Acute Thrombosis
Treatment with:	*Treatment with:*	*Treatment with:*
Heparin	Warfarin	Warfarin
Estrogen		Estrogen

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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

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Thrombophilia Tests and Prevalence of Risk Factors

Table 3. Thrombophilia Tests and Prevalence of Risk Factors.*

Thrombophilia Type	Assay	Prevalence
Inherited		
Increased procoagulant activity (common)		
Factor V Leiden	APCR and PCR	White, 5.0% Hispanic, 2.2% Black, 1.2% Native American, 1.2% Asian, 0.4%
Prothrombin gene mutation	PCR	White, 3%
Decreased anticoagulant activity (uncommon)		
Protein C	Activity assay	<0.5%
Protein S	Activity assay	<0.5%
Antithrombin	Activity assay	<0.5%
Acquired		
Lupus anticoagulants†	In vitro clotting assay: PTT-LA, dRVVT, silica clotting time ELISA: ACL IgG and IgM, beta-2 glycoprotein 1 IgG and IgM	Overall, 0–5% Patients with VTE, 10–12% Patients with SLE, 35%

et al.[24] and Petri et al.[25] ACL denotes anticardiolipin, APCR activated protein C resistance (a plasma test for the presence of

Connors
NEJM 2017

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Antiphospholipid Antibodies*

- 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

*** Please do not test for clot based assays when on an anticoagulant**

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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

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Clinical Clues for Inherited Thrombophilia

- Age of onset <50 years
- 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)	+	+

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Why Test?

- 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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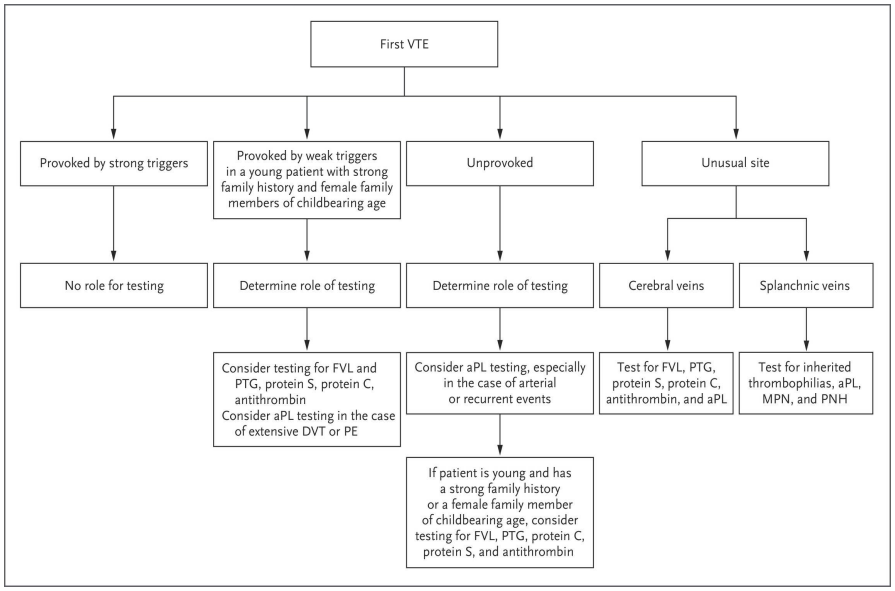
Algorithm for Selecting Patients with a First Venous Thromboembolism (VTE) for Thrombophilia Testing.



Connors NEJM 2017

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Summary: Hypercoagulable States

- 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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Direct Oral Anticoagulants

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Approach to DOAC Selection

Consider:

- Indication for treatment
- Duration of treatment
- Age
- Weight
- **Drug-drug interactions**
- **N/V/D**
- Renal function
- Hepatic function
- History and location of bleeding/bleeding risk
  - GI
  - Intracranial
- Niche populations: cancer, APS, ESRD
- **Insurance coverage—and timeliness of obtaining drug**
- Compliance

Properties of Direct Oral Anticoagulants

Property	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Bioavailability	6 – 7%	80%	66%	45%
Tmax	1.5 hours	2 – 4 hours	1 – 3 hours	1 – 2 hours
T½	12 – 14 hours	9 – 13 hours	8 – 15 hours	9 – 11 hours
Hepatic Metabolism	No	Yes	Yes	Yes
Drug Interactions	P-gp	CYP3A4/P-gp	CYP3A4/ P-gp	P-gp
Protein Binding	35%	90%	87%	55%
Renal Elimination	80%	35%	25%	50%
Reversal agent	idarucizumab	Andexanet 4F-PCC	Andexanet 4F-PCC	Andexanet* 4F-PCC

* Not approved for this indication but it works

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	

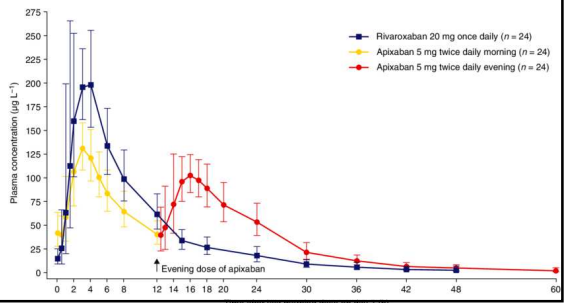
DOAC Dosing: Factor Xa Inhibitors

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)

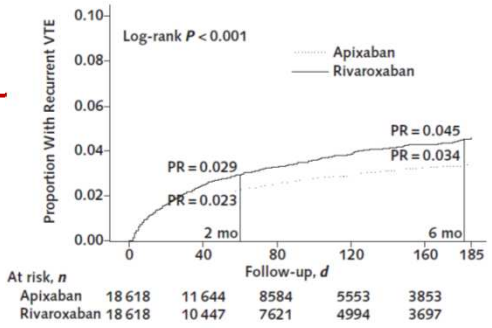
Apixaban vs rivaroxaban

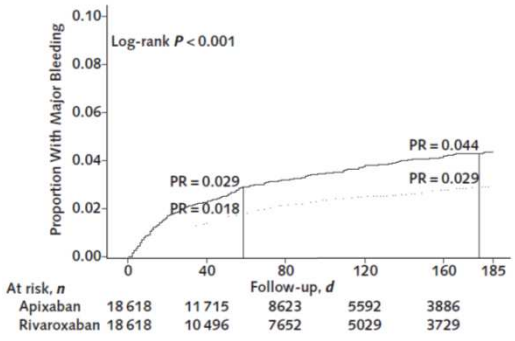
- Top prescribed DOACs
- The once-a-day dosing strategy for rivaroxaban compared to twice-a-day dosing for apixaban can result in increased bleeding in certain situations:
  - Decreased renal function
  - Age
  - GI bleeding
  - Menorrhagia
- Understanding the differences can help prescribe the appropriate drug, insurance not withstanding



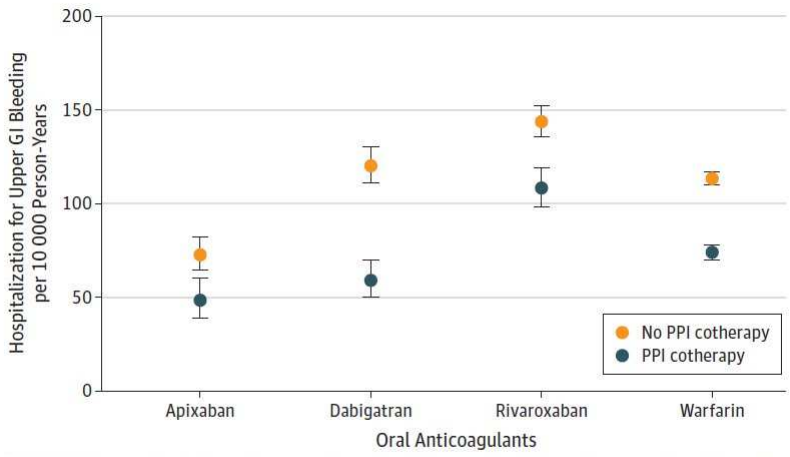
VTE: Apixaban vs rivaroxaban

- Retrospective new–user cohort from health insurance database
- Propensity score matched
  - Mean age 67 yrs after matching
- 18,618 patients in each group
- Median follow-up 102 and 105 days
- **Absolute reduction recurrent VTE** **0.011** (0.011-0.013) at 6 mo
- **Absolute reduction in GIB and ICH** **0.015** (0.013-0.015) at 6 mo





Dawwas Annals of IM, 2021



RD (95% CI)	-24 (-38 to -11)	-61 (-75 to -47)	-36 (-49 to -22)	-39 (-44 to -34)
IRR (95% CI)	0.66 (0.52 to 0.85)	0.49 (0.41 to 0.59)	0.75 (0.68 to 0.84)	0.65 (0.62 to 0.69)

Retrospective cohort study Medicare patients.
compare incidence of hospitalization for upper GI tract bleeding in patients using anticoagulants with and without PPI.

Ray, JAMA , Dec 2018

Hepatic Insufficiency

- **No or limited clinical trial data for use in patients with liver failure, so no dose recommendations available.**
- Use in patients with mild impairment Childs A probably ok, risk benefit analysis.
- Do not use with moderate or severe impairment, Childs B or C,
- Coagulopathy due to hepatic synthetic function is the primary concern

Extremes of Weight: summary of data

- **Most trials enrolled patients between 60-100 kg**
  only 12% in VTE studies had BMI > 35
- **Current package inserts:**

Edoxaban: for VTE treatment reduce dose to 30 mg qd for patients ≤ 60 kg

Apixaban: reduce dose for weight ≤ 60 kg and if age ≥ 80 years or creatinine ≥ 1.5 mg/dl

- **Use caution in patients <60 kg or >120 kg**

	Phase 3 Studies Comparing DOACs with VKA in VTE		Phase 4 Studies Comparing DOAC with VKA in VTE (Including Retrospective and Prospective Studies and Meta-analyses)	
	BMI >35 or BW >120 kg	BMI >40	BMI >35 or BW >120 kg	BMI >40
Apixaban	X	X	Similar outcomes[6]	Similar outcomes[5,6]
Dabigatran	X	X	X	X
Edoxaban	X	X	X	X
Rivaroxaban	Similar outcomes[7]	X	Similar outcomes[5,8-10]	Similar outcomes[5,9]
Pooled DOAC	Similar outcomes[11]	X	Similar outcomes [12-16]	Similar outcomes[12]

Note: Similar outcome = DOAC compared with LMWH/VKA; X = no available data.

Abbreviations: BMI, body mass index, expressed in kg/m^2; BW, body weight; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

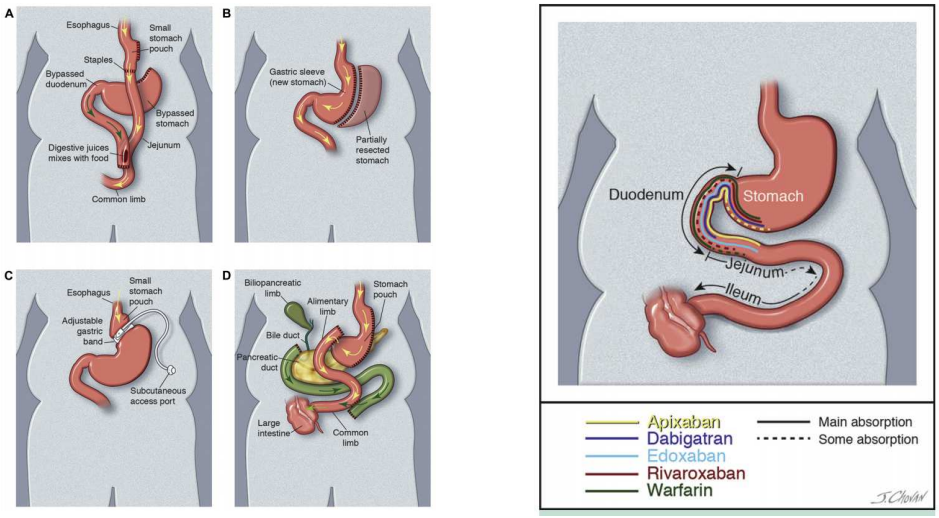
Martin, JTH, 2021

Updated Summary Guidance Statements for use of DOACs for VTE in patients with obesity

1) Consistent with the 2016 ISTH SSC recommendations, we conclude that the use of any DOAC is appropriate for patients with BMI up to 40 kg/m^2 or weight 120 kg. For patients with BMI > 40 kg/m^2 or weight >120 kg, we recommend that the individual DOACs should be used as follows:
2) For treatment of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Less supportive data exist for apixaban than rivaroxaban. VKA, weight-based LMWH (per manufacturers' recommendations), and fondaparinux are also options.
3) For primary prevention of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Drug approval is restricted to elective hip and knee arthroplasty and (in some countries) extended VTE prevention following acute medical illness.
4) We suggest not to use dabigatran, edoxaban or betrixaban for VTE treatment and prevention in patients with BMI >40 kg/m^2 or weight >120 kg, given unconvincing data for dabigatran, and lack of clinical or PK/PD data for edoxaban and betrixaban.
5) We suggest not to regularly follow peak or trough drug-specific DOAC levels because there are insufficient data to influence management decisions.
6) We suggest not to use DOAC for treatment or prevention of VTE in the acute setting after bariatric surgery because of concerns of decreased absorption), and instead, to initiate such patients on parenteral anticoagulation in the early postsurgical phase. We suggest that switching to VKA or DOAC may be considered after at least 4 weeks of parenteral treatment, and if so, suggest obtaining a DOAC trough level to check for drug absorption and bioavailability.

Martin et al *J Thromb Haemst* 2021

DOACs and Bariatric Surgery



Am J Med. 2017 May;130(5):517-524

DOAC in ESRD: caution

- Apixaban FDA approved for use in ESRD based on 1 dose given to 16 patients
- Apixaban and rivaroxaban have dosing guidelines for decreased creatinine clearance to 15 ml/min
- Data from many retrospective studies suggest improved outcomes with apixaban vs warfarin for efficacy and safety however:
  - Highly selected patients, many given reduced dose for unclear reasons
  - patient characteristics that influenced physicians initially to choose apixaban or switch to apixaban from warfarin are unknown
  - Even with propensity score matching and weighting there are significant limitations with this kind of data

Siontis *Circulation* 2018, Hanni *Blood Advances* 2020

DOAC in ESRD

- **RENAL–AF** an **RCT** of warfarin vs apixaban stopped early due to low accrual, loss of funding Pokorney *Circ* 2022
  - mITT: **82** patients apixaban: 24 on 2.5 bid; **72** warfarin, TTR 44%
    Primary outcome **CRNMB:** 31.5% apixaban vs 25.5% warfarin
- Need better data to ensure safety
- Data do show sustained increase in peak and trough plasma concentrations compared with patients with normal renal function
  - at least 30% higher, not clear if these are clinically relevant
  - Dosing strategy debated and not known: reduce dose vs full dose?
  - Reversal: if on kidney transplant list would use warfarin
- I rarely use apixaban in patients on dialysis, and only for short term treatment

DOAC in mechanical cardiac devices: do not use

Mechanical heart valves

- RE-ALIGN: dabigatran associated with increased strokes compared to warfarin
  Eikelboom NEJM 2013
- PROACT Xa: DSMB closed trial Sep 23, 2022 as apixaban associated with increased strokes compared to warfarin with the On-X aortic valve

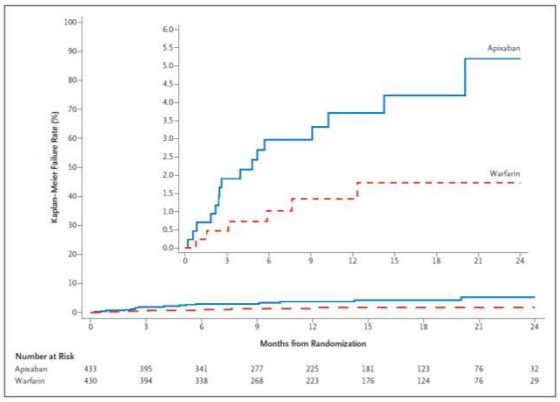


Figure 2. Cumulative Incidence of Valve Thrombosis or Valve-Related Thromboembolism.

Wang, NEJM Evidence, 2023

DOAC in antiphospholipid syndrome: use extreme caution

"triple positive" APS

- Anticardiolipin IgG or IgM
- beta 2 glycoprotein1 IgG or IgM
- Lupus anticoagulant or DRVVT

- TRAPS trial: more recurrent events with rivaroxaban than warfarin Pengo *Blood* 2018
- Arterial events: MI and stroke even if 1st event was venous *Blood*

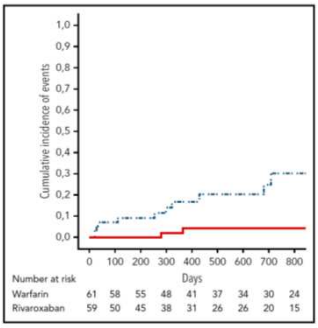


Figure 1. Cumulative incidence of events (death, thromboembolic events, and major bleeding) in the rivaroxaban group (dotted and dashed line) and in the warfarin group (solid line).

- **Do not use DOAC in triple positive APS**
- Would **not** use in patients with **arterial** events even if only single or double positive
- Would only use in low risk VTE and single positive if patient fully aware of the data

My Approach for VTE

- **Young patient limited duration**
  - Rivaroxaban
  - Apixaban
  - Why: no need for parenteral agent
    - Edoxaban and dabigatran need 5 days of enoxaparin or similar

- **Old patient limited duration**
  - Apixaban
  - Why: no need for parenteral agent
    - lowest renal clearance
    - less GI bleeding
    - lower peak intensity anticoagulation
    - Health claims database analysis show lowest bleeding

My Approach for VTE

- **Special situations**
  - Must must must be able to reverse: dabigatran or warfarin
    - Rivaroxaban and apixaban can use andexanet but shorter duration of reversal effect
  - Crushed for feeding tube: apixaban, rivaroxaban
  - GI disorders prone to bleeding: apixaban
  - Cancer associated VTE: apixaban→major bleeding rates are lower than other DOAC
- **Extended duration—prophylactic dose for secondary VTE prevention ***
  - Rivaroxaban
  - Apixaban

* Usually unprovoked VTE

My Approach for NVAF

- **Mitral Valve disease and AF: due to rheumatic valve disease**
  - **do not use DOAC**
    - INVICTUS study: NEJM Aug 28, 2022: rivaroxaban associated with increased mortality compared to VKA
- **Young patient**
  - Apixaban
  - Dabiagtran--superior for decreased ICH but 80% renal clearance
  - Rivaroxaban—once a day
  - No: edoxaban if CrCl > 95 ml/min
- **Older patient**
  - Based on renal function and GI bleed risk:
  - High GI bleed risk
    - Apixaban
    - Edoxaban
  - Low GI bleed risk: any DOAC at appropriate dose

My Approach VTE Prophylaxis

- **Post Orthopedic joint replacement**
  - Rivaroxaban: once a day
  - Over age 80 and increased creatinine: Apixaban
- **Extended Duration in the medically ill**
  - Controversial, betrixaban and rivaroxaban approved
  - Patient risk factors should be fully assessed
- **Off label VTE prophylaxis—air travel**
  - rivaroxaban 10 mg once a day
  - Apixaban 2.5 mg q 12 x 2

DOAC for cancer associated VTE: good for many

- Both risk of bleeding and recurrent VTE higher in patients with cancer regardless of type of anticoagulant
- Patient selection important when treating cancer associated VTE
- DOAC non-inferior to LMWH, some increased major bleeding
- GI bleeding in patients with GI tract tumors increased with rivaroxaban and edoxaban compared to apixaban and LWMH especially if
  - Non-resected luminal primary and active chemotherapy
- **Non-GI tract cancers**:
  - assess bleeding risk, problems with absorption, decreased renal function
  - DOAC should be ok if none of the above
- **GI tract cancers**:
  - Assess location of tumor, metastases
  - Recent GI tract surgery?
    - If yes, avoid DOAC or consider apixaban

Age: dose modification

- **Apixaban**—age >80 considered a reason to dose reduce in the presence of 1 or more other risk factors for stroke prevention for AF, only DOAC with FDA approved dose adjustment for age.

- **VTE studies: mean age 57 years**
- **AF studies: mean age 71.5 years**

- Age and renal insufficiency often concomitantly increased. Traditional methods of assessing CrCl may not apply to patients > 75 yrs+, however renal function not the only factor associated with increased bleeding in the elderly.

Approach to DOAC Selection

– **Do not use at all in the following populations:**
– Mechanical heart valves*, other cardiac hardware
– Pregnant patients
– Lactating women: maybe safe??

Would use with caution in:
– Significant drug interactions → check with pharmacist
– Difficult patients with recurrent events on standard therapy
– Extreme obesity for early acute VTE treatment
– Impaired GI absorption
– Lack of compliance

*absolute contraindication: RE-ALIGN trial, LVAD data

Summary: how to decide

- Younger patients do well with either DOAC or VKA with no real difference in bleeding rates. Older patients appear to do better with DOAC for ICH but not GI bleed
  - Assess factors such as compliance, testing, bleeding risk—ie inflammatory bowel disease, AVMs, elderly and GI bleed risk
- Dose adjustment for renal insufficiency varies by drug
  - Would use cautiously in patients with fluctuating renal function or close to the edge of recommended CrCl
  - Would use very cautiously in dialysis patients until more data available
    - Do not use in patients waiting for cadaveric renal transplant

Summary: how to decide

- Patients with acute VTE should be treated with DOAC unless contra-indications
  - Consider reduced dose for long-term secondary VTE prophylaxis
- Patients with AF should be treated with a DOAC unless mitigating factors
- Co-pay programs available from all companies although donut hole and other insurance issues may make DOAC cost prohibitive—be aware that this is also true for LMWH

Question 1

You are asked to evaluate a 42 yo woman 2 days post bariatric surgery for morbid obesity who has a new Left lower extremity DVT. She weighs 122 kg with a BMI of 47.6, renal function is normal. You recommend:

A. Enoxaparin 120 mg twice daily for 1 month then apixaban 5 mg bid

B. IV unfractionated heparin and then transition to warfarin

C. Edoxaban 60 mg once daily

D. A or B

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