Appropriate Use of DOACs (for Treatment of VTE)

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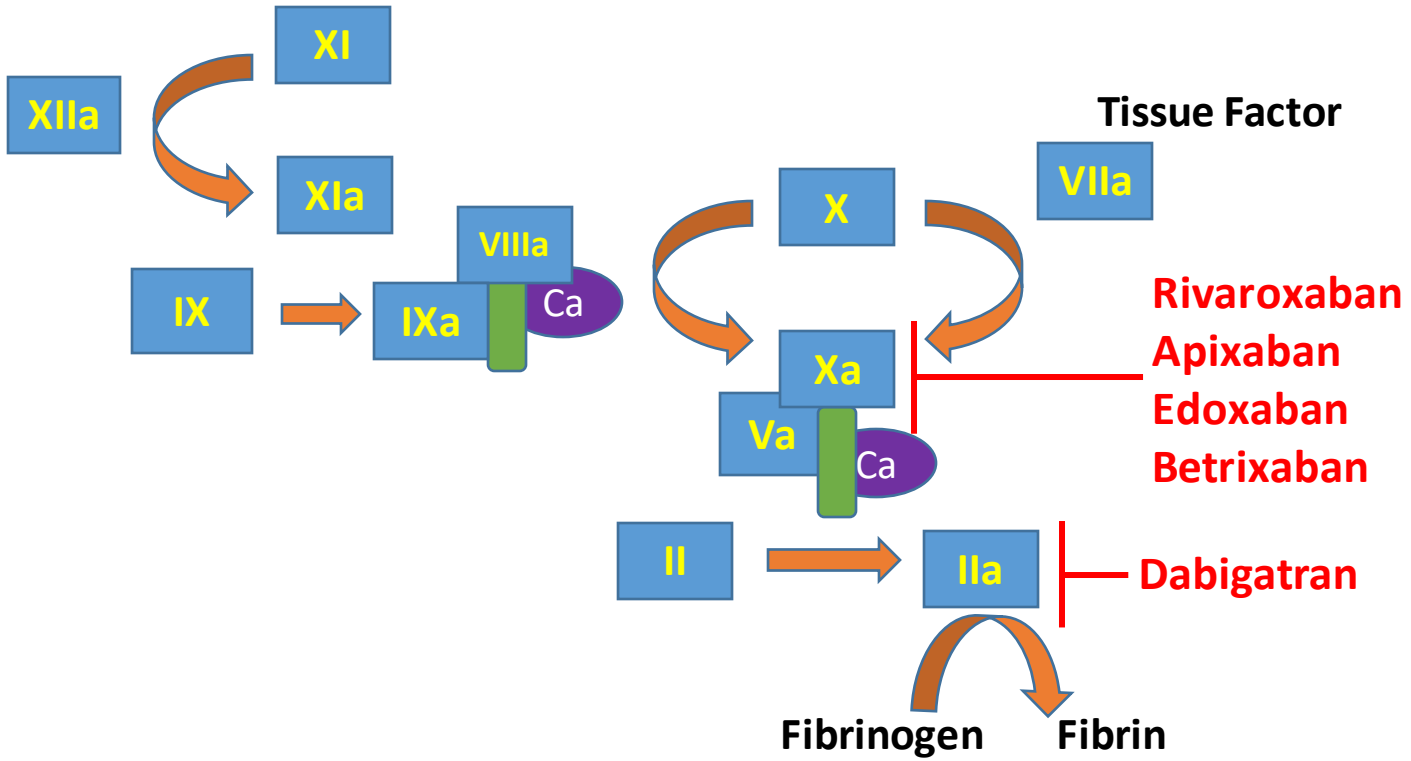
Update in Internal Medicine

4/10/2021

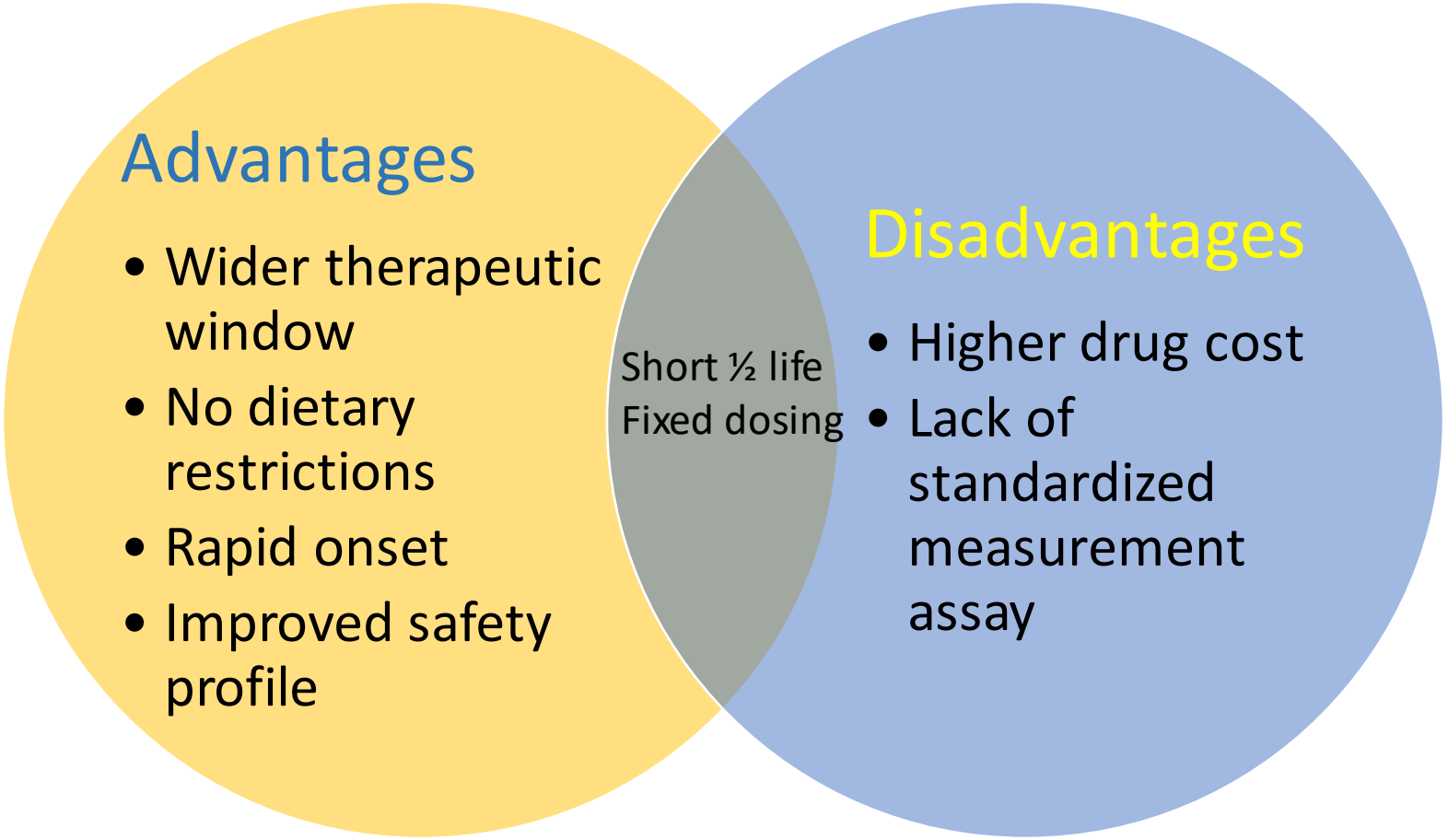
Site of Action of Direct Oral Anticoagulants



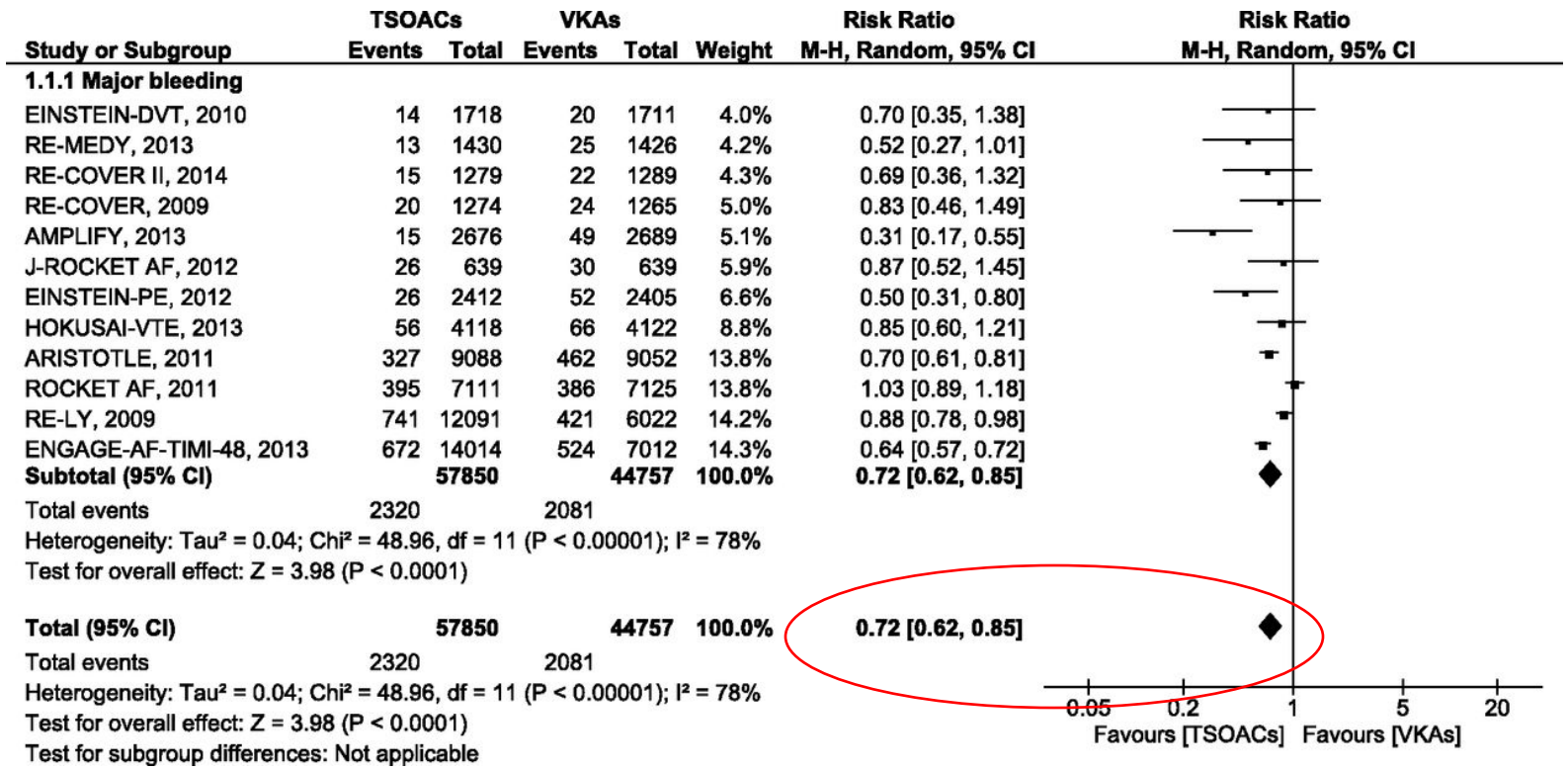
FDA-approved Indications for DOACs

	Stroke Prevention in NVAF	Prevention and Treatment of VTE	Secondary prevention of arterial events in patients with chronic CAD and PVD	Prophylaxis of VTE in hospitalized patients for an acute medical illness
Dabigatran	✓	✓		
Rivaroxaban	✓	✓	✓ in combination with ASA	✓
Apixaban	✓	✓		
Edoxaban	✓	✓		
Betrixaban				✓

DOACs versus Warfarin



Decreased rate of *major bleeding* with DOACs versus Warfarin



Study or Subgroup	TSOACs Events	Total	VKAs Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Major bleeding						
EINSTEIN-DVT, 2010	14	1718	20	1711	4.0%	0.70 [0.35, 1.38]
RE-MEDY, 2013	13	1430	25	1426	4.2%	0.52 [0.27, 1.01]
RE-COVER II, 2014	15	1279	22	1289	4.3%	0.69 [0.36, 1.32]
RE-COVER, 2009	20	1274	24	1265	5.0%	0.83 [0.46, 1.49]
AMPLIFY, 2013	15	2676	49	2689	5.1%	0.31 [0.17, 0.55]
J-ROCKET AF, 2012	26	639	30	639	5.9%	0.87 [0.52, 1.45]
EINSTEIN-PE, 2012	26	2412	52	2405	6.6%	0.50 [0.31, 0.80]
HOKUSAI-VTE, 2013	56	4118	66	4122	8.8%	0.85 [0.60, 1.21]
ARISTOTLE, 2011	327	9088	462	9052	13.8%	0.70 [0.61, 0.81]
ROCKET AF, 2011	395	7111	386	7125	13.8%	1.03 [0.89, 1.18]
RE-LY, 2009	741	12091	421	6022	14.2%	0.88 [0.78, 0.98]
ENGAGE-AF-TIMI-48, 2013	672	14014	524	7012	14.3%	0.64 [0.57, 0.72]
Subtotal (95% CI)		**57850**		**44757**	**100.0%**	**0.72 [0.62, 0.85]**
Total events	2320		2081			
Heterogeneity: Tau² = 0.04; Chi² = 48.96, df = 11 (P < 0.00001); I² = 78%						
Test for overall effect: Z = 3.98 (P < 0.0001)						
Total (95% CI)		**57850**		**44757**	**100.0%**	**0.72 [0.62, 0.85]**
Total events	2320		2081			
Heterogeneity: Tau² = 0.04; Chi² = 48.96, df = 11 (P < 0.00001); I² = 78%						
Test for overall effect: Z = 3.98 (P < 0.0001)						
Test for subgroup differences: Not applicable						

4.64% vs 4%

Absolute risk difference -0.64%, NNT 156

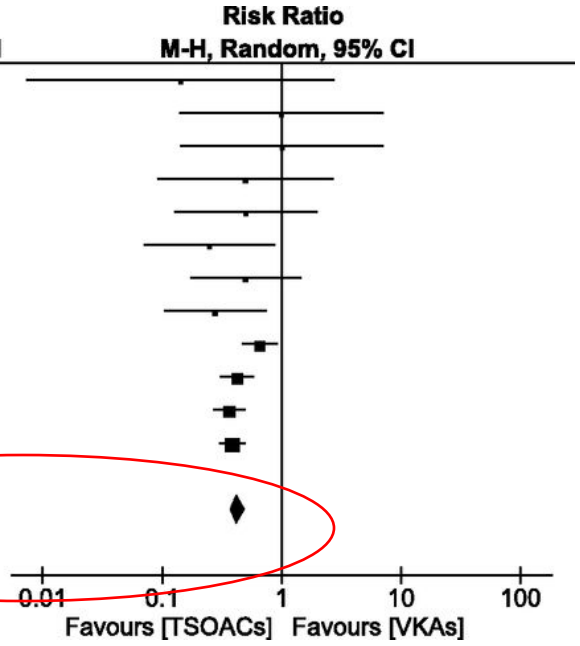
Blood (2014) 124 (15): 2450–2458.

Decreased rate of *intracranial hemorrhage* with DOACs versus Warfarin

Study or Subgroup	TSOACs Events	TSOACs Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
RE-COVER, 2009	0	1274	3	1265	0.3%	0.14 [0.01, 2.74]
EINSTEIN-DVT, 2010	2	1718	2	1711	0.6%	1.00 [0.14, 7.06]
RE-COVER II, 2014	2	1279	2	1289	0.6%	1.01 [0.14, 7.14]
RE-MEDY, 2013	2	1430	4	1426	0.8%	0.50 [0.09, 2.72]
AMPLIFY, 2013	3	2676	6	2689	1.2%	0.50 [0.13, 2.01]
EINSTEIN-PE, 2012	3	2412	12	2405	1.4%	0.25 [0.07, 0.88]
J-ROCKET AF, 2012	5	639	10	639	2.0%	0.50 [0.17, 1.45]
HOKUSAI-VTE, 2013	5	4118	18	4122	2.3%	0.28 [0.10, 0.75]
ROCKET AF, 2011	55	7111	84	7125	18.6%	0.66 [0.47, 0.92]
ARISTOTLE, 2011	52	9088	122	9052	20.3%	0.42 [0.31, 0.59]
RE-LY, 2009	66	12091	90	6022	21.1%	0.37 [0.27, 0.50]
ENGAGE-AF-TIMI-48, 2013	102	14014	132	7012	31.0%	0.39 [0.30, 0.50]
Total (95% CI)		**57850**		**44757**	**100.0%**	**0.43 [0.37, 0.50]**
Total events	297		485			

Heterogeneity: Tau² = 0.00; Chi² = 11.26, df = 11 (P = 0.42); I² = 2%

Test for overall effect: Z = 10.95 (P < 0.00001)



0.51% vs 1.08%

Absolute risk difference -0.57%, NNT 185

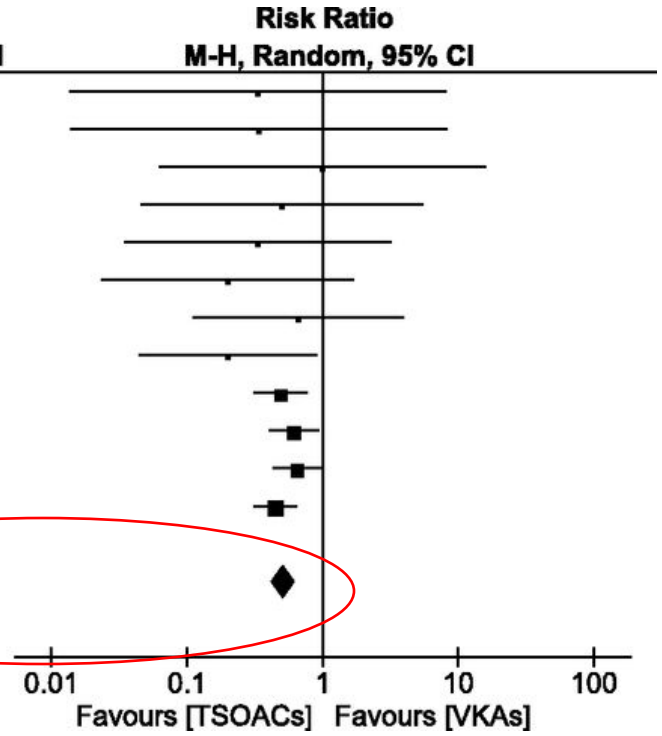
Blood (2014) 124 (15): 2450–2458.

Decreased rate of *fatal bleeding* with DOACs versus Warfarin

Study or Subgroup	TSOACs Events	Total	VKAs Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
RE-MEDY, 2013	0	1430	1	1426	0.4%	0.33 [0.01, 8.15]
RE-COVER II, 2014	0	1279	1	1289	0.4%	0.34 [0.01, 8.24]
RE-COVER, 2009	1	1274	1	1265	0.5%	0.99 [0.06, 15.86]
AMPLIFY, 2013	1	2676	2	2689	0.7%	0.50 [0.05, 5.54]
J-ROCKET AF, 2012	1	639	3	639	0.8%	0.33 [0.03, 3.20]
EINSTEIN-DVT, 2010	1	1718	5	1711	0.9%	0.20 [0.02, 1.70]
EINSTEIN-PE, 2012	2	2412	3	2405	1.3%	0.66 [0.11, 3.97]
HOKUSAI-VTE, 2013	2	4118	10	4122	1.7%	0.20 [0.04, 0.91]
ROCKET AF, 2011	27	7111	55	7125	19.0%	0.49 [0.31, 0.78]
ARISTOTLE, 2011	34	9088	55	9052	22.0%	0.62 [0.40, 0.94]
RE-LY, 2009	51	12091	39	6022	23.1%	0.65 [0.43, 0.99]
ENGAGE-AF-TIMI-48, 2013	53	14014	59	7012	29.3%	0.45 [0.31, 0.65]
Total (95% CI)		**57850**		**44757**	**100.0%**	**0.53 [0.43, 0.64]**
Total events	173		234			

Heterogeneity: Tau² = 0.00; Chi² = 5.25, df = 11 (P = 0.92); I² = 0%

Test for overall effect: Z = 6.30 (P < 0.00001)



0.3% vs 0.52%

Absolute risk difference -0.22%, NNT 454

Blood (2014) 124 (15): 2450–2458.

Guideline Recommendations

- **2016 CHEST Guidelines** recommend DOACs over VKAs for treatment of VTE (Grade 2B).

- **2020 American Society of Hematology VTE Guidelines** recommend DOACs over VKAs for treatment of VTE (conditional recommendation based on moderate certainty in the evidence of effects ⨁⨁⨁◯).

Kearon C, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315-352.

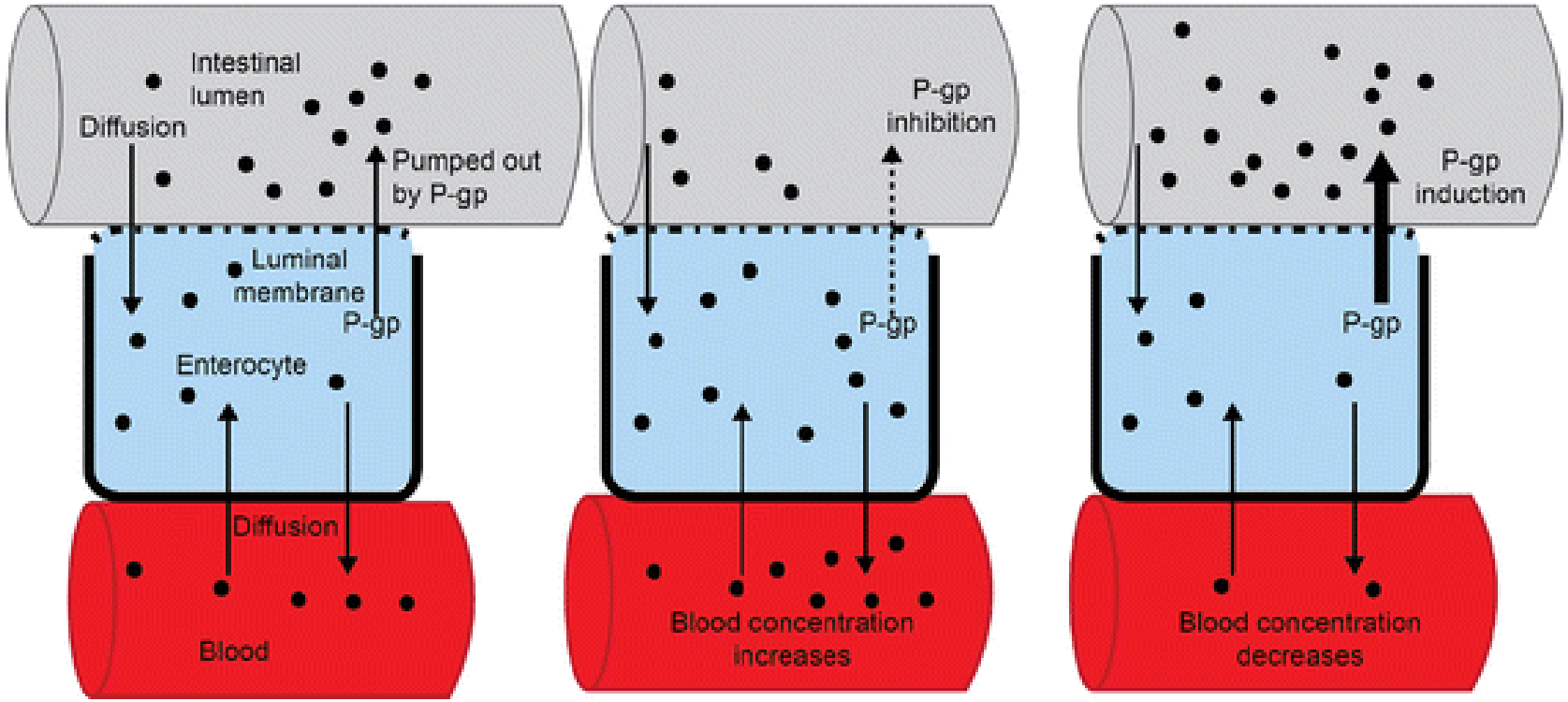
Ortel TL, et al. ASH 2020 guidelines for management of VTE: treatment of DVT and PE. Blood Adv. 2020 Oct 13;4(19):4693-4738.

Contraindications to DOACs

- Pregnancy or breastfeeding
- Mechanical heart valves
- Antiphospholipid antibody syndrome

	Dabigatran	Rivaroxaban	Edoxaban	Apixaban
Dosing (*for treatment of VTE*)	5 day lead-in with parenteral anticoagulation 150 mg BID	15 mg BID x21 days, then 20 mg daily Take with food	5 day lead-in with parenteral anticoagulation 60 mg daily	10 mg BID x7 days, then 5 mg BID
Metabolism elimination	Renal 80%	Renal 33%	Renal 50%	Renal 25%
Dose Adjustments (*for treatment of VTE*)	Avoid use if CrCl ≤30 mL/minute	Avoid use if CrCl ≤30 mL/min	30 mg once daily if: -CrCl 15-50 mL/min -Weight ≤60 kg Avoid use if CrCl <15 or >95 mL/min	Avoid if CrCl <25 mL/min

Drug Interactions: All DOACs are Permeability-glycoprotein substrates



DOAC drug interactions: CYP3A4 Metabolism

	Dabigatran	Rivaroxaban	Edoxaban	Apixaban
CYP3A4 metabolism	No	Yes	Very minimal (<4%)	Yes

DOAC Drug Interactions

Dual CYP3A4 and P-gp Inhibitors

- Clarithromycin
- Azole antifungals
- Diltiazem
- Protease Inhibitors

Dual CYP3A4 and P-gp Inducers

- Rifampin
- Carbamazepine
- Phenytoin
- Barbiturates
- St. John’s wort

DOAC Drug Interactions: agents affecting hemostasis

- Aspirin
- NSAIDs
- Selective serotonin reuptake inhibitors

Case #1

- 51 year old man with hypertension is transitioning care to your clinic. He had a right lower extremity common femoral vein DVT 5 months ago after a 7 hour plane flight. He has been on anticoagulation with warfarin. He is compliant with the medication and home INR monitoring, but has difficulty maintaining a therapeutic INR. He has had no bleeding events on anticoagulation.

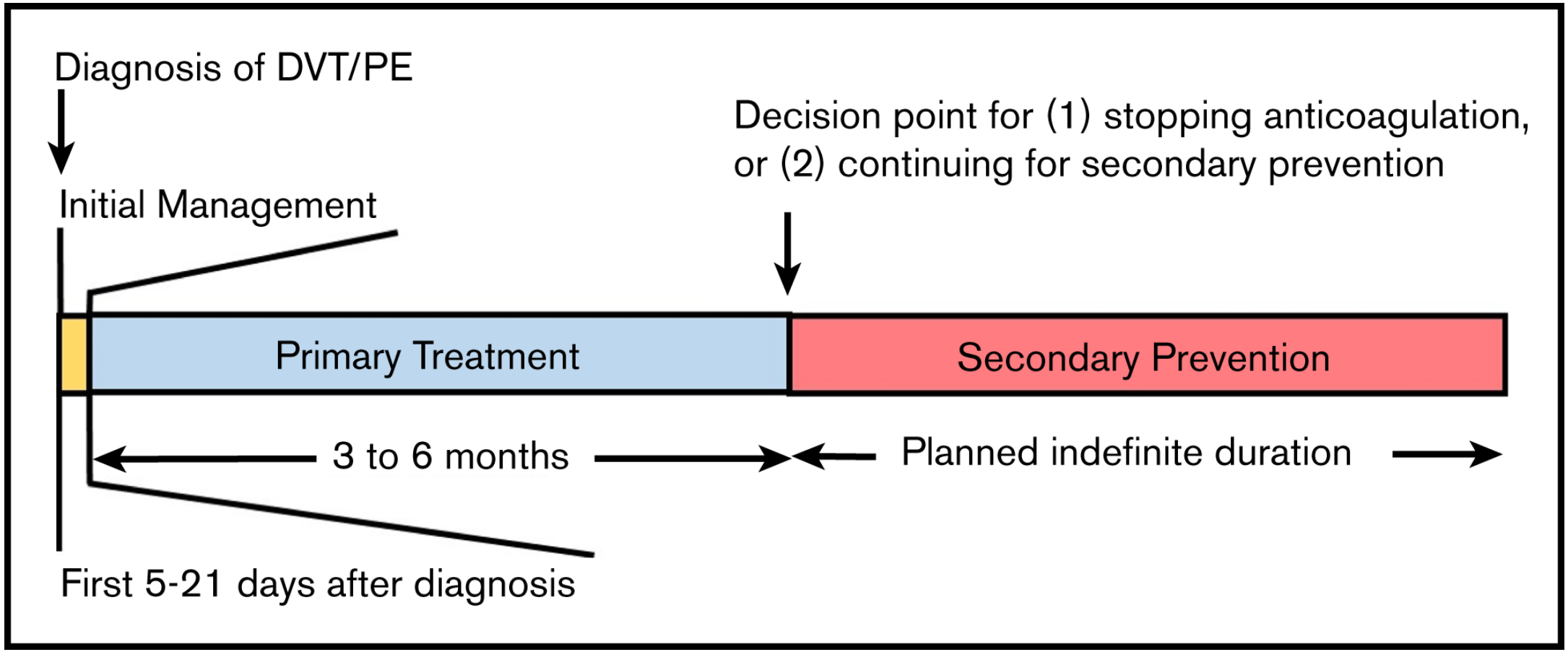
- On exam, he has some evidence of post-thrombotic syndrome in the right leg with hyperpigmentation around the ankle and calf size 1 cm greater than the left.

- Renal function and liver function are normal.

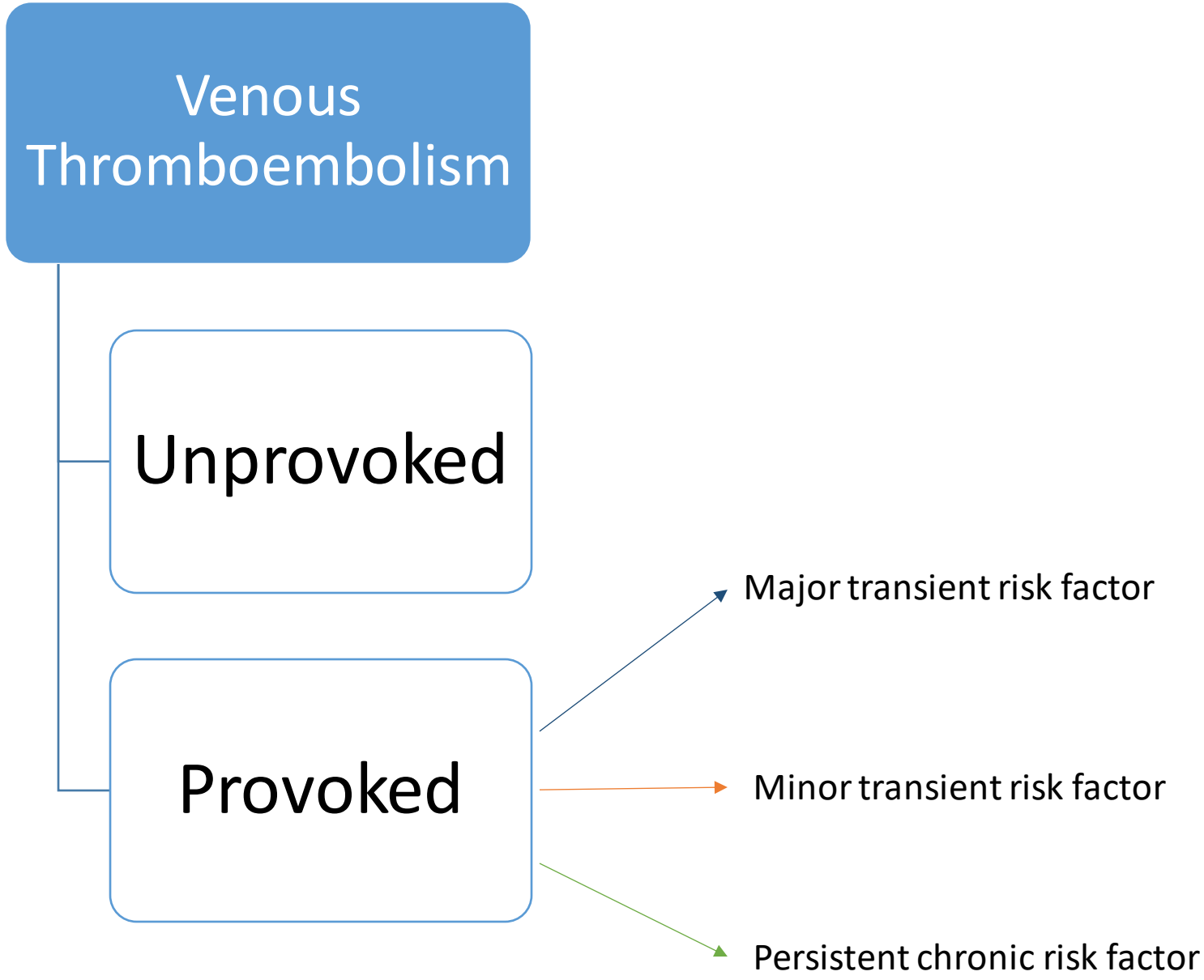
Questions for Case #1

- Does this patient need to remain on indefinite anticoagulation?
- If he remains on indefinite anticoagulation, should he be switched to a DOAC?
- How do you safely transition from warfarin to a DOAC?

Timeline for Management of VTE



Ortel TL, et al. ASH 2020 guidelines for management of VTE: treatment of DVT and PE. Blood Adv. 2020 Oct 13;4(19):4693-4738.


Venous Thromboembolism
Unprovoked
Provoked
Major transient risk factor
Minor transient risk factor
Persistent chronic risk factor

Major transient risk factors

- Surgery with general anesthesia for >30 minutes
- C-section
- Hospitalization with acute illness for at least 3 days
- Recurrence risk off anticoagulation: 1% in first year, then 0.2%/year

Minor transient risk factors

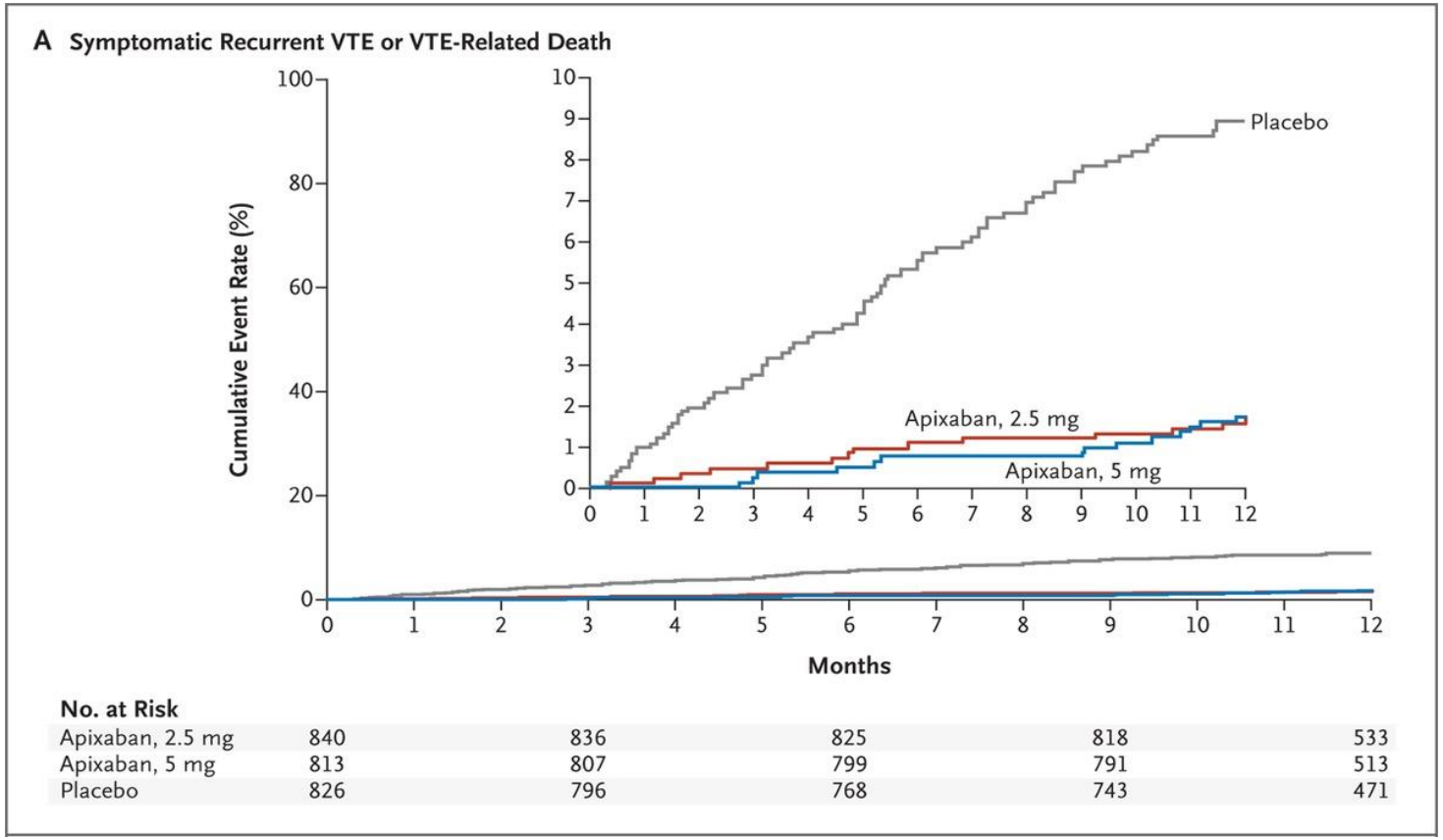
- Surgery with general anesthesia for <30 minutes
- Admission to hospital for <3 days with acute illness
- Estrogen therapy, pregnancy and puerperium
- Long-distance travel
- Recurrence risk off anticoagulation: 5% in first year, 15% at 5 years

Persistent risk factors

- Antiphospholipid antibody syndrome
- Active cancer
- Inflammatory bowel disease
- Recurrence risk off anticoagulation may be >10% per year

Low-dose maintenance DOAC

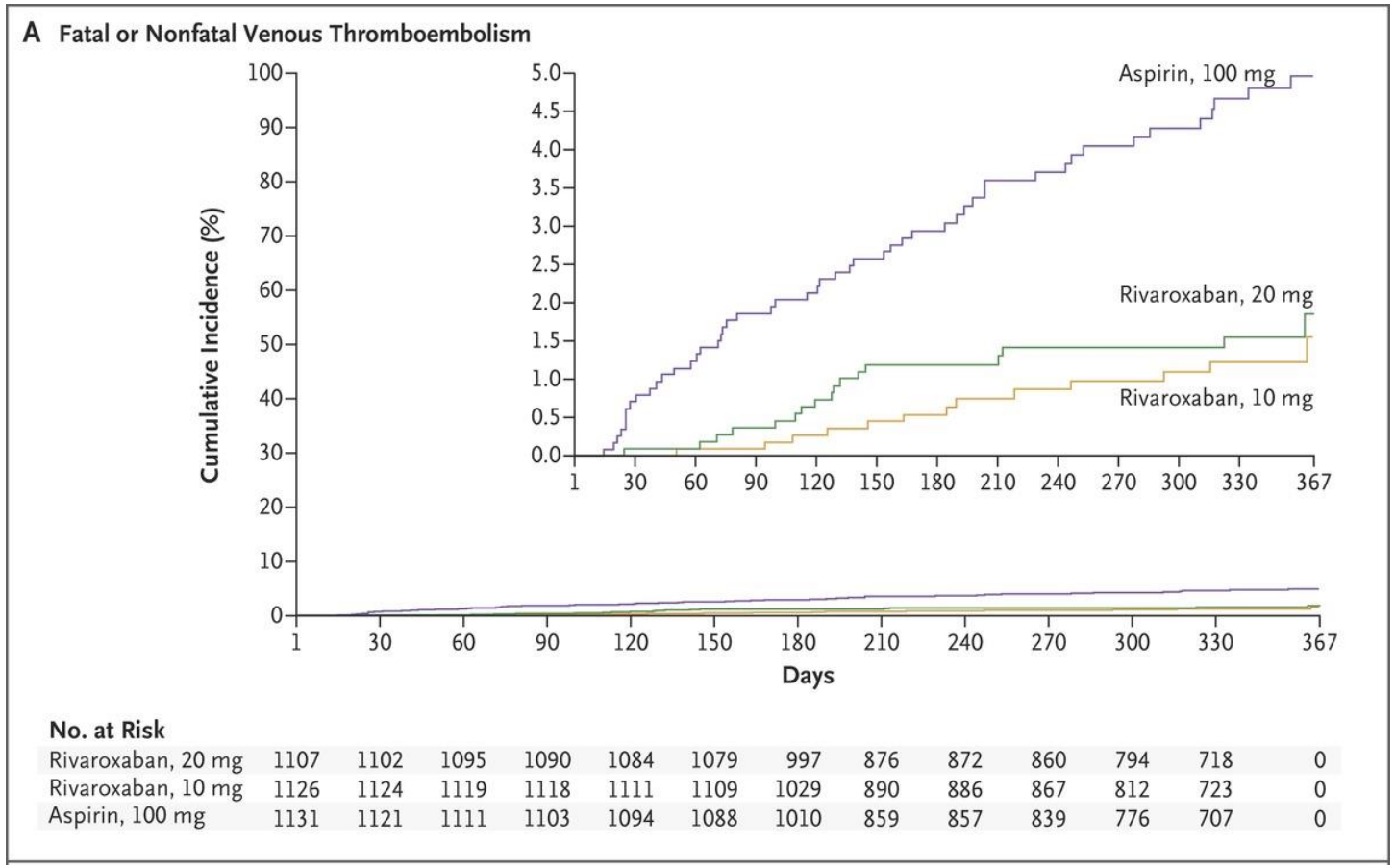
AMPLIFY-EXT



There was no difference in major or clinically relevant non-major bleeding between the 3 groups.

Agnelli G et al. N Engl J Med 2013;368:699-708.

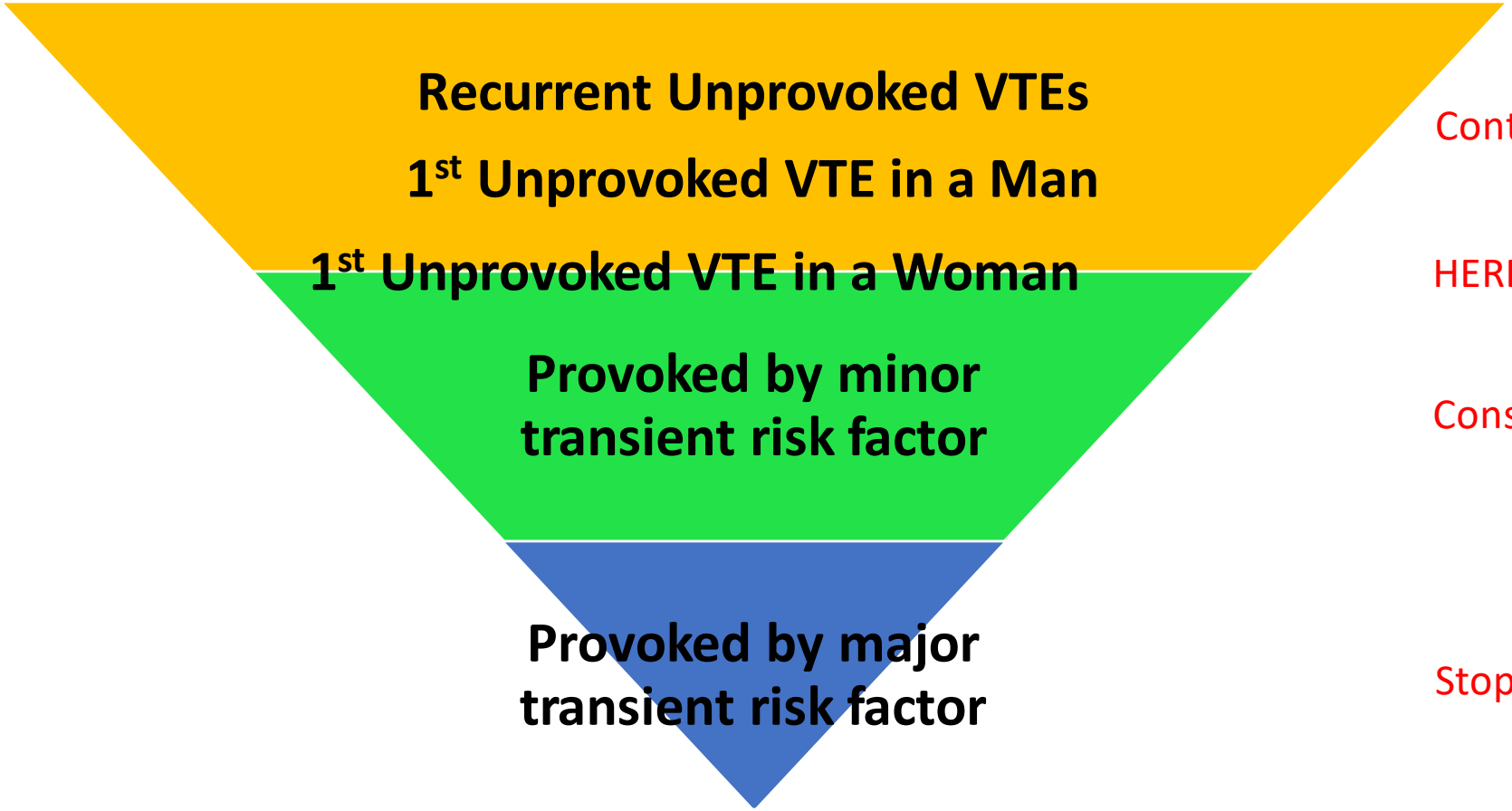
EINSTEIN CHOICE study



No difference in the rates of major bleeding between the 3 groups

Weitz JI et al. N Engl J Med 2017;376:1211-1222.

VTE Recurrence Pyramid



Continue full therapeutic dose

HERDOO2 score

Consider maintenance dose DOAC

Stop anticoagulation after 3 months

Clinical Risk Prediction Score for Women with Unprovoked VTE: HERDOO2

Risk factor	Points
Hyperpigmentation, edema, redness	1
D-dimer >250 micrograms/L	1
BMI >30	1
Older age >65	1
Low risk: 0 or 1, may safely discontinue anticoagulation	

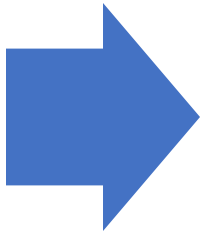
Back to Our Case

- After discussion of risk/benefit ratio, the patient decides to continue indefinite anticoagulation and would like to switch to a maintenance dose DOAC.

Transitioning to a DOAC

You do not need to give the “loading dose” of DOAC if the patient has been on chronic anticoagulation and does not have an acute VTE.

Warfarin

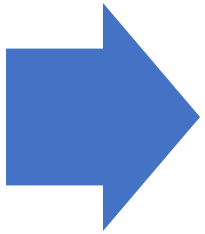


Start DOAC when INR <2.5

Rivaroxan: start when INR <3
Apixaban and Dabigatran: start when INR <2
Edoxaban: start when INR <2.5

Transitioning to a DOAC

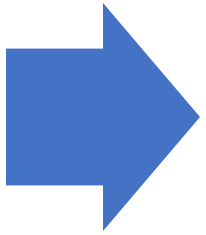
Lovenox *or* Fondaparinux *or* alternative DOAC



Start DOAC when next scheduled dose is due

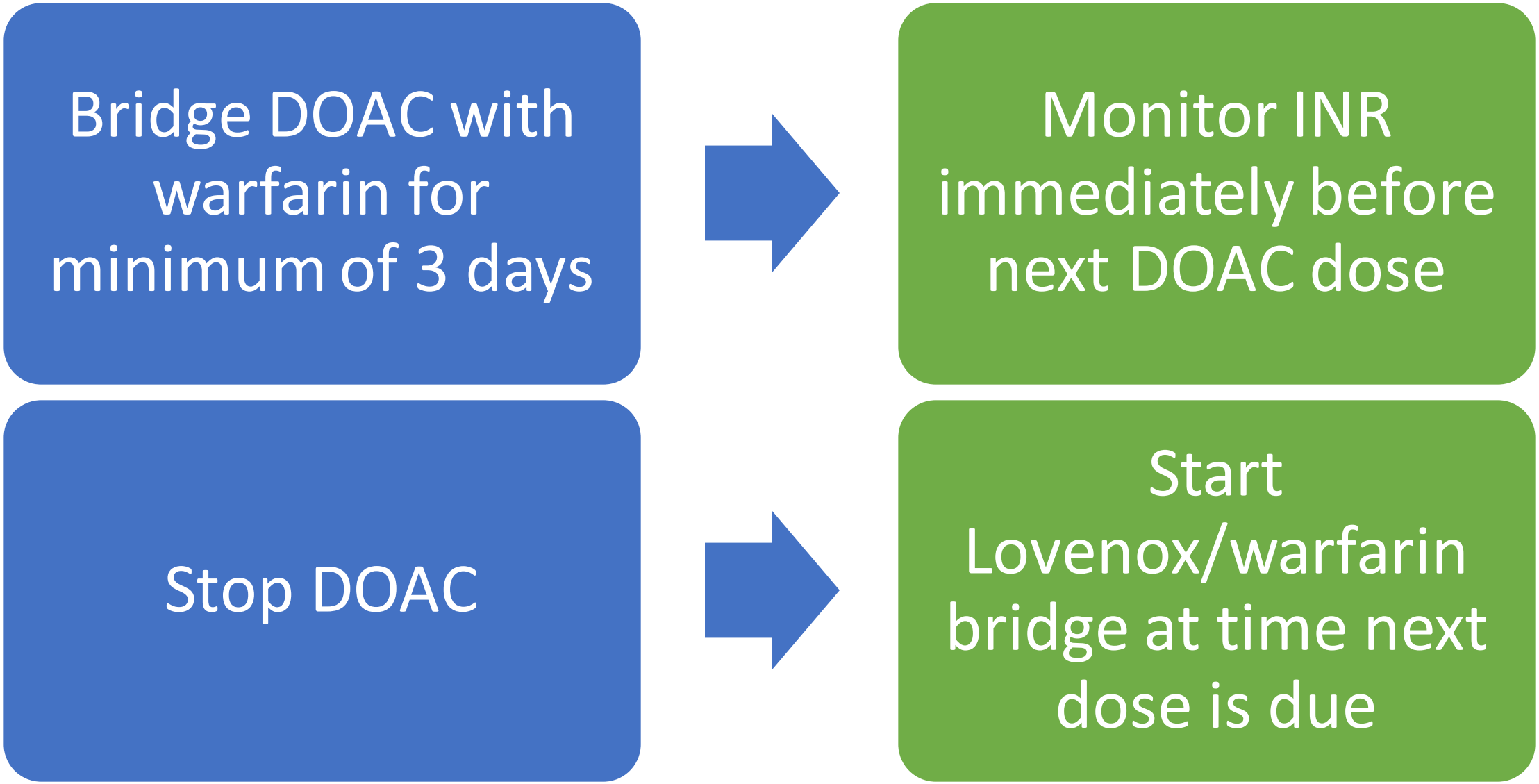
Transitioning to a DOAC

IV Unfractionated Heparin



Start DOAC within 30 minutes of discontinuation

Transitioning from a DOAC to Warfarin



Case #2

- A 78 year old man with Stage III CKD, hypertension, and history of unprovoked submassive PE on long-term anticoagulation with apixaban presents after falling off a ladder and hitting his head on the pavement. CT Head shows a large subdural hematoma. The patient is altered and unable to give a history. His wife is unsure of when he took his last dose of apixaban. His dose of apixaban is 5 mg twice daily.
- Cr 1.4 (stable)
- PT, PTT and INR are normal
- Does this patient require reversal of apixaban?

Laboratory Monitoring of DOACs

FXa Inhibitors (Rivaroxaban, Apixaban, Edoxaban)

- PT *may* be prolonged for on-therapy drug levels
- Anti-Xa sensitive for presence of any anticoagulant effect
  - >0.5: patient may need reversal for major bleeding
  - >0.3: patient may need reversal for emergency surgery

Dabigatran

- PTT sensitive for on-therapy level
- Thrombin time sensitive for presence of any anticoagulant effect

Management of Bleeding on DOACs

	Dabigatran	Rivaroxaban	Edoxaban	Apixaban
• Supportive measures: Volume resuscitation, transfusion support, local compression, anti-fibrinolytics • Activated charcoal if last ingestion <2-6 hours prior				
FDA approved agent	Idarucizumab Two 2.5 gram IV boluses administered consecutively	Andexanate alpha IV bolus followed by 2 hour infusion	Andexanate alpha (off label, high dose)	Andexanate alpha
Alternative option	Dialysis	4-Factor PCC	4-Factor PCC	4-Factor PCC

Andexanet alfa dosing

Anti-xa DOAC	> 8 hours since last dose	<8 hours since last dose or unknown
Apixaban	Low-dose	2.5 mg BID: Low-dose 5 mg BID: High-dose
Rivaroxaban		10 mg once daily: Low-dose 20 mg once daily: High-dose

- Low-dose regimen: 400 mg IV bolus followed by 4 mg/min infusion for up to 120 minutes
- High-dose regimen: 800 mg IV bolus followed by 8 mg/min infusion for up to 120 minutes

Back to Our Case

- Patient's anti-xa level was 0.9.
- He received Andexanet (high dose given unknown time of last ingestion and dose of 5 mg twice daily).
- Consider re-initiation of anticoagulation in 2-4 weeks.

Restarting anticoagulation after a bleed

- ASH 2018 VTE Guidelines Recommendation:
- For patients receiving anticoagulation therapy for VTE who survive an episode of major bleeding, the ASH guideline panel *suggests* resumption of oral anticoagulation therapy within 90 days rather than discontinuation of oral anticoagulation therapy (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯).
- **Remark:** This recommendation specifically applies to patients who require long-term or indefinite anticoagulation (ie, are at moderate to high risk for recurrent VTE, are not at high risk for recurrent bleeding, and are willing to continue anticoagulation therapy).

Blood Adv. 2018 Nov 27;2(22):3257-3291

Case #3

- 48 year old man with no significant past medical history had a provoked PE 2 months ago after knee replacement surgery and is on Xarelto 20 mg once daily. He needs an urgent tooth extraction. You receive a clearance form from his dentist asking how many days he should hold the anticoagulant.

Temporary Interruption of DOACs

- Bridging is not necessary for DOACs
- 3 things to consider:
  - ½ life of anticoagulant (it takes 5 half-lives to eliminate 95% of the drug)
  - Renal function
  - Bleeding risk of procedure.
    - *In general*:
    - Hold for 2-3 half lives with low risk procedure, and 4-5 half lives for high bleeding risk procedure
    - Resume 24 hours post for low bleeding risk procedure, and 48-72 hours after for high bleeding risk procedure

Bleeding Risks of Common Procedures


anticoagulation may be continued

Very Low Bleeding Risk	Low bleeding risk	High Bleeding Risk Procedures
1-2 Dental extractions	Cholecystectomy	Coronary artery bypass
Cataract surgery	Abdominal hysterectomy	Hip/knee arthroplasty
Minor dermatologic procedures	Carpal tunnel surgery	Kidney and liver biopsy
Endoscopy with no planned biopsies	Endoscopy with planned biopsies	Spinal anesthesia

Back to our Case

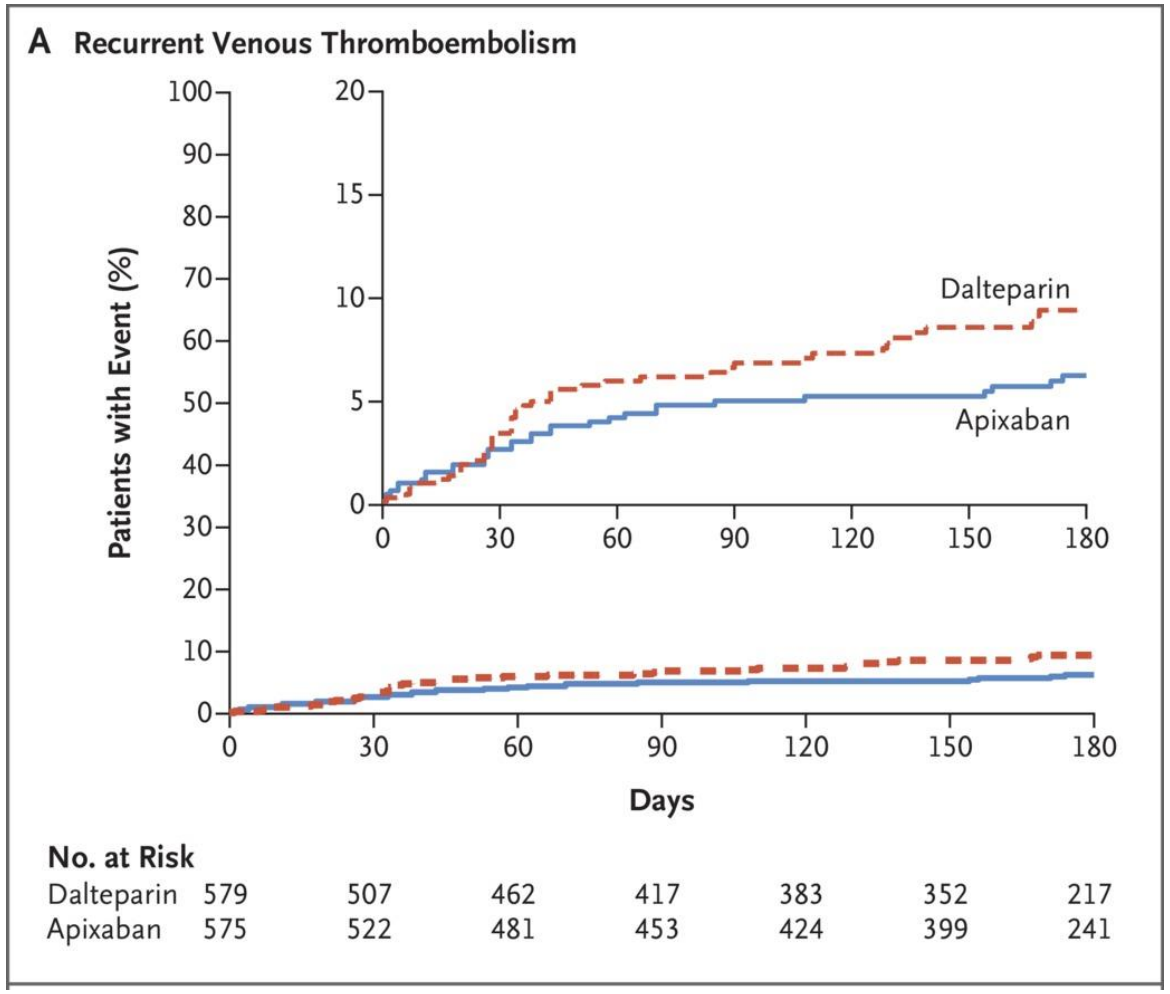
- Patient continued Xarelto peri-procedurally
  - 1 dental extraction is a very low bleeding risk procedure
  - He is at high thrombotic risk <3 months from acute VTE

- Amicar solution was prescribed for 7 days.

Case #4: Malignancy associated VTE

- 58 year old woman with newly diagnosed metastatic lung adenocarcinoma is found to have a left popliteal vein DVT. She has normal renal and hepatic function. Vital signs are stable. You are asked if she can be started on a DOAC and discharged from the ED.

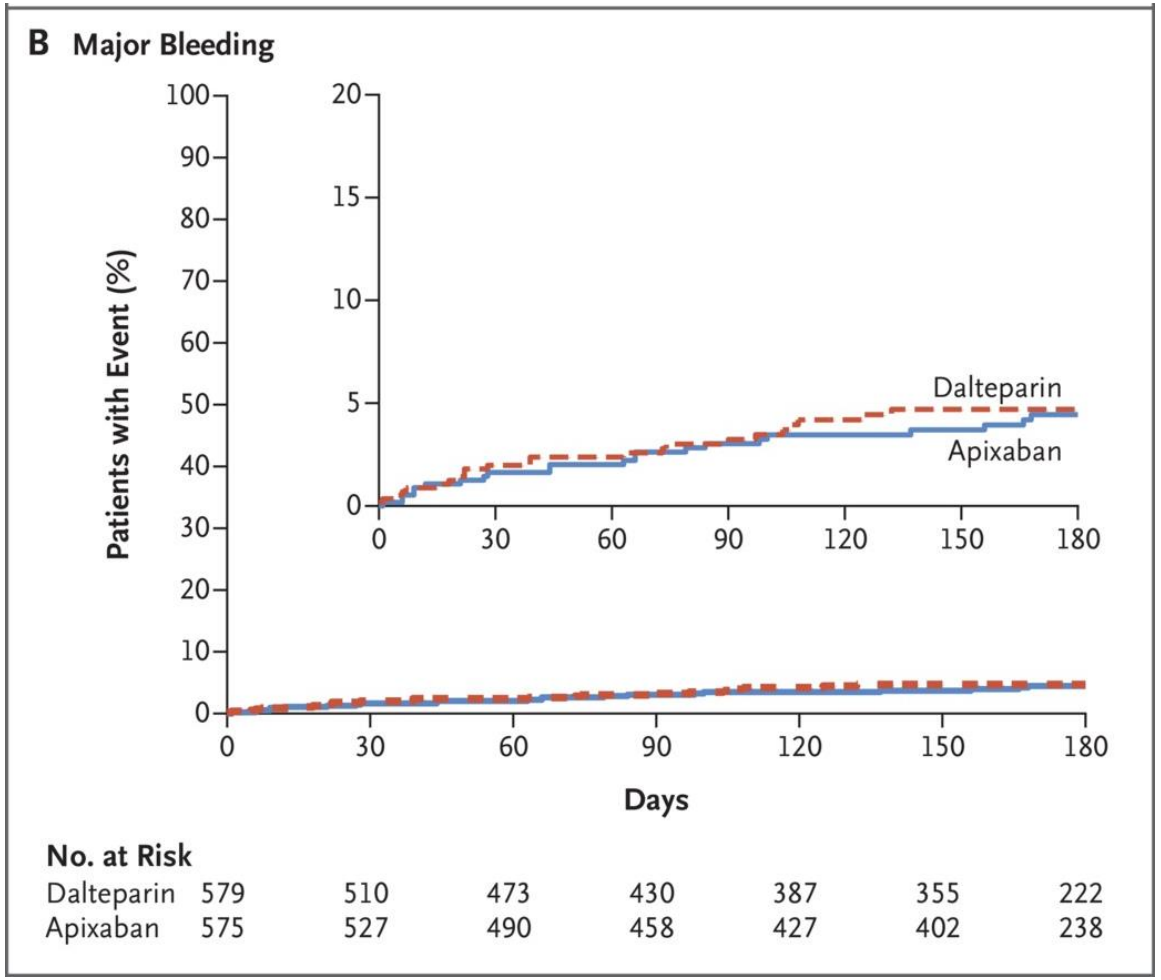
Caravaggio trial (Apixaban for the treatment of cancer associated VTE)



Primary Efficacy Outcome: Recurrent VTE
7.9% Dalteparin vs 5.6% Apixaban
HR 0.63 (0.37-1.07)
P<0.001 for noninferiority

N Engl J Med 2020; 382:1599-1607

Caravaggio trial (Apixaban for the treatment of cancer associated VTE)



Primary Safety Outcome: Major bleeding
4% Dalteparin vs 3.8% Apixaban
P=0.60

N Engl J Med 2020; 382:1599-1607

Guideline Recommendations

- National Comprehensive Cancer Network (**NCCN**) and American Society of Hematology (**ASH**) Guidelines list DOACs as first line options for management of VTE.

Back to Our Case

- After discussion with oncology and pharmacy, it was determined that there would be no drug-drug interactions between the DOAC and her other medications.

- She was prescribed Apixaban 10 mg BIDx7 days, followed by 5 mg BID.

- Duration of anticoagulation will be indefinite given ongoing risk factor of active metastatic cancer.

Case #5

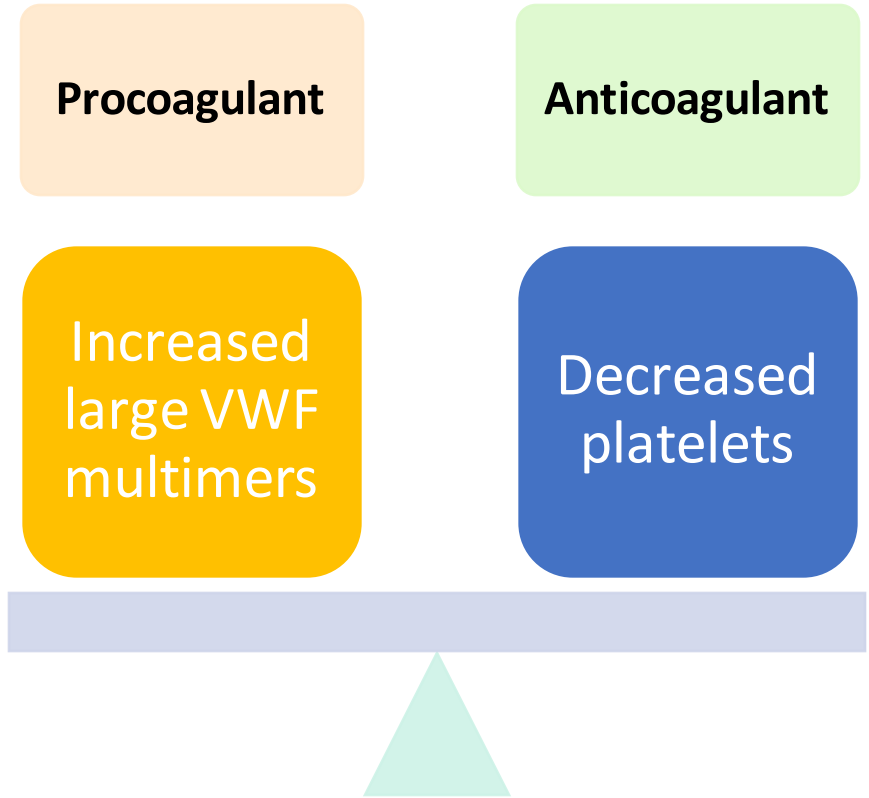
- 58 year old man with Child's Pugh A alcoholic cirrhosis is admitted with abdominal pain and found to have an acute symptomatic portal vein thrombosis.

- Creatinine 0.8
- Albumin 3.4
- AST and ALT <2 times upper limit of normal
- Total bilirubin 1.5
- INR 1.6

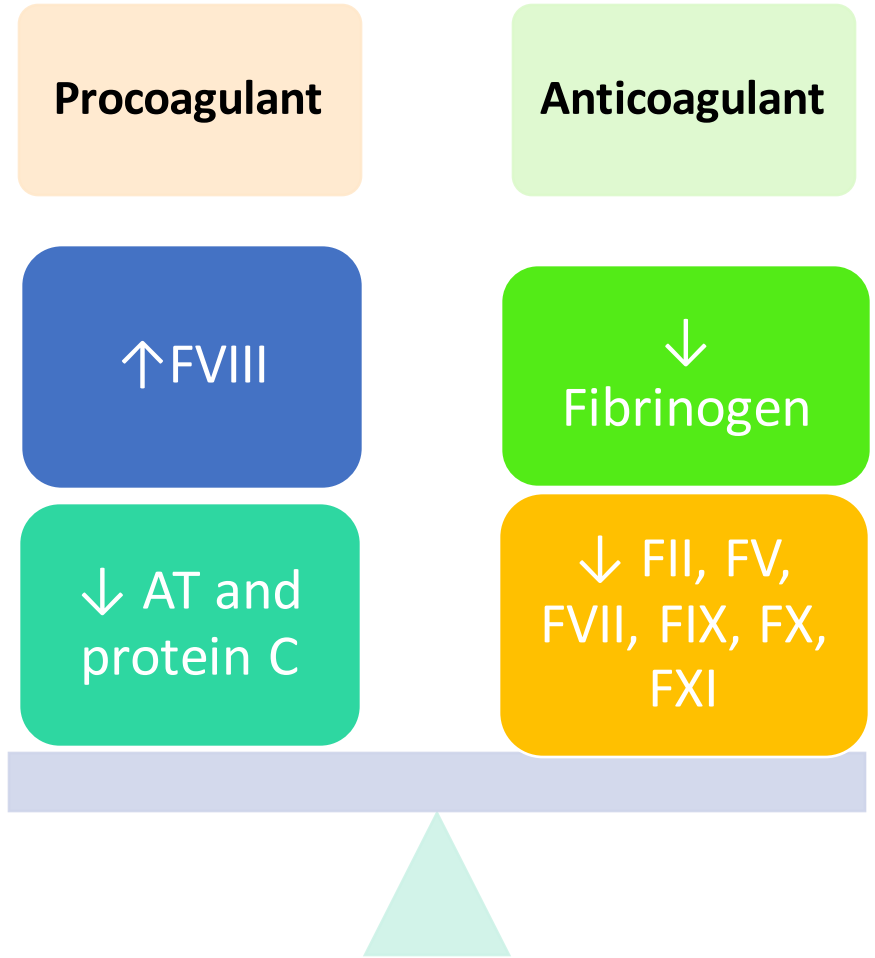
Case #5

- Does this patient need anticoagulation?
- What are his options for anticoagulation?

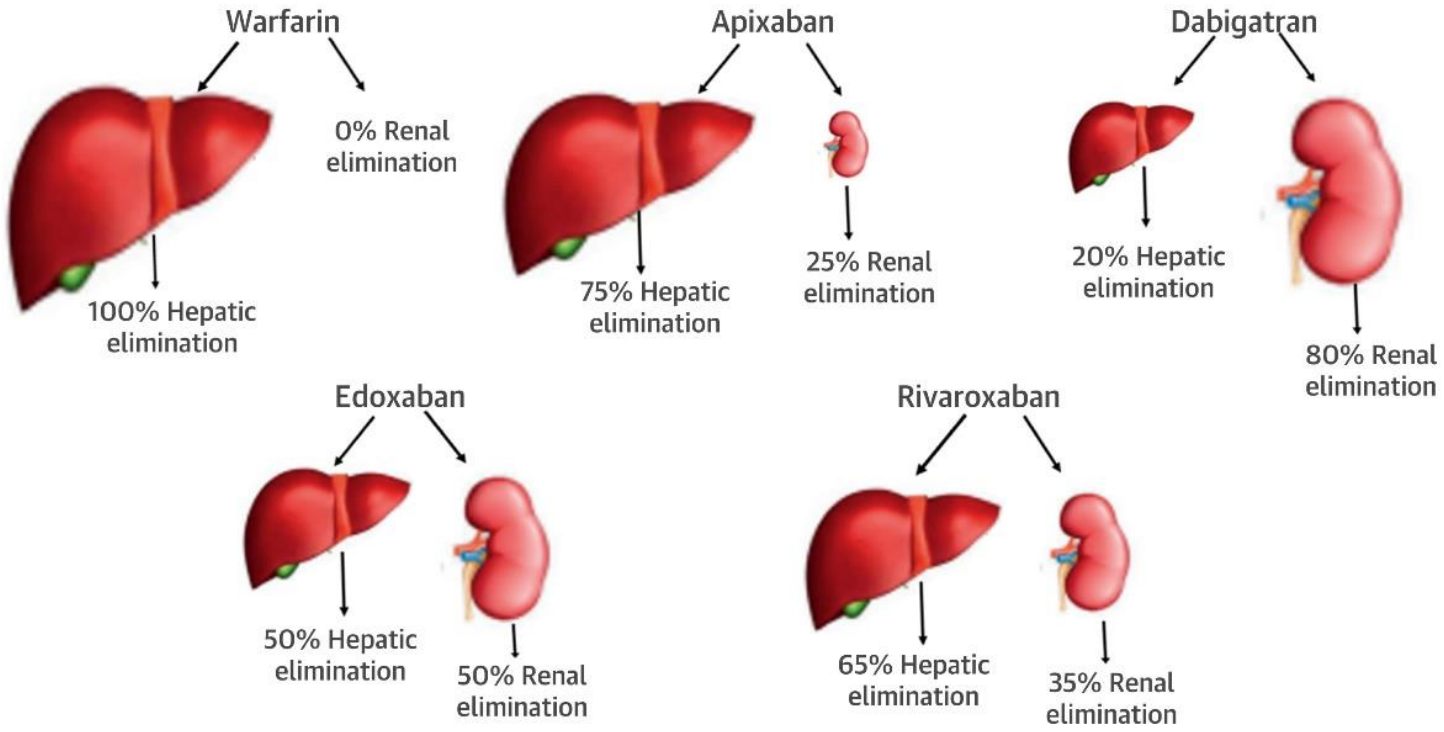
Rebalanced Hemostasis of Liver Disease: Primary Hemostasis



Rebalanced Hemostasis of Liver Disease: Secondary Hemostasis



Hepatic Metabolism of DOACs



Journal of the American College of Cardiology, Volume 71, Issue 19

FDA Recommendations for use of DOACs in Liver Disease

DOAC	Child Pugh A	Child Pugh B	Child Pugh C
Apixaban	Ok to use with no dose adjustment	Use with caution	Avoid
Edoxaban		Avoid	Avoid
Rivaroxaban		Avoid	Avoid
Dabigatran		Use with caution	Avoid

Back to Our Case #5

- Screening EGD showed small esophageal varices that were successfully banded.
- Testing for H. pylori was negative.
- He was started on a PPI and told to avoid NSAIDs and aspirin.
- Counseled on continued abstinence from alcohol cessation.
- Initiated on apixaban 10 mg BID x7 days, then 5 mg BID with close clinic follow up.

Case #6

- 40 year old woman with morbid obesity (BMI 50 kg/m2) is admitted with acute onset shortness of breath and found to have bilateral pulmonary emboli and an extensive right lower extremity DVT. This VTE occurred in the setting of active smoking and taking a combined hormone OCP.
- Surgical history is pertinent for roux-en-y gastric bypass.
- Her vital signs are stable and she has been started on a heparin drip.
- You are asked if she can be transitioned to a DOAC upon discharge.

Summary of ISTH Guidance Statement 2016 for use of DOACs in Obese Patients

- Panel suggests that DOACs should not be used in patients with a BMI of > 40 kg/m^2 or a weight of > 120 kg.

- If DOACs are used in this population, the panel suggests checking a drug-specific peak and trough level
  - If the level falls within the expected range, continuation of the DOAC seems reasonable.
  - If the drug-specific level is found to be below the expected range, switch to a VKA rather than adjusting the dose of the DOAC.

Journal of Thrombosis & Haemostasis. Jun2016, Vol. 14 Issue 6, p1308-1313.

DOAC	Site of absorption
Apixaban	Primarily proximal small intestine (with small amount in distal small intestine and proximal colon)
Dabigatran	Lower stomach and duodenum
Edoxaban	Proximal small intestine
Rivaroxaban	Primarily gastric absorption
Warfarin	Proximal small intestine

Back to Our Case

- DOAC was not ideal in our patient given BMI >40 kg/m2 and prior gastric bypass surgery. She was bridged from heparin to warfarin for goal INR 2-3.

- Risk factor modification:
  - OCPs were stopped.
  - Smoking cessation was recommended.
  - Weight loss program was initiated.

- Reassessment of the need for continued anticoagulation planned for 6 months.

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