NB Internal Medicine Update

ABCs of Anticoagulation Therapy

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Disclosures

➢Advisory Board Committee Member:

- Janssen
- Pfizer
- AstraZeneca

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Horizon Health Network

ABCs of Anticoagulation Therapy

- Objectives:

1. Understand the pharmacodynamics of the most commonly used anticoagulants
2. Identify the indications of the anticoagulation therapy in different clinical settings
3. Determine the potential side effects and bleeding risk assessment with anticoagulation therapy

Pharmacodynamics of Anticoagulation Therapy

1. Heparin: UFH and LMWH (Dalteparin, Enoxaparin)
2. Warfarin
3. Direct Oral Anticoagulants: Rivaroxaban, Apixaban, Edoxaban, Dabigatran

Case 1

- 62M with mechanical aortic valve
- On warfarin for 8 years
- Recently diagnosed with staph aureus infected knee joint prosthesis
- Rifampicin is indicated by ID for 3 months
- What would you do to his warfarin while on Rifampicin?

Case 2

- 75F with AFIB on Rivaroxaban 20 mg
- Recently diagnosed with metastatic breast cancer, started on chemo
- Admitted for urosepsis around 1 week post chemo
- While in hospital, developed new RT sided body weakness
- CT showed acute ischemic stroke
- Stroke management?

Parenteral Anticoagulants: UFH vs. LMWH

	UFH	LMWH
Molecular wt:	15 kDa	5000-6000 kDa
Mode:	Antithrombin	Antithrombin
½ life:	1.5 hrs	4-6 hrs
Route:	IV infusion	Subq – fixed dose per kg
Pharmacokinetics:	Needs monitoring	Monitoring not required Predictable pharmacokinetics
Clearance	Hepatic	Renal
Risk of HIT	2.7%	Low: 0.6%

Oral Anticoagulants: Warfarin vs. DOACs

	VKA (warfarin)	DOACs – Anti Xa
Half life	40 hrs	5-12 hrs
Monitoring	Needs monitoring	Monitoring not required
Clearance	Hepatic	Renal
Drug interaction	+++ (metabolized via P450 system)	+ (multiple elimination pathways)
Reversal	Vitamin K, PCC, etc	- PCC has been used with good results - Andexanet: inactivated recomb Xa
Cost $	Low cost $$	Higher cost $$$

Pharmacodynamics of Anticoagulation Therapy:

Useful tips in daily practice

Diet: VKA

- **Alcohol:**

❑Binge drinking decreases warfarin metabolism → ↑ INR

❑Chronic daily ethanol use increases warfarin metabolism → ↓ INR

❑ Management: Limit alcohol consumption; monitor INR closely.

- **Food:**

❑ Vitamin K rich food: ↓ Warfarin effect

❑ Vitamin E/ Cranberry juice: ↑ Warfarin effect.

❑ Management: **Consistent diet**; Take warfarin at the same time each day, preferably PM.

Diet, DAOCs

❑No interactions with specific food per se, but ..

❑Rivaroxaban:

- Absorbed primarily in the stomach
- Depends on the presence of food for optimal absorption
- **MUST be taken with food** to achieve high bioavailability (≥ 80%)

❑Apixaban: does not need to be taken with food

Significant drug-drug interactions with DOACs/VKA:

Potent CYP3A4 enzyme inducers:	**Potent CYP3A4 enzyme inhibitors:**
↓ anticoagulant effect	↑ anticoagulant effect
. Antiepileptics: phenytoin, CBZ, phenobarb . Rifampicin . Anti- HIV medications (protease inhibitors)	. Amiodarone . Azoles

What should we do when anticipating significant drug interaction?

- **Always discuss with Hematology/Anticoagulation pharmacists**
- **If for short period of time (5-7 days):**

1. Discuss with the pt; education
2. If on DOACS: no change/switch to LMWH (pt's preference)
3. If on warfarin: repeat INR sooner

What should we do when anticipating significant drug interaction, Cont.

➢**If for long period of time (weeks to months):**

1. Discuss with physicians re: alternative medications: e.g., phenytoin vs. switching to Keppra
2. If not applicable, the safest approach is to switch to LMWH
3. Frequent INR q 7-10 days could be considered. However, obtaining therapeutic INR could be challenging leading to high risk of thrombosis in the interim.

Case 1

- 62M with mechanical aortic valve
- On warfarin for 8 years
- Recently diagnosed with staph aureus infected knee joint prosthesis
- Rifampicin is indicated by ID for 3 months
- What would you do to his warfarin while on Rifampicin?

- Warfarin was stopped (D0)
- Dalteparin was started (D4)
- Dalteparin continued for 3 months until Rifampicin course was completed
- Warfarin restarted with dalteparin bridging

Case 2

- 75F with AFIB on Rivaroxaban 20 mg
- Recently diagnosed with metastatic breast cancer, started on chemo
- Admitted for urosepsis around 1 week post chemo
- While in hospital, developed new RT sided body weakness
- CT showed acute ischemic stroke
- Stroke management?

- Rivaroxaban failure due to:

1. Vomiting post chemo
2. Poor oral intake while sick with urosepsis

- Switched to Apixaban 5 mg b.i.d
- Chemo resumed with no new thrombotic events
- Still undergoing physio

Indications of anticoagulants, How to choose the right anticoagulant?

1- Indications:

DVT/PE (primary or secondary prevention), Afib, mechanical heart valve, Antiphospholipid syndrome

2- CrCl

3- Risk of bleeding: age, h/o major bleeding (GI/Genitourinary/CNS), h/o of Cancer

4- Cost

Case 3

- A 45 yr old lady, works as a cashier
- Unprovoked PE
- Body weight of 136 kg
- BMI: 32
- CrCl: 83
- Good drug coverage
- Which anticoagulant would you choose?

Case 4

- 54M
- Previously healthy
- Presented with NSTEM
- No CV risk factors found - kept on ASA
- Two months later, presented with confusion → Ischemic Stroke
- Thrombophilia work up: persistently positive lupus X2
- How would you manage his stroke?

Indications and Contraindications of Anticoagulants

	Warfarin	DOACs	LMWH
DVT/PE: Primary proph DVT/PE: Secondary prevention	No Yes	Yes Yes	Yes Yes
Non-Valvular Afib	Yes	Yes	Yes
Mechanical aortic/mitral valve	**Yes**	**No**	Yes
Antiphospholipid syndrome	**Yes**	**No**	Yes
CrCl <30	**Yes**	**No**	No
HIT	Not in acute stage	Yes – limited data	No
Pregnancy Breast feeding	**No** **Yes**	**No** **No**	**Yes** **Yes**

Indications of Anticoagulation in certain populations

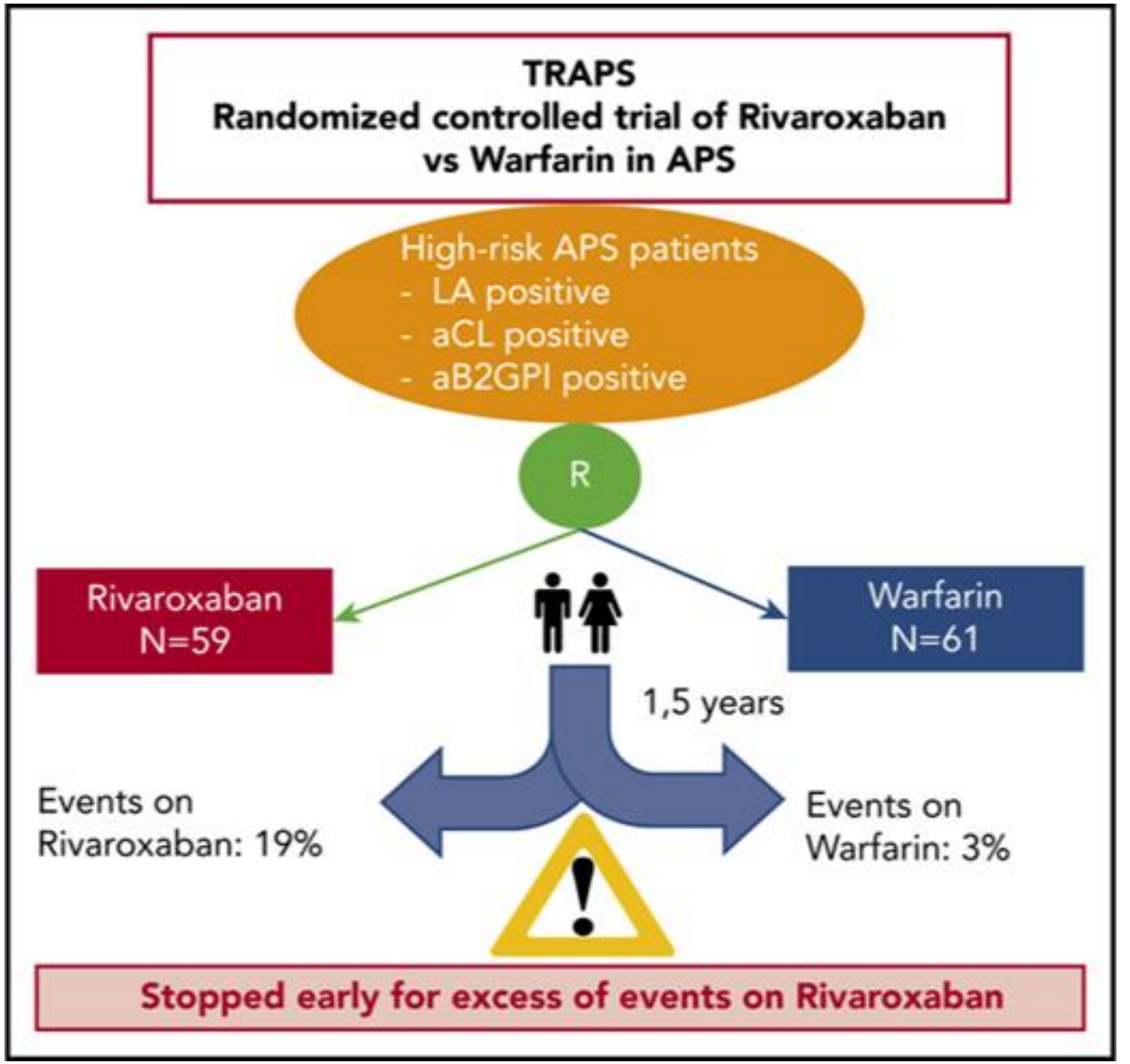
Pts undergoing Gastrectomy:

- **Apixaban is generally preferred**
- **Rivaroxaban/Dabigatran should be avoided**

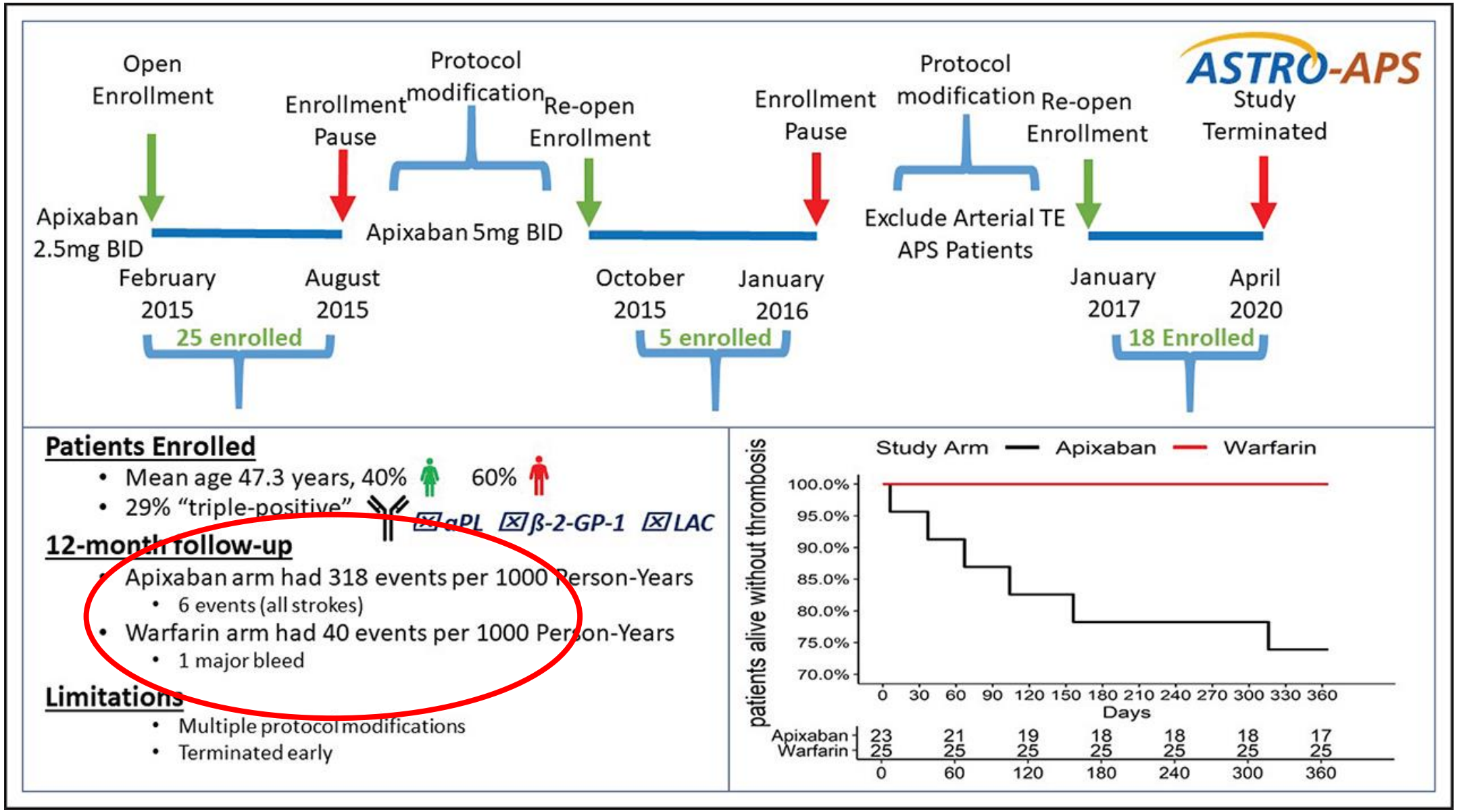
**Hakeam HA, et al. Effect of major gastrointestinal tract surgery on the absorption and efficacy of direct acting oral anticoagulants (DOACs). J Thromb Thrombolysis. 2017*

Antiphospholipid Syndrome (APLAS)

- Two randomized trials compared warfarin vs. Rivaroxaban/Apixaban in APLAS
- Both studies were terminated prematurely due to increased rate of events with rivaroxaban/apixaban compared with warfarin



*Pengo V. et al. Blood 2018.



*Woller S. et al. Blood 2022.

Anticoagulants in APLAS

- **DOACs are inferior to warfarin in APLAS**
- **Warfarin remains the drug of choice in APLAS**

DOACs in Obese patients (BMI >40 or weight >120 kg)

- Evidence is limited - Those pts were excluded in the 4 known trials (RELY, ROCKET, ARISTOTLE, and ENGAGE)
- A systematic review of 5 observational studies* done on those pts with VTE (n=6585) – only Rivaroxaban and Apixaban
- The study concluded: DOAC's are non-inferior to warfarin: efficacy and safety
- Several retrospective and post-Hoc analysis of RCTS: encouraging results

*Elshafei MN, et al. J Thrombosis Thrombolysis 2021

DOACs in Obese patients, cont.

- Overall, clinical efficacy and safety results are encouraging
- Pts should be informed of the limitations of available information and potential risk of under-dosing.

**Thrombosis Canada.2021*

Case 3

- A 45 yr old lady, works as a cashier
- Unprovoked PE
- Body weight of 136 kg
- BMI: 32
- CrCl: 83
- Good drug coverage
- Which anticoagulant would you choose?

- Discussed with the pt re: Warfarin vs. DOACs (given limited evidence but e encouraging results of DAOCs in obese pts)
- Pt opted for DOACs
- Started on Rivaroxaban
- Did very well ☺

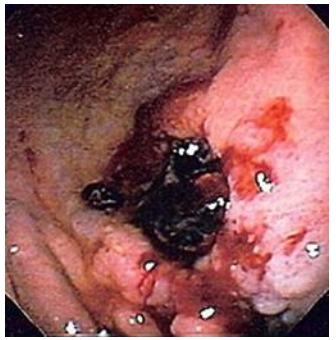
Case 4

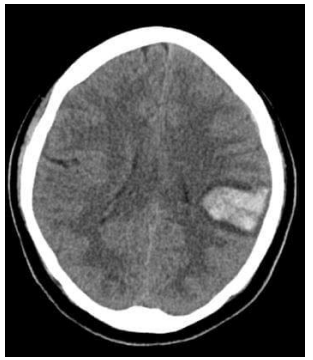
- 54M
- No Cardiovascular risk factors
- But recent MI two months ago
- Presented with confusion → ischemic stroke
- On Aspirin
- Thrombophilia work up: persistently positive lupus X2
- How would you manage his stroke?

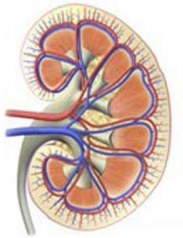
- **APLAS**
- **WARFARIN – life long**
- **Aspirin was stopped**

Assessing Bleeding Risk prior starting anticoagulants

- Age
- H/O bleeding?
- Source of bleeding: GI/Genitourinary vs. Intracranial
- GI diseases: peptic ulcers, IBD, GI cancers
- Concomitant anti-platelets
- CrCl
- Compliance, social habits, support system, etc







*Intracerebral Hemorrhage. Ji Y. Chong JY. Weill Cornell Medical College/Modified Sep 2022

**Wikimedia Commons, the free media repository

Case 4

- An 82M with non-valvular Afib
- On warfarin for years
- Presented with a fall complicated by subdural hemorrhage
- INR: 3.2
- CrCl: 42
- Management?

Case 5

- 62M with saddle PE post knee replacement 1 week ago
- Hemodynamically stable
- Started on UFH infusion
- Hb ↓↓ 132 to 71 -> bleeding from the joint
- UFH on hold
- New PE while off heparin

Assessment of Bleeding Risk

❑Age and warfarin

- The risk of bleeding among patients taking warfarin increases with age*
- Causes: poorer control of INR, comorbidities, comedications, high risk of fall
- Sharp increase in the risk of thrombosis in pts ≥80 yrs"

*Fihn SD, et al. Ann Intern Med. 1996. Palareti G, et al. Lancet. 1996. Poli D. et al. Circulation. 2011.

“Hilde A. et al. JAMA Internal Med. 2016.

Assessment of Bleeding Risk, Intracranial Bleeding

❑DOACs vs. Warfarin

- Four large head-to-head RCTs* included ≈70,000 pts: Warfarin vs. DOACs
- DOACs **significantly** reduce the risk of:

1. **Stroke or systemic embolism by 19%**
2. **Major bleeding by 14%**
3. **Fatal bleeding by 51%**
4. **Mortality by 10%**
5. **Hemorrhagic stroke by 51%**

**RELY, ARISTOTLE, ROCKET-AF, ENGAGE-AF*

blood

ISSUES FIRST EDITION ABSTRACTS COLLECTIONS

HOW I TREAT | MAY 23, 2019

How I manage anticoagulant therapy in older individuals with atrial fibrillation or venous thromboembolism

Noel C. Chan, John W. Eikelboom

Blood (2019) 133 (21): 2269–2278.

Efficacy and safety of NOACs compared with warfarin in patients with AF aged 75 y or older

Trial acronym	Comparisons	Number of patients ≥75 y	Stroke/SEE	Major bleeding	Intracranial bleeding
			HR (95% CI)	HR (95% CI)	HR (95% CI)
RE-LY	DE 150 mg bid vs warfarin	7258	0.67 (0.49-0.90)	1.18 (0.98-1.42)	0.42 (0.25-0.70)
	DE 110 mg bid* vs warfarin		0.88 (0.66-1.17)	1.01 (0.83-1.23)	0.37 (0.21-0.64)
ROCKET-AF	Rivaroxaban daily vs warfarin	6229	0.80 (0.63-1.02)	1.11 (0.92-1.34)	0.80 (0.50-1.28)
ARISTOTLE	Apixaban bid vs warfarin	5678	0.71 (0.53-0.95)	0.64 (0.52-0.79)	0.34 (0.20-0.57)
ENGAGE-AF	Edoxaban 60 mg daily vs warfarin	8474	0.83 (0.66-1.04)	0.83 (0.70-0.99)	0.40 (0.26 -0.62)
	Edoxaban 30 mg† daily vs warfarin*		1.12 (0.91-1.37)	0.47 (0.38 -0.58)	0.31 (0.19-0.49)

bid, twice daily; DE, dabigatran etexilate; SEE, systemic embolic event.

* Dabigatran 110 mg is not approved in the United States for stroke prevention in AF.

Assessment of Bleeding Risk, GI Bleeding

- Compared with warfarin, real-world studies showed:
- DOACs were associated with lower rates of stroke, but varying risks of MB compared with warfarin:
  - Lower risk of GI bleed with apixaban
  - Lower-to-similar risk with dabigatran
  - **Rivaroxaban was associated with a higher GI bleeding risk** (HR, 1.11; 95% CI, 1.05-1.16), but similar risk of MB
- The 2020 European Society of Cardiology (ESC) guidelines indicate that Apixaban or low-dose Dabigatran should be considered for patients with a recent bleeding event.

**Lip GYH. Et al. JAMA Netw Open. 2021*

Warfarin vs. DOACs

**Noel C. et al. Blood. 2019*

Choice of NOACs for stroke prevention in AF according to patient characteristics or preference

Patient characteristics	Considerations	Drug choices
Older patients	Consider anticoagulants with the lowest risk of major bleeding and the most convenience	NOACs preferred over VKAs
		Apixaban, dabigatran 110 mg, and edoxaban are associated with lower rates of major bleeding than warfarin
High risk of bleeding	Consider anticoagulants with lowest risk of major bleeding	Apixaban, dabigatran 110 mg, or edoxaban.
Previous GI bleeding	Consider anticoagulants with lowest risk of GI bleeding	Apixaban or edoxaban
Severe renal impairment	Consider anticoagulants with the least renal clearance	Apixaban > rivaroxaban > edoxaban
Dyspepsia or GERD	Consider agent less likely to cause GI side effects	Apixaban, rivaroxaban, or edoxaban
Feeding via nasogastric or PEG tube	Consider anticoagulants with pharmacokinetic data suggesting bioequivalence between oral and enteral administration*	Apixaban or rivaroxaban
Nonadherence to twice-daily regimens or request to minimize pill burden	Consider anticoagulant with once-daily dosing regimen	Rivaroxaban or edoxaban

UFH vs. LMWH

- In PE: Chest guidelines 2012 and 2016:
- "*In patients with acute PE, we suggest LMWH or fondaparinux over IV UFH (Grade 2C for LMWH; Grade 2B for fondaparinux)*"
- **LMWH is preferred over UFH unless CrCl <30 or HD instability requiring thrombolysis**
- In post-op prophylaxis: *Gaitanidis A. et al. J Surg Res.2021*
- **"LMWH prophylaxis is superior to UFH for VTE prevention in trauma patients. LMWH is associated with fewer bleeding complications."**

Case 4

- An 82M with non-valvular Afib
- On warfarin for years
- Presented with a fall complicated by subdural hemorrhage
- INR: 3.2
- CrCl: 42
- Management?

- Warfarin was stopped
- 0.5 mg Vitamin K
- INR: 1.2 next day
- After clearance from Neurology, started on Rivaroxaban 15 mg od long term
- Did well

Case 5

- 62M with saddle PE post knee replacement 1 week ago
- Hemodynamically stable
- Started on UFH infusion
- Hb ↓↓ 132 to 71 -> bleeding from the joint
- UFH on hold
- New PE while off heparin

- Dalteparin started with daily CBC, Blood tx, etc
- Hb dropped again
- Required IVC filter insertion
- Prolonged ICU stay
- Eventually switched to apixaban
- IVC filter was removed
- Recovered

❑Heparin infusion was not indicated in the first place

Take home message

- DOACs have been widely used due to its efficacy and convenience
- However, warfarin remains superior/drug of choice in certain indications: CKD, mechanical valve, APLAS, breast feeding.
- Rivaroxaban has peculiar pharmacodynamics; needs a stable GI system and has higher risk of GI bleed.
- Warfarin has higher risk of intracranial bleed
- If not indicated, antiplatelets should be stopped while on anticoagulants
- UFH can cause higher bleeding events vs. LMWH with no proven superior efficacy
- With anticoagulation therapy, the aim should be to minimize/prevent bleeding rather than reversing the anticoagulant when bleeding happens
- Consider lower dose DOACs (Apixaban 2.5mg/Rivaroxaban 10/15mg), esp in older patients, or with high risk of bleeding