Current Recommendations of DOAC

Prof. Yin Nwe Tun
Senior Consultant Cardiologist
Department of Cardiology
Yangon General Hospital

19.12.25

Outline:

1. Introduction of DOAC
2. Types and Mechanisms of action
3. Recommendations : Prevention of Stroke in Atrial Fibrillation (AF)
4. Recommendations : Treatment and Prevention of Venous Thrombo Embolism (VTE)
5. Practical tips in using DOAC

References

DOAC Guidelines

Direct Oral Anticoagulants

Version 1.1

March 2025

NSW GOVERNMENT | CLINICAL EXCELLENCE COMMISSION

2025 Guidelines for direct oral anticoagulants: a practical guidance on the prescription, laboratory testing, peri-operative and bleeding management

Huyen A. Tran,[1,2] Eileen Merriman,[3] Ross Baker,[4] Jennifer Curnow,[5] Laura Young,[6] Chee Wee Tan,[7] Simon McRae[8] and Sanjeev D. Chunilal[9]

2024 ESC Guidelines for the management of atrial fibrillation

American Heart Association.

AMERICAN COLLEGE of CARDIOLOGY

2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation

ASH VTE Guidelines: Treatment of Deep Vein Thrombosis and Pulmonary Embolism

CONTEMPORARY REVIEW

Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges

Ashley Chen, PharmD; Eric Stecker, MD, MPH; Bruce A. Warden, PharmD, BCPS-AQ Cardiology, CLS

Introduction: Direct oral anticoagulants (DOAC)

- **Quickly become attractive alternatives to the long-standing standard of care in anticoagulation, vitamin K antagonist**

- **Used in adult patients for the prevention of stroke in non-valvular AF, treatment and prevention of VTE and prevention of major cardiovascular events in patients with atherosclerotic disease**

- **The terms 'non-Vitamin K Antagonist Oral Anticoagulant' and 'novel oral anticoagulant' (NOAC) used in the past**

- **International Society on Thrombosis and Haemostasis (ISTH), along with several other international societies recommend using the term 'direct oral anticoagulant' (DOAC) as it indicates their pharmacological specificity and is less likely to be misinterpreted**

Introduction: Direct oral anticoagulants (DOAC)

- **Since the first approval in 2010, DOACs have emerged as leading therapeutic alternatives that provide both clinicians and patients with more effective, safe, and convenient treatment options in thromboembolic settings.**

- **With the expanding role of DOACs, clinicians are faced with increasingly complex decisions relating to appropriate agent, duration of treatment, and use in special populations.**

- **Need to optimize DOAC use among common challenging scenarios**
  - **(1) appropriate indications**
  - **(2) use in patients with specific comorbidities**
  - **(3) monitoring parameters**
  - **(4) transitioning between anticoagulant regimens**
  - **(5) major drug interactions**
  - **(6) cost considerations**

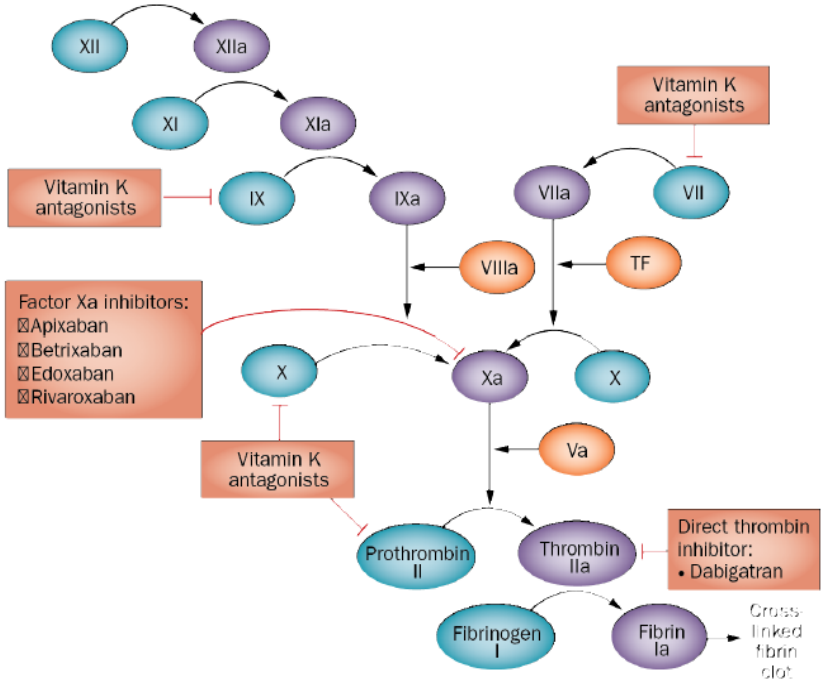
The ideal anticoagulant

- **PREDICTABLE PHARMACOKINETICS and ANTICOAGULANT PROFILE**
- **FEW DRUG AND FOOD INTERACTIONS**
- **ORAL ADMINISTRATION**
- **NO NEED FOR MONITORING**
- **SIMPLE DOSING**
- **SHORT HALF-LIFE**
- **ANTIDOTE**

Types and Mechanisms of actions

- **2 main classes:**
- **Oral direct factor Xa inhibitors:**
  - **Rivaroxaban(2011)**
  - **Apixaban(2013)**
  - **Edoxaban (2015)**
  - **Betrixaban(2017)**
- **Direct thrombin inhibitors:**
  - **Dabigatran (1st DOAC 2010)**

Direct Acting Oral Anticoagulants (DOACs) and Vitamin K Antagonists



Direct Thrombin Inhibitor

- Dabigatran

Factor Xa Inhibitors

- Apixaban
- Betrixaban
- Edoxaban
- Rivaroxaban

Factors II, VII, IX, and X Inhibitors

- Vitamin K antagonists - Warfarin

John N. Makaryus, Jonathan L. Halperin & Joe F. Lau, Oral anticoagulants in the management of venous thromboembolism, Nature Reviews Cardiology Volume 10

Characteristics of DOAC

Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
Time to maximum effect	1.5-2h	2h	3-4h	1-2h	5 days
Half-life	12-17h	5-9h	8-15h	9-10h	36-48h
Plasma protein binding	35%	92-95%	87%	40-59%	99%
Renal elimination	80%	33%	25%	35-39%	0%
Interactions	P-gp	P-gp, CYP3A4	P-gp, CYP3A4	P-gp, CYP3A4	CYP2C9 (S) CYP1A2 (R)
Food effect	Absorption delayed	Required for absorption	No	No	Dark green vegetables etc

- The direct oral anticoagulants exert effect almost immediately

- rivaroxaban and apixaban do not need initial overlap with heparin or LMWH

-No need for bridging anticoagulation with heparin pre-operatively in view of half-life

- Stop 1-2 days before elective surgery if renal function is normal

Recommendations for Prevention of Stroke in AF

2024 ESC Guidelines for the management of atrial fibrillation

2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation

Recommendations to access and manage thromboembolic risks in AF

Oral anticoagulation is recommended in patients with clinical AF at elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism.	I	A
A CHA_2DS_2-VA score of 2 or more is recommended as an indicator of elevated thromboembolic risk for decisions on initiating oral anticoagulation.	I	C

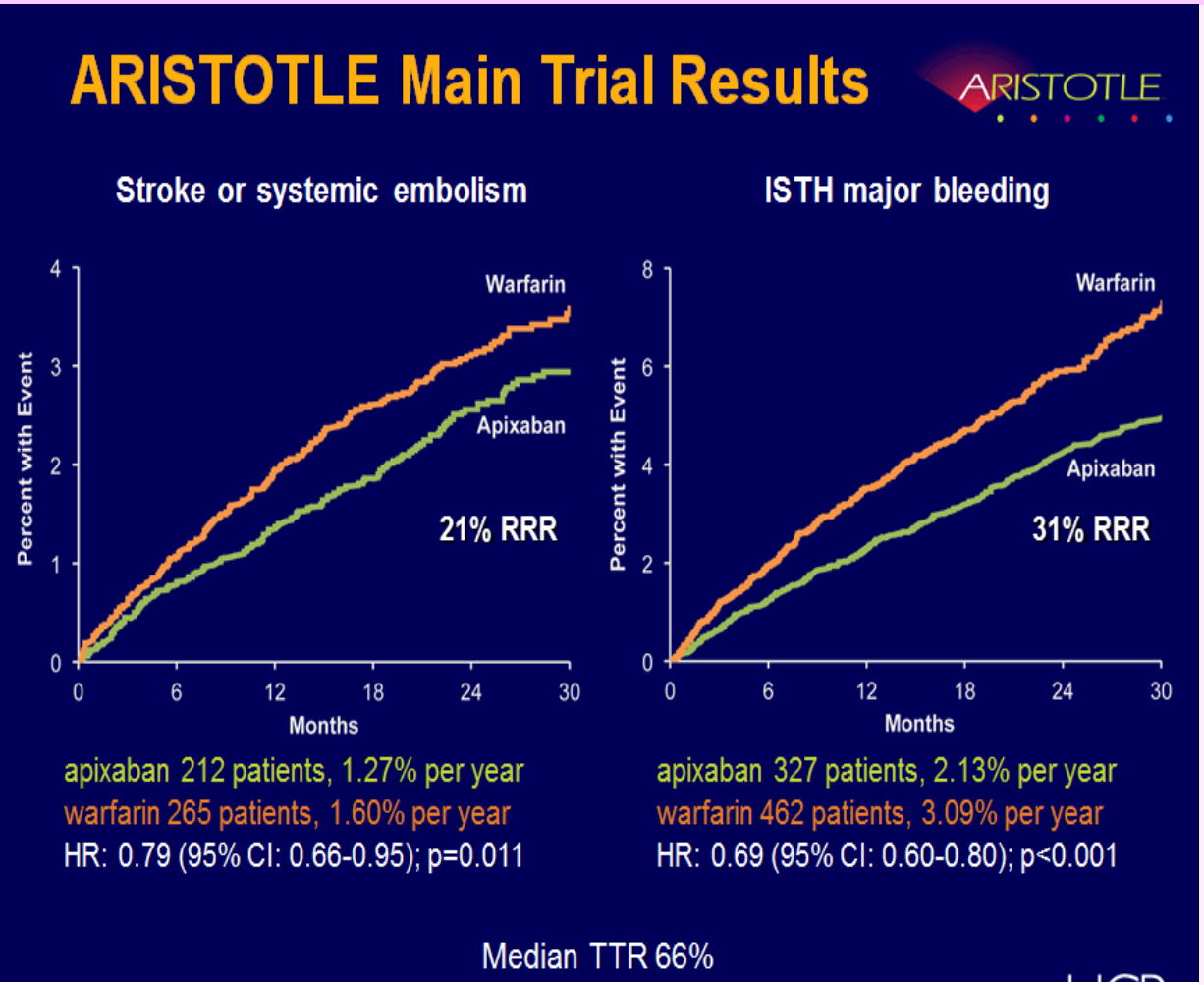
Recommendations for oral anticoagulation in atrial fibrillation

ESC

Recommendations	Class	Level
Direct oral anticoagulants are recommended in preference to VKAs to prevent ischaemic stroke and thromboembolism, except in patients with mechanical heart valves or moderate-to-severe mitral stenosis.	I	A

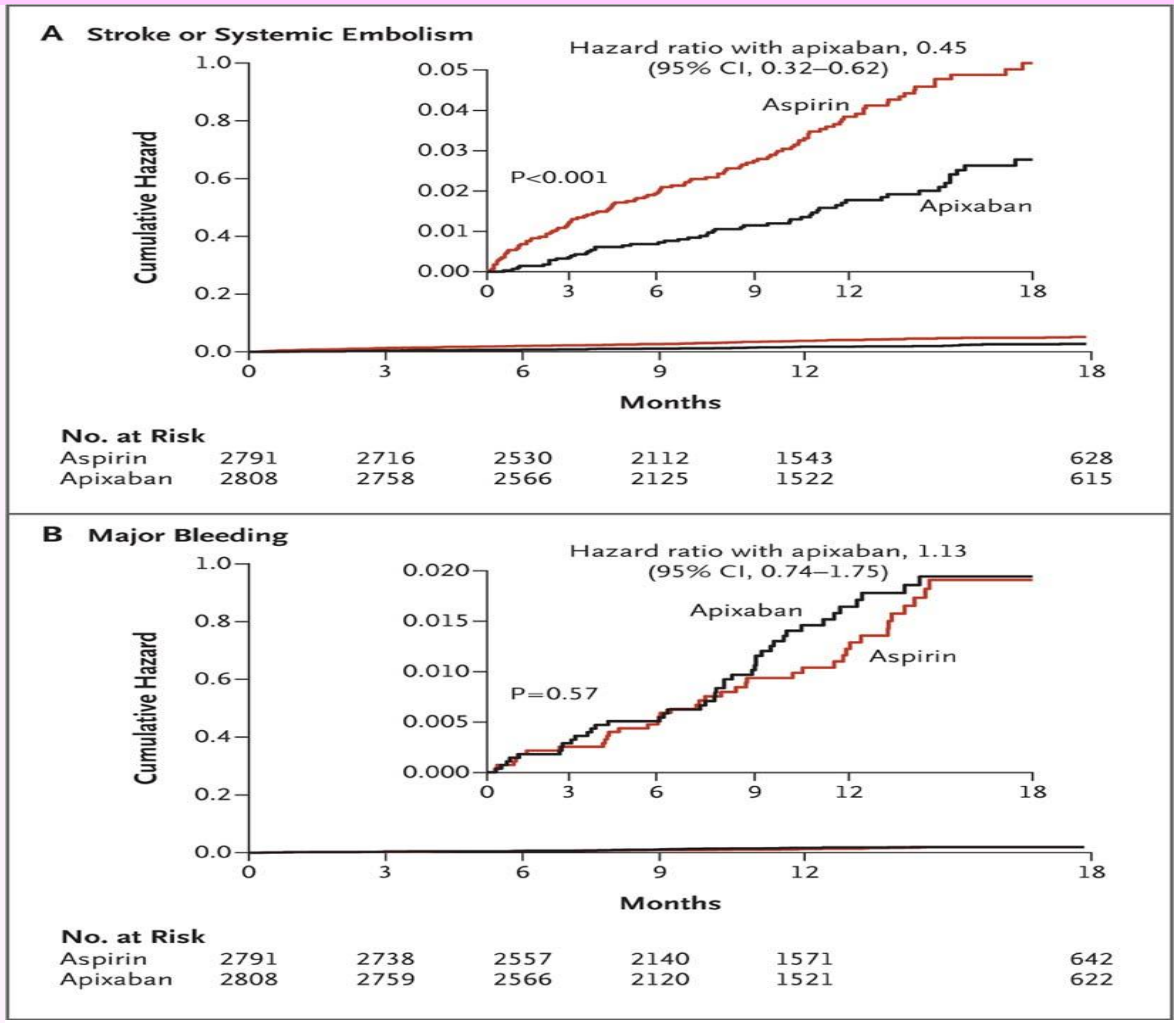
Switching to a DOAC is recommended for eligible patients that have failed to maintain an adequate time in therapeutic range on a VKA (TTR <70%) to prevent thromboembolism and intracranial haemorrhage.	I	B

Trials of DOAC



- **Stroke/Systemic Embolism:** Apixaban reduced the risk of stroke or systemic embolism by 21% (relative risk reduction).
- **Major Bleeding:** Apixaban significantly reduced major bleeding events by 31%.
- **Mortality:** Apixaban resulted in a 11% reduction in all-cause death.

AVERROES TRIAL

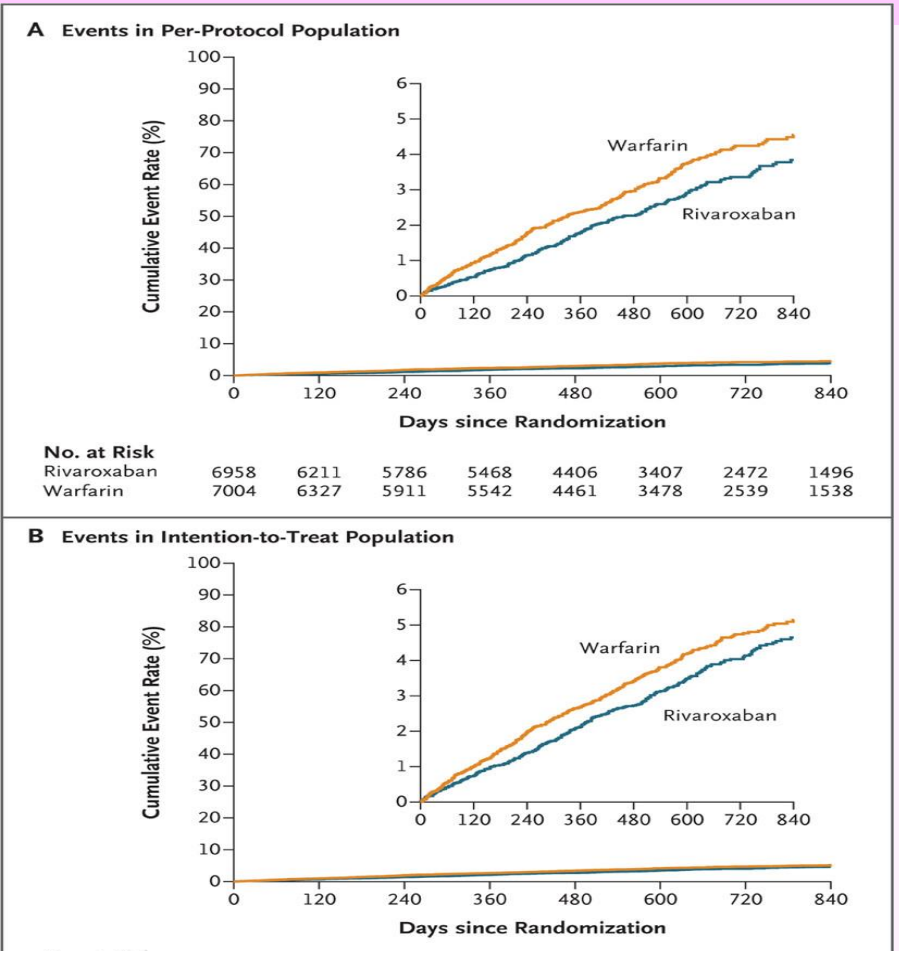


Stroke/Systemic Embolism: Apixaban significantly reduced the risk of stroke or systemic embolism by 54% compared with aspirin (Hazard Ratio [HR] 0.46, 95% confidence interval [CI] 0.34–0.62).

Major Bleeding: There was no statistically significant increase in the risk of major bleeding with apixaban compared to aspirin (HR 1.14, 95% CI 0.8–1.62). There was no increased risk of fatal or intracranial hemorrhage.

Mortality: Apixaban also resulted in lower all-cause mortality compared to aspirin.

Rocket AF

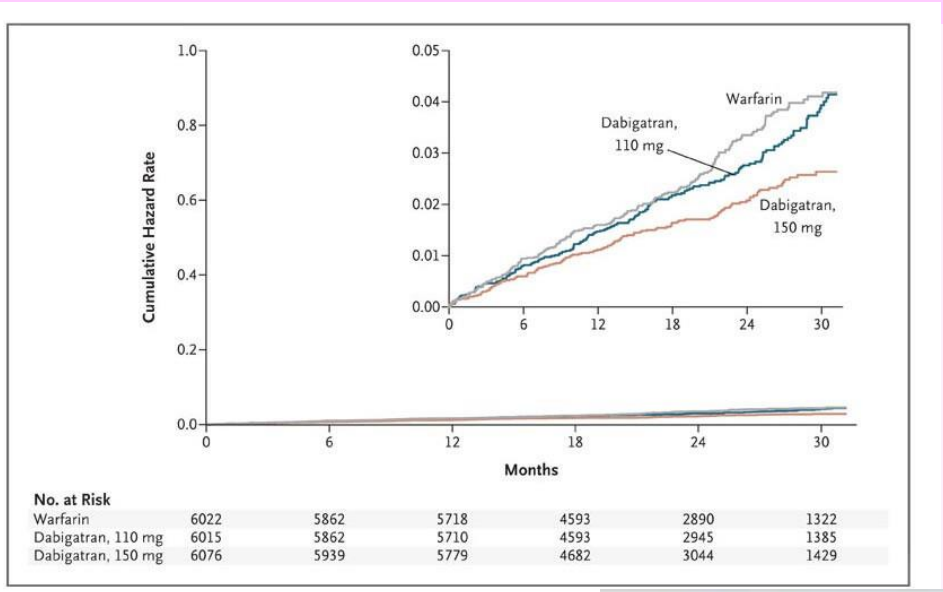


Efficacy: Rivaroxaban effectively prevented strokes and systemic embolisms, meeting the noninferiority standard compared to warfarin.

Safety (Bleeding):

- **Lower Risk:** Intracranial hemorrhage (bleeding in the brain) and fatal bleeding were lower with rivaroxaban.
- **Higher Risk:** Bleeding from the gastrointestinal (GI) tract and bleeding requiring transfusion or causing significant hemoglobin drops were higher with rivaroxaban.

Rely Study



RE-LY: Results with Dabigatran Etexilate

- Dabigatran (DE) 150 mg BID and 110 mg BID versus warfarin
- An 18,113 Patient Global Clinical Trial Mean follow up 2 years
- DE 150 reduced stroke/SEE by 35% versus warfarin
- DE 110 non-inferior to warfarin, with 20% reduction in major bleeding
- Greater than 50% reduction in intracranial bleeding with both doses compared to warfarin
- Regulatory approval in 79 countries as of November 2012

ARISTOPHANES Study

- Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients

- Large, retrospective, real-world study comparing DOAC like apixaban, dabigatran, and rivaroxaban against Warfarin for preventing stroke systemic embolism and major bleeding(MB) in patients with NVAF

- DOAC generally had lower stroke/SE rates than warfarin

- Apixaban showing the lowest major bleeding risk and rivaroxaban having a slightly higher bleed risk compared to warfarin, aligning with randomized trial findings but providing extensive real-world data, including in elderly populations

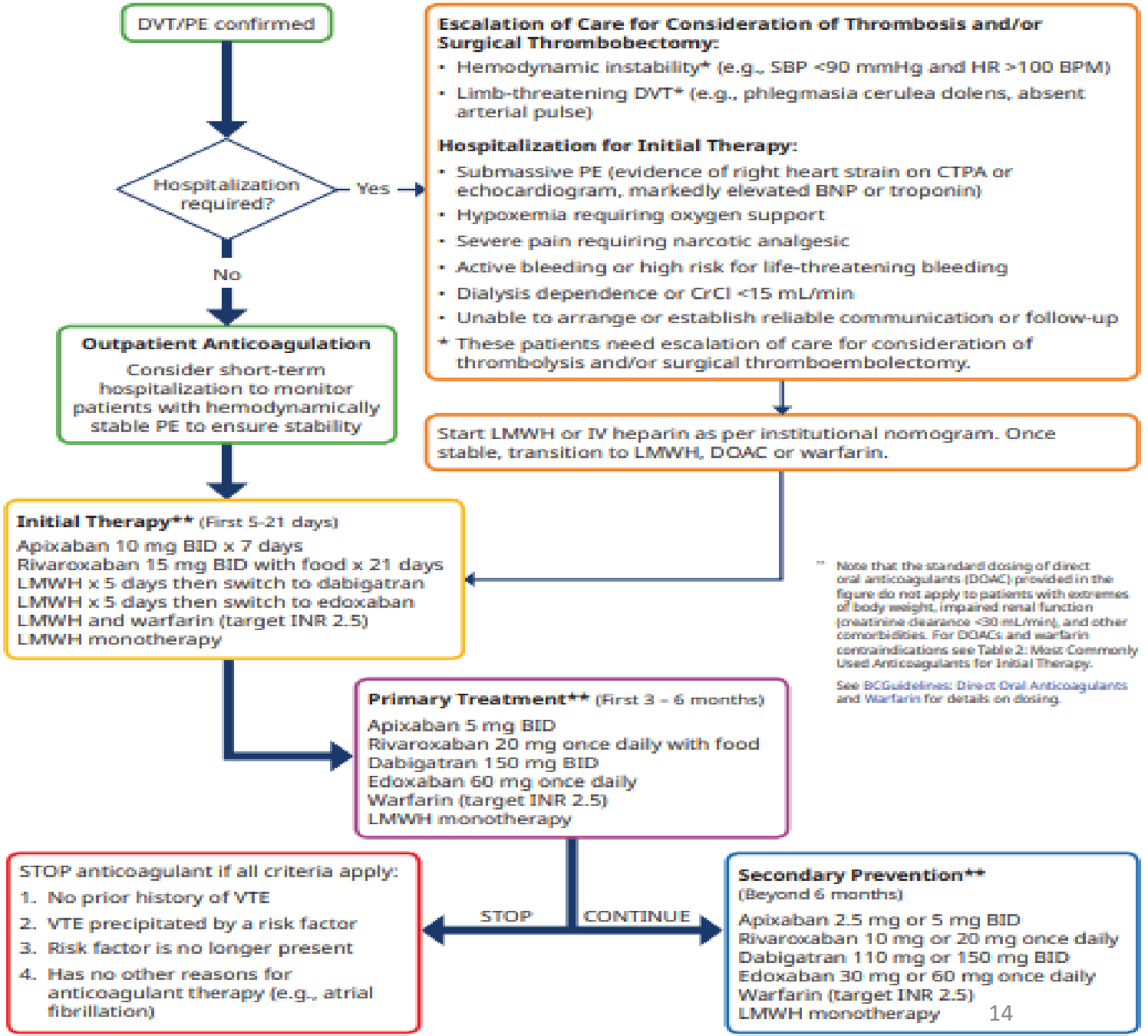
- Key Findings:
- Stroke/SE: All DOAC (apixaban, dabigatran, rivaroxaban) were associated with lower rates of stroke/SE compared to warfarin

- Major Bleeding (MB):
  - Apixaban: Lower MB risk than warfarin.
  - Dabigatran: Lower MB risk than warfarin.
  - Rivaroxaban: Similar or slightly higher MB risk than warfarin in some analyses

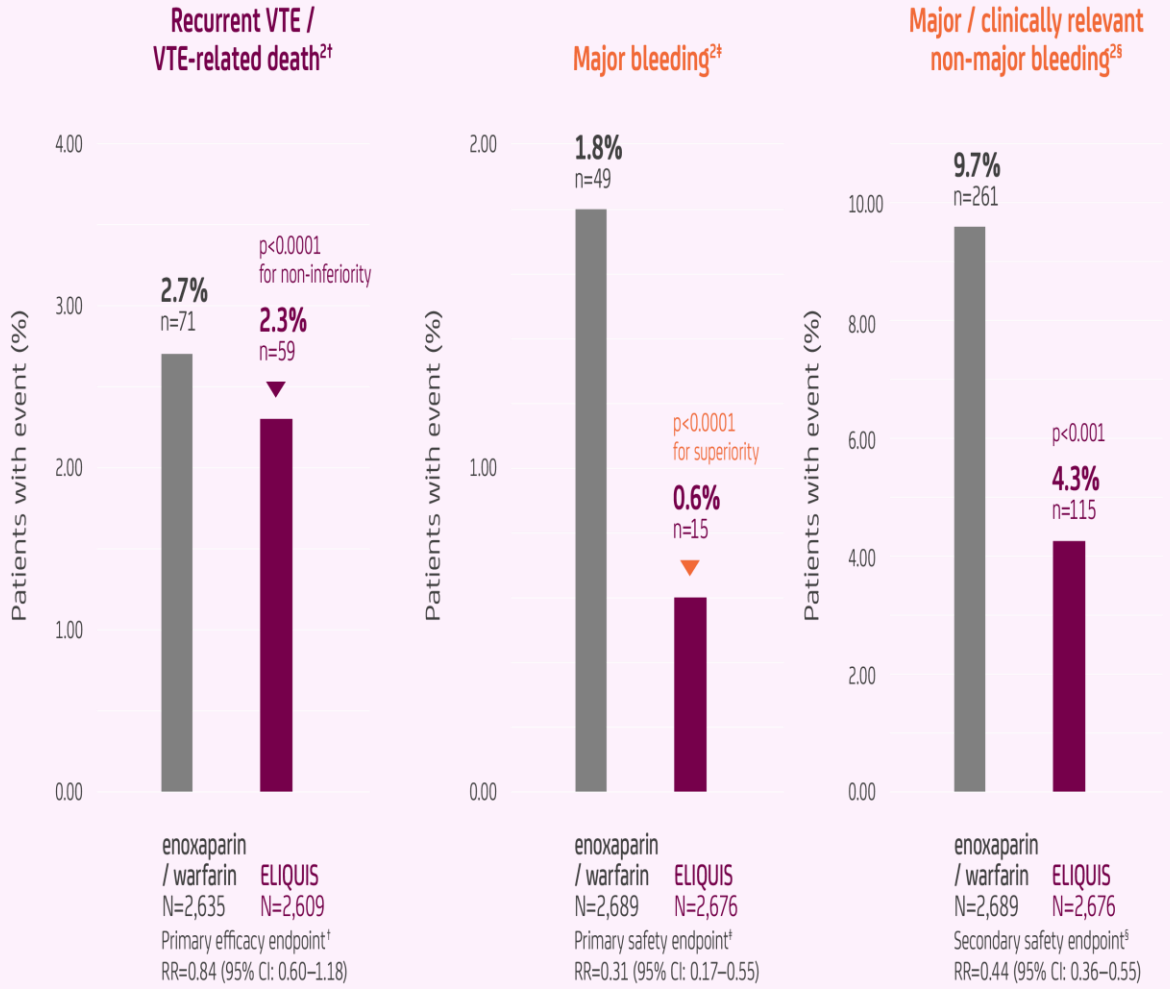
- Specific Comparisons: Apixaban had fewer major bleeds compared to dabigatran and rivaroxaban.

Recommendations for Treatment and Prevention of DVT/PE

Figure 4: Treatment Algorithm for DVT/PE



Amplify and Amplify Ext



Key Findings of AMPLIFY (Initial Treatment)

- **Efficacy:** Apixaban was noninferior to enoxaparin/warfarin for preventing symptomatic recurrent VTE or VTE-related death.
- **Safety:** Apixaban significantly lowered the risk of major bleeding compared to conventional therapy, with low overall major bleeding rates.
- **Hospitalizations:** An analysis showed apixaban reduced all-cause hospitalizations and shortened hospital stays for VTE patients.

AMPLIFY EXT TRIAL

2013

Apixaban for Extended Treatment of Venous Thromboembolism (low and full dose apixaban)

Randomized, double-blind, multicenter study

Patients >18 years of age with confirmed DVT and/or PE treated for 6-12 months with anticoagulation with apixaban or enoxaparin + warfarin (extension of AMPLIFY trial); n=2,486

Administered for 1 year

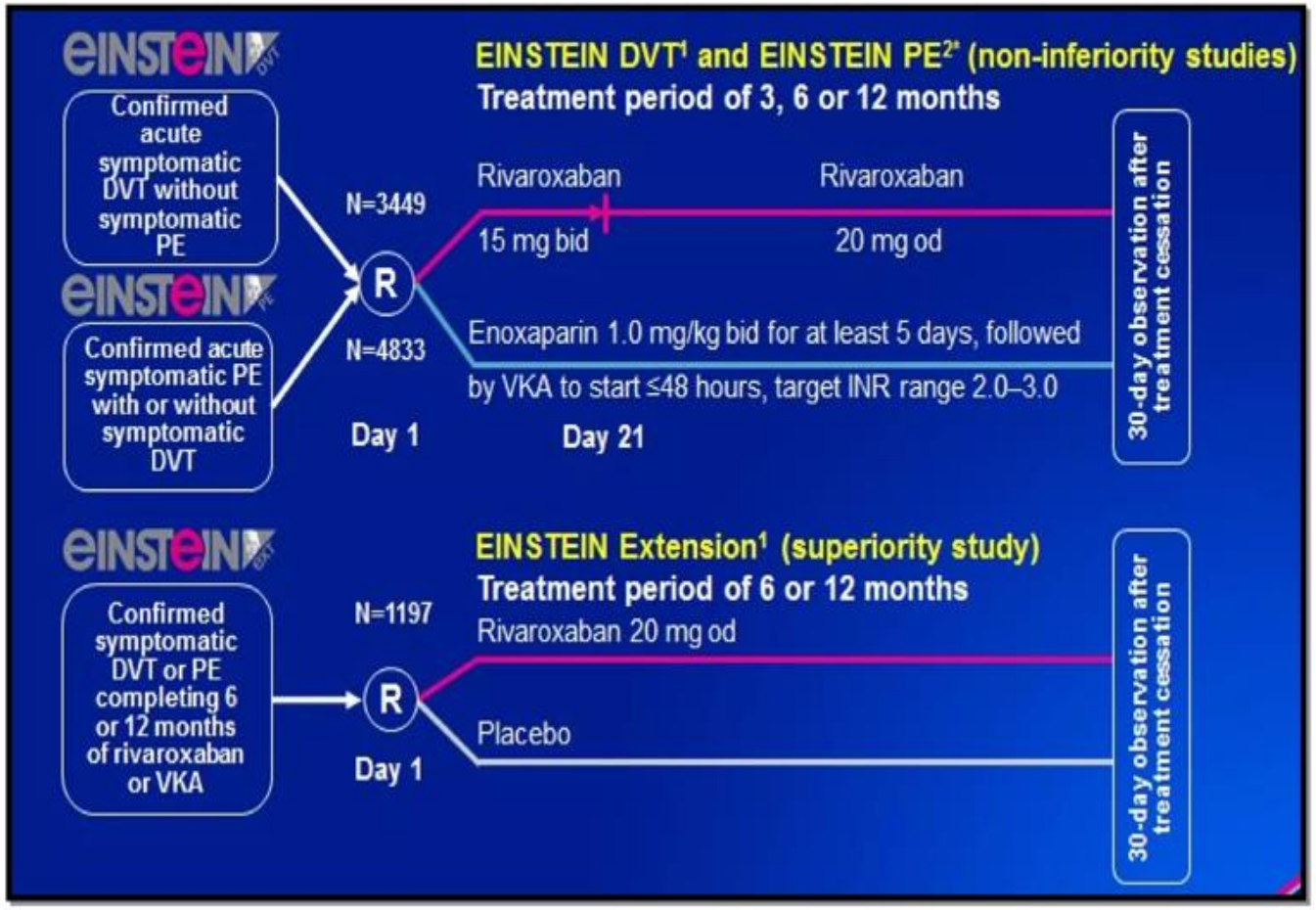
	Apixaban 2.5 mg BID n=842	Apixaban 5 mg BID n=815	Placebo n=829
Primary Outcome: Recurrent VTE or all-cause mortality	3.8% RR 0.33; 95% CI 0.22-0.48; NNT=13	4.2% RR 0.36; 95% CI 0.25-0.53; NNT=14	11.6%
Primary Outcome: Major Bleeding	0.2% RR 0.49 95% CI 0.09-2.64	0.1% RR 0.25 95% CI 0.03-2.24	0.5%
Second. Outcome: Clinically-relevant non-major bleeding	3.0% RR 1.29 95% CI 0.72-2.33	4.2% RR 1.82 95% CI 1.05-3.18	2.3%

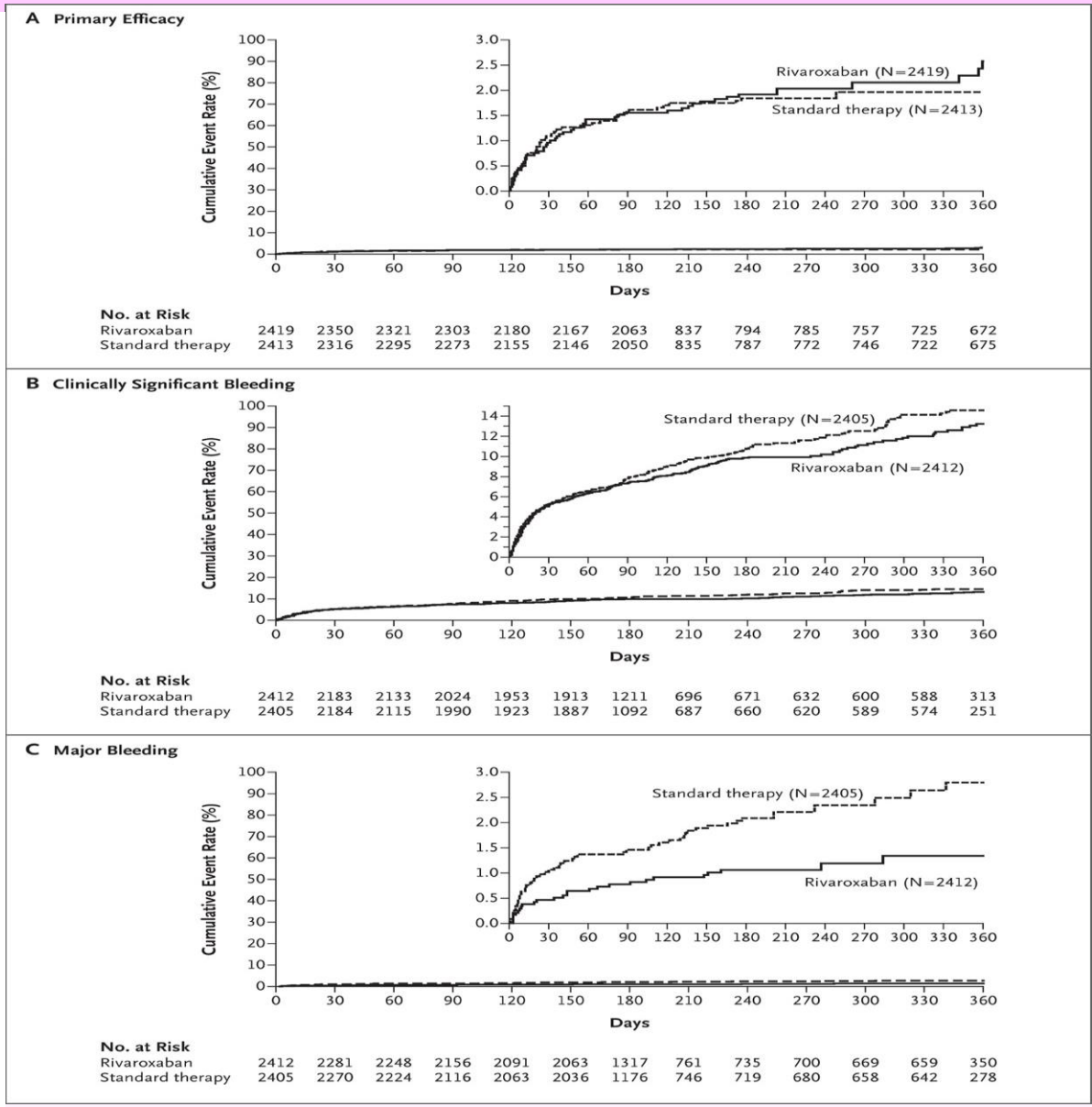
Long term apixaban (both doses) reduces recurrent VTE or all-cause mortality without increased risk of major bleeding after 6-12 months of initial anticoagulation

Agnelli G, et al. NEJM 2013. 368(8):699-708.

Einstein program

Phase III programme for VTE treatment for Rivaroxaban





Rivaroxaban was non-inferior in preventing recurrence and had fewer major bleeding events

Einstein program

EINSTEIN EXT trial evaluated extended rivaroxaban treatment and found it better than placebo at preventing recurrent VTE with a low rate of major bleeding

EINSTEIN CHOICE study compared two rivaroxaban doses to aspirin for extended VTE prevention, finding both rivaroxaban doses superior to aspirin with comparable major bleeding rates

EINSTEIN Junior program studied rivaroxaban in children with VTE

EINSTEIN trials collectively showed rivaroxaban is an **effective and safe single-drug option for VTE across various patients**

Systematic review and meta-analysis of the efficacy and safety of apixaban compared to rivaroxaban in acute VTE in the real world

- In an analysis involving 24 041 patients
- Recurrent VTE within 6 months occurred in 56 of 4897 patients (1.14%) in the apixaban group and 258 of 19 144 patients (1.35%) in the rivaroxaban group (RR, 0.89; 95% confidence interval [CI], 0.67-1.19; P 5 .45)
- Clinically relevant major bleeding occurred in 85 of 11 559 patients (0.74%) in the apixaban group and 350 of 33 909 patients (1.03%) in the rivaroxaban group (RR, 0.73; 95% CI, 0.58-0.93; P 5 .01)
- Clinically relevant nonmajor bleeding occurred in 169 of 3417 patients (4.95%) in the apixaban group and 1094 of 12 475 patients (8.77%) in the rivaroxaban group (RR, 0.59; 95% CI, 0.50-0.70; P , .01)
- Apixaban shows equivalent efficacy in prevention of recurrent VTE but decreased risk of major and minor bleeding events compared with rivaroxaban.

Meta-analysis of Apixaban vs Rivaroxaban in Acute VTE in real world

Study or Subgroup	Apixaban Events	Apixaban Total	Rivaroxaban Events	Rivaroxaban Total	Weight	Risk Ratio M-H, Random, 95% CI
Bott-Kitslaar 2018	3	302	2	298	2.6%	1.48 [0.25, 8.79]
Dawwas 2019	20	3091	108	12163	37.1%	0.73 [0.45, 1.17]
Sindet-Pedersen 2018	33	1504	148	6683	60.3%	0.99 [0.68, 1.44]
Total (95% CI)		**4897**		**19144**	**100.0%**	**0.89 [0.67, 1.19]**
Total events	56		258			

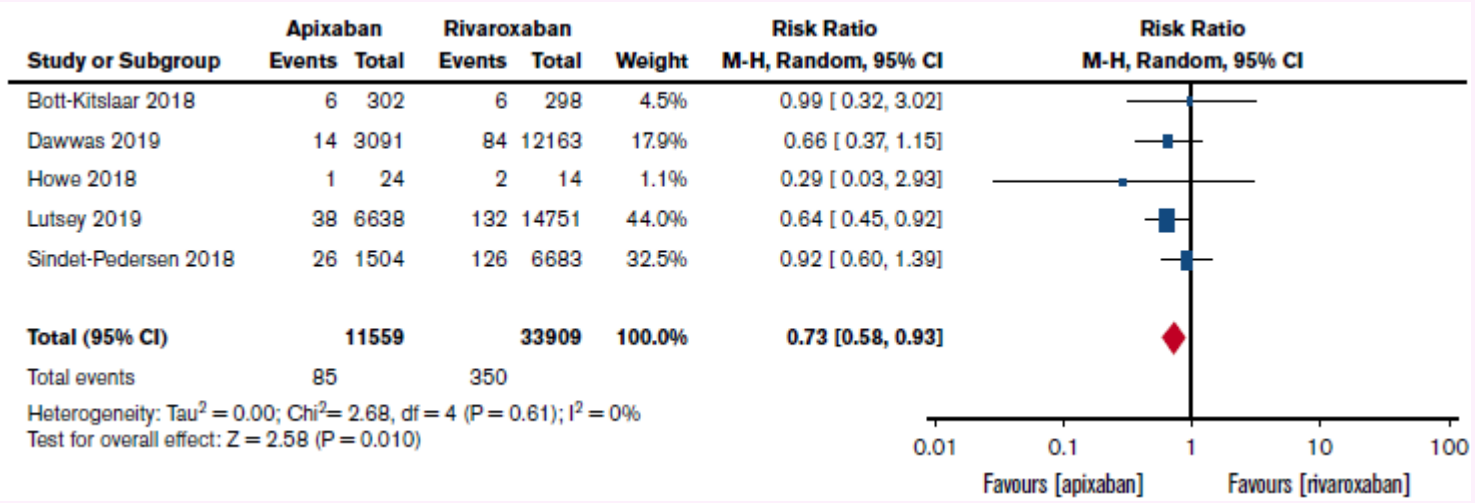
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.31$, df = 2 (P = 0.52); $I^2 = 0\%$
Test for overall effect: Z = 0.76 (P = 0.45)

Risk Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours [apixaban] Favours [rivaroxaban]

11% relatively less recurrent VTE events with apixaban as compared to rivaroxaban



Study or Subgroup	Apixaban Events	Apixaban Total	Rivaroxaban Events	Rivaroxaban Total	Weight	Risk Ratio M-H, Random, 95% CI
Bott-Kitslaar 2018	6	302	6	298	4.5%	0.99 [0.32, 3.02]
Dawwas 2019	14	3091	84	12163	17.9%	0.66 [0.37, 1.15]
Howe 2018	1	24	2	14	1.1%	0.29 [0.03, 2.93]
Lutsey 2019	38	6638	132	14751	44.0%	0.64 [0.45, 0.92]
Sindet-Pedersen 2018	26	1504	126	6683	32.5%	0.92 [0.60, 1.39]
Total (95% CI)		**11559**		**33909**	**100.0%**	**0.73 [0.58, 0.93]**
Total events	85		350			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.68$, df = 4 (P = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 2.58 (P = 0.010)

Risk Ratio M-H, Random, 95% CI

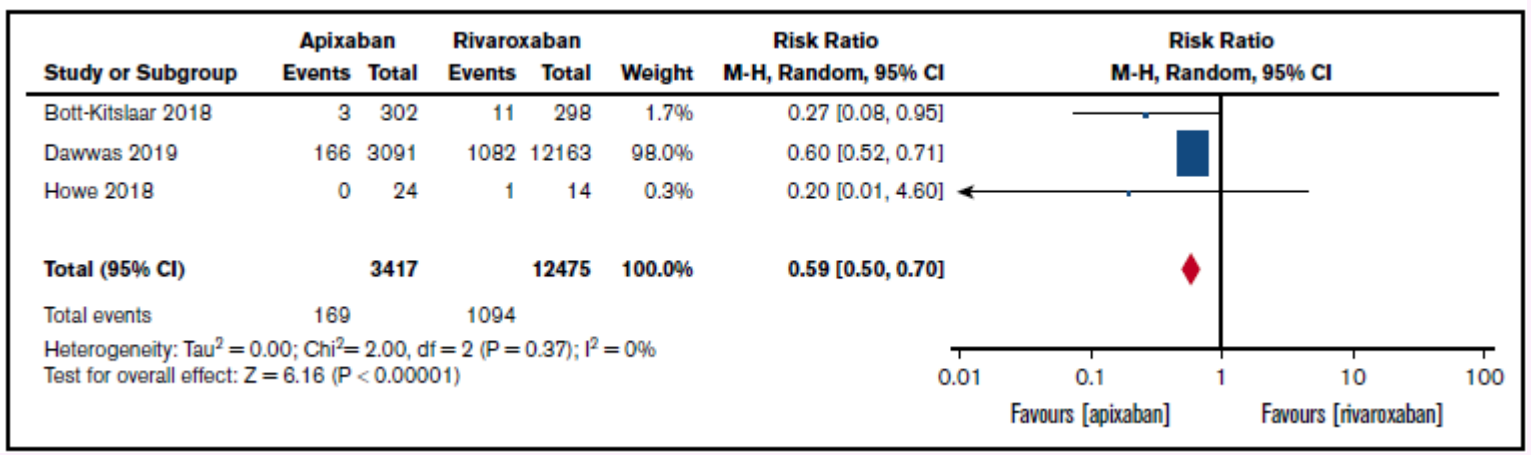
0.01 0.1 1 10 100

Favours [apixaban] Favours [rivaroxaban]

27% relatively less major bleeding with apixaban as compared to rivaroxaban

Aryal MR et al. Blood Adv. 2019 Aug 13; 3(15): 2381–2387.

Meta-analysis of Apixaban vs Rivaroxaban in Acute VTE in real world



Study or Subgroup	Apixaban Events	Apixaban Total	Rivaroxaban Events	Rivaroxaban Total	Weight	Risk Ratio M-H, Random, 95% CI
Bott-Kitslaar 2018	3	302	11	298	1.7%	0.27 [0.08, 0.95]
Dawwas 2019	166	3091	1082	12163	98.0%	0.60 [0.52, 0.71]
Howe 2018	0	24	1	14	0.3%	0.20 [0.01, 4.60]
Total (95% CI)		**3417**		**12475**	**100.0%**	**0.59 [0.50, 0.70]**
Total events	169		1094			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.00$, $df = 2$ ($P = 0.37$); $I^2 = 0\%$
Test for overall effect: $Z = 6.16$ ($P < 0.00001$)

41% relatively less Clinically relevant nonmajor bleeding with apixaban as compared to rivaroxaban

Aryal MR et al. Blood Adv. 2019 Aug 13; 3(15): 2381–2387.

Practical Tips in Using DOAC Indications and Contra indications

DOAC	Primary VTE Prophylaxis in Hip/Knee Replacement Surgery	Non-Valvular Atrial Fibrillation	DVT/PE Treatment	Secondary Prevention of Recurrent DVT/PE	Primary VTE Prophylaxis of Adult Patients Hospitalized for an Acute Medical Illness	Reduce Risk of Major Cardiovascular Events in CAD and PAD patients (in combination with aspirin use)
Apixaban	X	X	X	X		
Betrixaban					X	
Dabigatran	X (Hip)	X	X	X		
Edoxaban		X	X			
Rivaroxaban	X	X	X	X	X	X

Table 1 Currently approved indications for the use of direct oral anticoagulant drugs[†]

	VTE prevention	VTE treatment[‡]		Atrial fibrillation (AF)	Stable atherosclerotic vascular disease
		Initiation	Maintenance		
Apixaban[‡,§,¶]	2.5 mg twice daily post hip and knee replacements	10 mg twice daily for 7 days	5 mg twice daily; consider 2.5 mg twice daily beyond 6 months	5 mg twice daily/or 2.5 mg twice daily[††]	
Rivaroxaban[‡‡]	10 mg daily post hip and knee replacements	15 mg twice daily for 21 days	20 mg daily; consider 10 mg daily beyond 6 months	20 mg daily / 15 mg daily[§§]	2.5 mg twice daily (combined with aspirin)[¶¶,a]
Dabigatran[bc]	110 mg 1–4 h post-surgery, then 220 mg once daily post hip and knee replacements[d]		150 mg twice daily or 110 mg twice daily[e]	150 mg oral twice daily or 110 mg oral twice daily[f]	

Practical Tips in Using DOAC
Indications and Contra indications

Indication for Anticoagulation	DOAC of choice
Venous Thromboembolism (VTE) Treatment	
Acute treatment of VTE	**Apixaban** or rivaroxaban
Cancer-associated thrombosis	**Apixaban**
Non-valvular AF / flutter	
First line	**Apixaban**
Second line	Rivaroxaban Edoxaban Dabigatran
Other conditions	
High-risk acute coronary syndrome (in combination with aspirin +/- clopidogrel)	Rivaroxaban 2.5mg bd (Consultant Cardiologist initiation only)
Combined coronary artery disease / peripheral artery disease (CAD/PAD) – in combination with aspirin	Rivaroxaban 2.5mg bd
VTE prophylaxis following orthopaedic surgery	**Apixaban**, rivaroxaban, or dabigatran
Moderate to severe mitral stenosis	DOAC not suitable
Mechanical prosthetic heart valve	DOAC not suitable
Antiphospholipid syndrome	DOAC not suitable

Contra indications

- Known hypersensitivity to the active ingredient or to one of the excipients of the formulation
- Mechanical heart valve
- Rheumatic mod-severe mitral stenosis
- Renal impairment:
  - Apixaban: CrCl < 15 mL/min
  - Rivaroxaban: CrCl < 15 mL/mina
  - Dabigatran: CrCl < 30 mL/min
- Triple positive antiphospholipid syndrome
- Significant inherited or acquired bleeding disorder
- Clinically significant active bleeding
- Pregnancy or breastfeeding
- Hepatic disease with associated coagulopathy including Child-Pugh C
- Lesions or conditions at significant risk of bleeding including intracranial haemorrhage unless under the advice of neurologist /neurosurgeon
- Indwelling spinal or epidural catheter and during the first six hours after removal
- Co-administration with strong inhibitors (or inducers) of CYP3A4 and P-glycoprotein (P-gp)

Selected indications and contraindications for DOAC therapy in AF patients

Condition	Eligibility for NOAC	Comment
Mechanical prosthetic valve	Contraindicated	Excluded from pivotal RCTs Data indicating worse outcome[15,16]
Moderate to severe mitral stenosis (usually rheumatic)	Contraindicated	Excluded from pivotal RCTs Little rationale for less efficacy and safety vs. VKA
Other mild to moderate valvular disease (e.g. degenerative aortic stenosis, mitral regurgitation etc.) Bioprosthetic valve/valve repair (after >3 months postoperative)	Included in NOAC trials Acceptable	Data regarding efficacy and safety overall consistent with patients without valvular heart disease[12,17–22] Some data from NOAC RCTs Single RCT indicating non-inferiority to VKA[24] Patients without AF usually on ASA after 3–6 months post-surgery, hence NOAC therapy acceptable for stroke prevention if diagnosed with AF
Severe aortic stenosis	Limited data (excluded in RE-LY)	No pathophysiological rationale for less efficacy and safety Most will undergo intervention
Transcatheter aortic valve implantation	Acceptable	Single RCT + observational data May require combination with APT[25,26]
Percutaneous transluminal aortic valvuloplasty	With caution	No prospective data May require combination with APT
Hypertrophic cardiomyopathy	Acceptable	No rational for less efficacy and safety vs. VKA Observational data positive for NOACs[33–36]

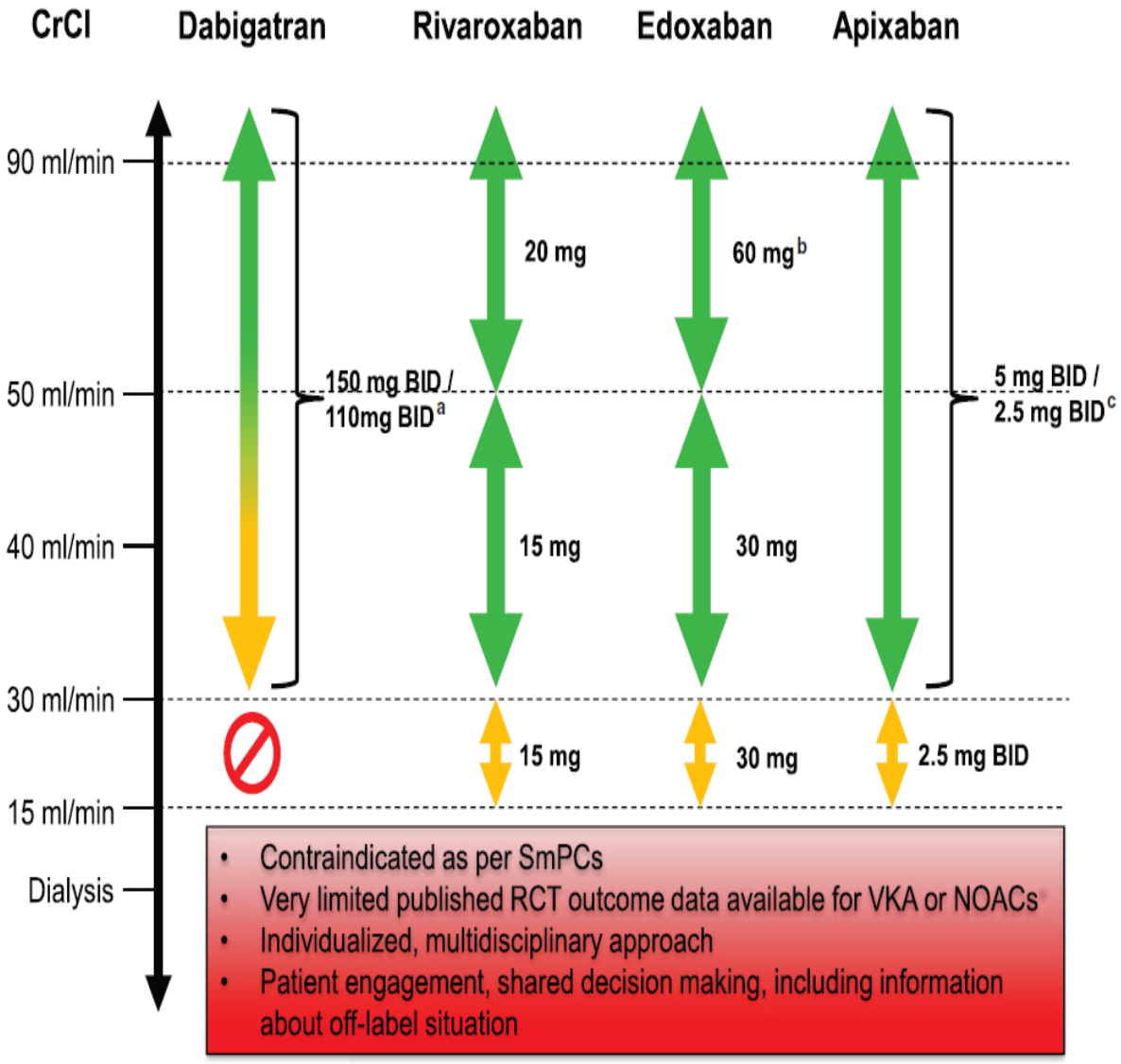
Choice of DOAC

- There are no completed head-to-head clinical trials of any of the DOACs. In the landmark stroke prevention and VTE treatment trials, all three available DOACs were compared to warfarin. These trials demonstrated that the safety and efficacy of all three drugs was comparable or superior to warfarin.
- In the absence of direct comparison trials, it is not possible to recommend one DOAC over another in all cases, but patient-related factors and dosing regimens may make one agent and dose optimal for individual patients. (Clinician-patient discussion)

Comorbidities to consider prior to commencing a DOAC

Consideration	Clinical advice
Renal impairment	Dose adjustment may be required .
Hepatic impairment	All DOACs are contraindicated in hepatic disease with associated coagulopathy, including Child-Pugh C. Apixaban and dabigatran can be used with caution in mild to moderate hepatic impairment (Child-Pugh A or B). Rivaroxaban can be used with caution in mild hepatic impairment (Child-Pugh A) and is contraindicated in moderate hepatic impairment (Child-Pugh B).
Gastrointestinal bleeding	Use with caution and seek specialist advice in patients with any history of gastrointestinal bleeding.
Critically unwell (for example, sepsis)	DOACs should not be commenced in critically unwell patients.
Extremes in body weight	Dose adjustment is not required for extremes of body weight for all agents (excluding apixaban). It is recommended that a reduced dose of apixaban be considered for patients weighing 60 kg or less for stroke prevention in non-valvular AF if another factor is present . At the time of publication there has been limited published data for dosing of DOACs in patients with a BMI of over 40 kg/m^2 or a weight over 120 kg. It is important to note that DOAC activity is linked to lean body weight and the relationship becomes inversely proportional for individuals with a total body weight over 100 kg.

DOAC dose in Renal insufficiency



ADNEXA AF TRIAL

Key Findings:

- **Design:** A randomized, open-label trial comparing apixaban (2.5 mg twice daily) to a VKA (phenprocoumon) in AF patients with end-stage kidney disease on chronic hemodialysis.
- **Primary Outcome (Safety):** A composite of major bleeding, clinically relevant non-major bleeding, or death occurred at similar rates in both groups (45.8% apixaban vs. 51% VKA).
- **Primary Efficacy Outcome:** A composite of stroke, cardiovascular death, MI, and VTE showed numerically fewer events with apixaban (20.8%) than VKA (30.6%), though the study's limited size made definitive conclusions difficult.
- **Major Bleeding:** Rates were similar (10.4% apixaban vs. 12.2% VKA).

promising trends for apixaban but was underpowered to prove superiority, indicating it's a reasonable choice, but more definitive evidence is required for this complex patient population

DOAC in patients with Liver disease

Baseline assessment:

- H/o thromboembolism or bleeding?
- Relevant co-medications and over-the-counter drugs?
- CBC, liver function test, PT/INR, aPTT, renal function
- High bleeding risk (e.g., H/o major bleeding (varices), uncontrolled alcohol intake, etc.)?

Highest risk patients → Consider no anticoagulation / evaluate alternative stroke prevention strategy

All other patients

Parameter	1 point	2 points	3 points
Encephalo-pathy	No	Grade 1-2	Grade 3-4
Ascites	No	Mild	≥ Moderate
Bilirubin	< 2 mg/dL < 34 µmol/L	2-3 mg/dL 34-50 µmol/L	> 3 mg/dL > 50 µmol/L
Albumin	> 3.5 g/dL > 35 g/L	2.8-3.5 g/dL 28-35 g/L	< 2.8 g/dL < 28 g/dL
INR	< 1.7	1.71-2.30	>2.30

NOAC Use recommendations in liver disease

	A (<7 pts)	B (7-9 pts)	C (>9 pts)
Dabigatran	Normal dose	Use with caution	Not recommended
Apixaban			
Edoxaban			
Rivaroxaban		Not recommended	

- ✓ Assess Child-Pugh score
- ✓ Check NOAC use recommendations in liver disease
- ✓ Check for drug-drug interactions
- ✓ Discuss in multidisciplinary team

Close follow-up (see also Fig. 3)

- Signs of (occult) bleeding?
- Adherence? Side effects?
- (New) co-medications, incl. NSAIDs, aspirin, OTC?
- CBC, liver function, PT/INR, aPTT, renal function
- Continue bleeding risk minimization strategies
- Re-enforce education, incl. alcohol abstinence

DOAC in patients with Extreme body weight

- Based on the pharmacokinetic properties and the available evidence the use of all NOACs appears to be safe and effective up to a BMI of 40 kg/m2.
- Low body weight may increase exposure to any DOAC and as such increase the risk of bleeding compared to normal weight patients.
- Special care is needed when anticoagulating low weight patients Body weight ≤60 kg requires dose reduction of apixaban [in patients with age ≥80 years and/or serum Creatinine ≥ 133 mmol/ (1.5mg/dl)] as well as for endoxaban.
- Weight and body mass index (BMI) are important variables in drug distribution and plasma concentration levels.

Dose of DOAC

Name/Cost	Dose in NVAF	Dose in VTE	Dose in CAD/PAD	Therapeutic Considerations

Apixaban
ELIQUIS, generics
Tabs: 2.5, 5 mg
 	
PharmaCare regular benefit[a]
~$30/month[b]
	5 mg BID
	OR
	2.5 mg BID if ≥ 2 of the following:
	• age ≥ 80 years
	• weight ≤ 60 kg
	• Serum creatinine ≥ 133 µmol/L
		Acute: 10 mg BID x 7 days then 5 mg BID x 3 to 6 months
		
		Chronic (> 6 months): 2.5 or 5 mg BID
			Not indicated	• Contraindicated/avoid use:
				• CrCl < 15 mL/min, Child-Pugh class C
				  • (↑ bleed risk): azole-antimycotics (e.g., ketoconazole), cobicistatc, HIV protease inhibitors (e.g., ritonavir)
				  • (↑ thromboembolic risk): carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort
				• Discuss with specialist for CrCl 15 to 29 mL/min

Rivaroxaban
XARELTO, generics
Tabs: 2.5, 10, 15, 20 mg
 	
Oral suspension:
1 mg/mL
 	
PharmaCare regular benefit (tablets only)[a]
~$25/month[b]
	20 mg daily with food
	OR
	15 mg daily with food if CrCl 30 to 49 mL/min
		Acute: 15 mg BID with food x 21 days then 20 mg daily with food x 3 to 6 months
		
		Chronic (> 6 months): 20 mg daily with food or 10 mg daily
			2.5 mg BID with ASA 81 mg daily	• Contraindicated/avoid use:
				  • CrCl < 15 mL/min, Child-Pugh class B and C
				  • (↑ bleed risk): azole-antimycotics (e.g., ketoconazole), cobicistat, dronedarone, HIV protease inhibitors (e.g., ritonavir)[d]
				  • (↑ thromboembolic risk): carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort[c], post-gastrectomy (highly absorbed in stomach)
				  • Data limited for CrCl 15 to 30 mL/min
				• Take 15 mg and 20 mg doses with food to facilitate adequate absorption

Dose of DOAC

Name/Cost	Dose in NVAF	Dose in VTE	Dose in CAD/PAD	Therapeutic Considerations

Dabigatran
PRADAXA, generics
Caps: 75, 110, 150 mg
	150 mg BID
	OR
	110 mg BID if any of the following:
	• age ≥ 80 years
	• higher risk of bleeding, including age ≥ 75 years with ≥ 1 risk factor for bleeding (refer to *product monograph*)
		Acute: LMWH x 5 to 10 days followed by 150 mg BID (or 110 mg BID) x 3 to 6 months
		
		Chronic (> 6 months): 150 mg or 110 mg BID
			Not indicated	• Contraindicated/avoid use:
				  • CrCl < 30 mL/min, Child-Pugh class C
				  • (↑ bleed risk): azole-antimycotics (e.g., ketoconazole), dronedarone, glecaprevir/pibrentasvir (Maviret™), verapamil, clarithromycinc, erythromycin
				  • (↑ thromboembolic risk): carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort
				• Increased gastric pH may ↓ absorption (antacids, PPIs)
				• Take with food to reduce dyspepsia
				• Must be stored in original packaging

Name/Cost	Dose in NVAF	Dose in VTE	Dose in CAD/PAD	Therapeutic Considerations

Edoxaban
LIXIANA
Tabs: 15, 30, 60 mg
	60 mg daily
	OR
	30 mg daily if any of the following:
	• CrCl 15 to 50 mL/min
	• weight ≤ 60 kg
	• concomitant P-gp inhibitors (see Therapeutic Considerations)
		Acute: LMWH x 5 to 10 days followed by 60 mg daily (or 30 mg daily) x 3 to 6 months
		
		Chronic (> 6 months): 60 mg or 30 mg daily
			2.5 mg BID with ASA 81 mg daily	• Contraindicated/avoid use:
				  • CrCl < 15 mL/min, Child-Pugh class C
				  • (↑ thromboembolic risk): carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort[c]
				• Reduce dose (30 mg daily) with: cyclosporine, dronedarone, clarithromycin[c], erythromycin, ketoconazole, quinidine (↑ bleed risk)

DOAC Administration instruction

DOAC	Administration instructions
Apixaban	• Swallow whole with or without food. • Can be used in dose administration aids. • Can be crushed (if required) and administered orally or via a gastric tube
Rivaroxaban	• **15 mg** and **20 mg** tablet should be **taken with food.** • 2.5 mg and 10 mg tablet may be taken with or without food. • Can be used in dose administration aids. • Can be crushed (if required) and administered orally or via a gastric tube
Dabigatran	• Swallow whole with or without food. • Do not chew or open capsule. • Keep in original packaging. • Do not transfer capsule to a dose administration aid.

DOAC Follow up

- Initiation and structured follow-up of patients on DOACs.
- It is crucial to ensure a structured follow-up of patients on NOACs.

Initiator of anticoagulant treatment

- Indication (contraindication?) for anticoagulation
- Baseline blood works, incl. hemoglobin, renal / liver function, full coagulation panel
- Choice of anticoagulant and correct dose
- Education and handover of anticoagulation card
- Organization of follow-up (when, where, by whom, what?)

first FU: 1 month

Regular follow-up: GP; cardiologist, anticoagulation / AF clinic, ...
(may be performed via phone / video call, particularly if in-person visit is not possible or deemed risky, e.g., during Covid-19 pandemic)

- Thromboembolic / bleeding events?
- Side effects?
- Adherence (discussion, explanation, remaining pills, NOAC card, ...)?
- Change in co-medication (incl. over-the-counter drugs)?
- Need for blood sampling? Hemoglobin, renal function, coagulation panel etc.
- Re-assessment of CHA_2DS_2-VASc and HAS-BLED score
- Modifiable stroke- and bleeding risk factor assessment and -improvement
- Re-assessment of optimal NOAC and correct dosing

Interval "quick check" / blood sampling

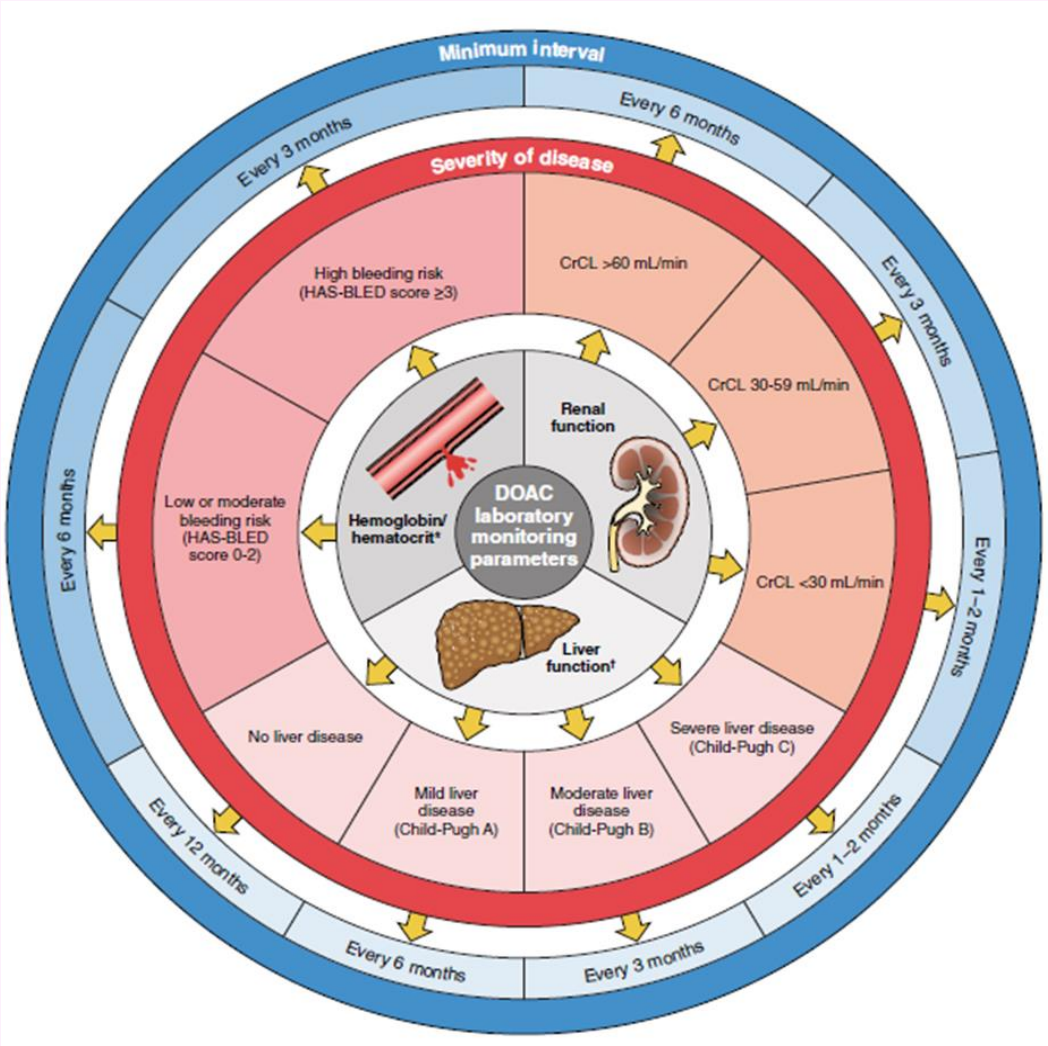
- 4-monthly: ≥75y (especially if on dabigatran), or frail.
- Every "CrCl/10" months if CrCl ≤60 ml/min
- Immediately in case of intercurrent conditions, esp. with potential impact on renal or hepatic function (e.g., infection, NSAID use, dehydration etc.).

No severe problems or challenges

Severe problems or challenges

Consultation with specialist / multi-disciplinary team

- Filling of anticoagulation card
- Reinforcement of key educational aspects
- Schedule of date/place for next follow-up

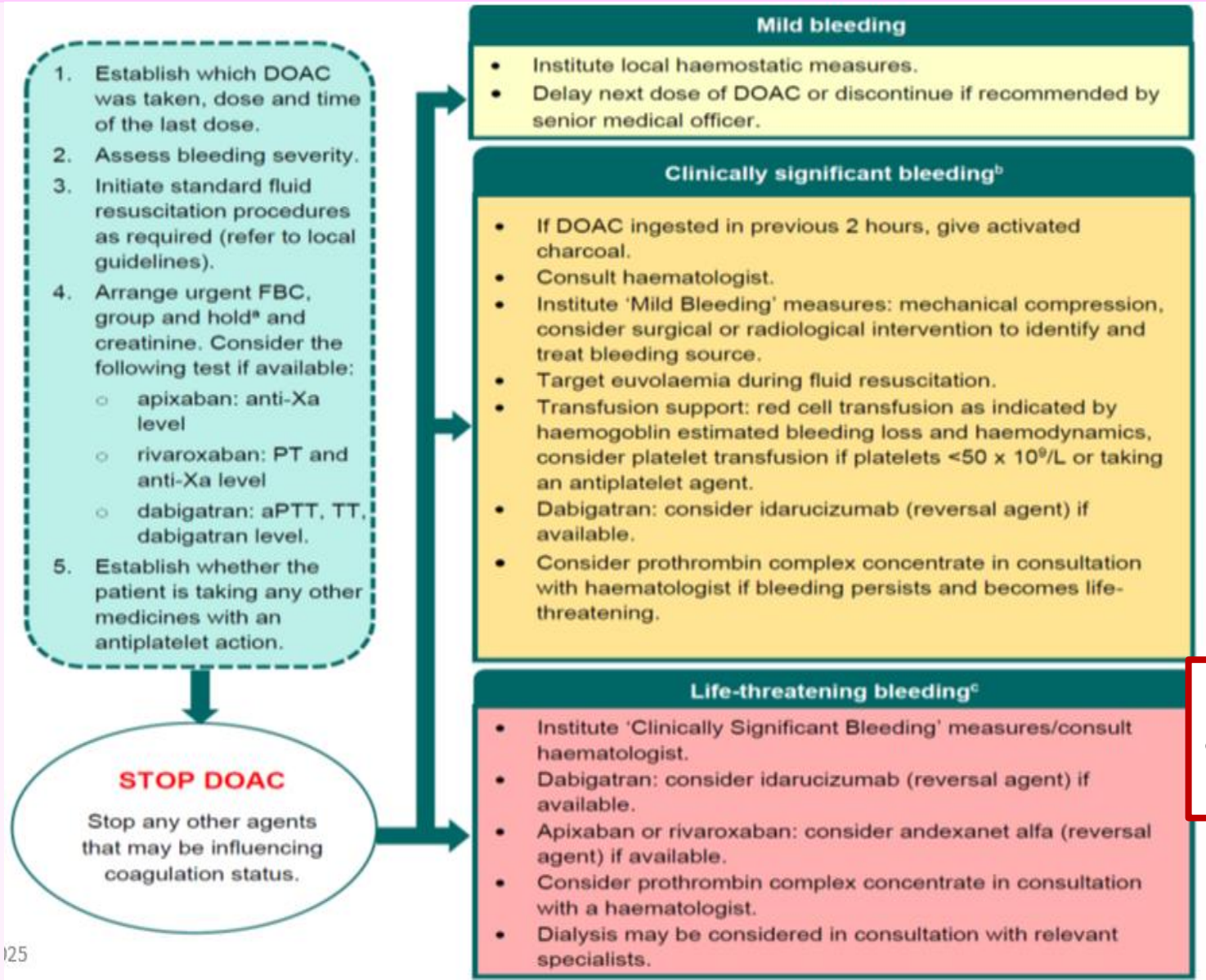


When to measure DOAC anticoagulant effect

Effect	Apixaban	Rivaroxaban	Dabigatran
Significant anticoagulant effect unlikely	Normal PT[a] **does not** exclude presence of therapeutic apixaban	PT[a] normal	TT normal aPTT normal
Anticoagulant effect present	PT[a] prolonged or normal	PT[a] prolonged	TT prolonged aPTT prolonged
Specific assays to quantify drug presence	Modified anti-Xa assay specific for apixaban	Modified anti-Xa assay specific for rivaroxaban	Dilute thrombin clotting time (Hemoclot® assay)

- 1. Major bleeding
- 2. Urgent Surgery
- 3. New or deteriorating renal impairment
- 4. Recurrence or extension of thromboembolism when therapeutic adherence is assumed
- 5. Using concomitant medications which induce or inhibit liver enzymes
- 6. Before instituting thrombolysis for treatment of ischaemic stroke and other indications for thrombolysis

Managing Bleeding on DOAC



No role for dialysis in rivaroxaban and apixaban related bleeding due to high protein binding

Reversal agents

TABLE Guidance on indications for use or nonuse of specific antidotes and other therapies.

Guidance on indications for use of specific antidotes and other therapies	Idarucizumab[a] Licensed for reversal of dabigatran in major hemorrhage and emergency surgery since 2016	Andexanet alfa[a] Licensed for reversal of rivaroxaban and apixaban in major hemorrhage since 2019	PCC[b] Not licensed for specific DOAC reversal	Tranexamic acid[c] Not licensed for specific DOAC reversal
Guidance on indications for use	• Life-threatening bleeding: intracranial hemorrhage, expanding or uncontrollable bleeding • Bleeding in a critical organ or closed space • Urgent or emergency surgery or intervention that cannot be delayed in patients with a high risk for procedural bleeding, ie, neurosurgery	• Life-threatening bleeding: intracranial hemorrhage, expanding or uncontrollable bleeding • Bleeding in a critical organ or closed space • Urgent relief surgery for intracranial hemorrhage	• Life-threatening bleeding: intracranial hemorrhage, expanding or uncontrollable bleeding • Bleeding in a critical organ or closed space • Urgent or emergency surgery or intervention that cannot be delayed in patients with a high risk for procedural bleeding, ie, neurosurgery • Might be useful in trauma patients with dilution coagulopathy due to massive blood loss	• Life-threatening bleeding: intracranial hemorrhage, expanding or uncontrollable bleeding • Bleeding in a critical organ or closed space • Urgent or emergency surgery or intervention that cannot be delayed in patients with a high risk for procedural bleeding, ie, neurosurgery • Might be useful in trauma patients with dilution coagulopathy to prevent hyperfibrinolysis

Reversal agents

Guidance on indications for use of specific antidotes and other therapies	Idarucizumab[a] Licensed for reversal of dabigatran in major hemorrhage and emergency surgery since 2016	Andexanet alfa[a] Licensed for reversal of rivaroxaban and apixaban in major hemorrhage since 2019	PCC[b] Not licensed for specific DOAC reversal	Tranexamic acid[c] Not licensed for specific DOAC reversal
Guidance on indications in which the antidote or other therapies should not be used	• Elective surgery • Gastrointestinal bleeds that can be stopped by local supportive measures • High DOAC drug levels without associated bleeding • Need for surgery or intervention that can be delayed long enough to permit drug clearance	• Urgent or emergency surgery or intervention (not licensed, will interfere with perioperative heparin treatment) • Elective surgery • Gastrointestinal bleeds that can be stopped by local supportive measures • High DOAC drug levels without associated bleeding • Need for surgery or intervention that can be delayed long enough to permit drug clearance	• Elective surgery • Gastrointestinal bleeds that can be stopped by local supportive measures • High DOAC drug levels without associated bleeding • Need for surgery or intervention that can be delayed long enough to permit drug clearance	• Elective surgery • Gastrointestinal bleeds that can be stopped by local supportive measures • High DOAC drug levels without associated bleeding • Need for surgery or intervention that can be delayed long enough to permit drug clearance

Transitioning of anticoagulants

From IV UFH to a DOAC

Stop IV UFH.

Start DOAC within one hour.

From LMWH to a DOAC[b]

Stop LMWH.

Start DOAC when the next dose of LMWH would have been due.

From warfarin to a DOAC

Stop warfarin.

Measure INR daily.

Wait until INR is less than 2.5.

Start DOAC.

From a DOAC to IV UFH

Stop DOAC.

If apixaban or rivaroxaban:

- Start IV UFH when the next DOAC dose would have been due.[a]

If dabigatran, check renal function (CrCl):

- If CrCl ≥ 30 mL/min, start IV UFH when the next dabigatran dose would have been due.[a]
- If CrCl < 30 mL/min, start IV UFH 48 hours after the last dabigatran dose.[a]

From a DOAC to a LMWH

Stop DOAC.

Check renal function (CrCl):

- If CrCl ≥ 30 mL/min, start LMWH when the next DOAC dose would have been due.
- If CrCl < 30 mL/min, seek specialist advice.

From one DOAC to another DOAC

Stop DOAC and start the other DOAC when the next dose of the first DOAC would have been due.

Transitioning of anticoagulants

From a DOAC to warfarin CrCl ≥ 50 mL/min

1. Start warfarin while still taking the DOAC.
2. Measure INR daily, with the blood sample for the test being taken immediately before the DOAC dose, i.e., a 'trough' level.
3. Continue taking both the warfarin and DOAC until the INR has been greater than the patient's 'baseline' INR plus 1.0 for two consecutive days.[a]

For example, if the patient's baseline INR is 1.7, the DOAC should be ceased when INR has been greater than 2.7 (i.e., 1.7 plus 1.0) on two consecutive days.

4. If the baseline INR is NOT elevated (i.e. ≤ 1), then cease the DOAC when the INR has been greater than 2 for two days.
5. Ongoing warfarin dosing is according to the usual target range for the patient's specific indication.

From a DOAC to warfarin CrCl < 50 mL/min

Reduced clearance of a DOAC can increase the risk of bleeding, the transition should be taken with a high degree of caution under the direction of a specialist.

Perioperative management

- **Thromboembolic risk and bleeding risk**
- **DOACs have shorter half-lives compared to warfarin, often making them easier to discontinue and resume rapidly.**
- **Bridging anticoagulation is usually not required for patients taking DOACs**

When to Interrupt and Restart DOAC during Elective procedure

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Minor-bleeding-risk procedure					
Recommended to not stop in most minor surgical procedures					NA†
STOP: 12–24 h before procedure* Skip 1 dose			Skip 1 dose		
RESTART: 6 h after intervention					
Low-bleed-risk procedure Stop 24–96 h before procedure					
CrCl ≥80 mL/min	STOP: ≥24	STOP: ≥24	STOP: ≥24	STOP: ≥24	STOP: ≥96
CrCl ≤50–79 mL/min	STOP: ≥36	STOP: ≥24	STOP: ≥24	STOP: ≥24	STOP: ≥96
CrCl ≤30–49 mL/min	STOP: ≥48	STOP: ≥24	STOP: ≥24	STOP: ≥24	Not indicated
CrCl ≤15–29 mL/min	Not indicated	STOP: ≥36	STOP: ≥36	STOP: ≥36	Not indicated
CrCl ≤15 mL/min	Consider measuring drug activity to determine absence of drug affect				Not indicated
RESTART	≥24 h after intervention				
High-bleed-risk procedure Stop 48–96 h before procedure					
CrCl ≥80 mL/min	STOP: ≥48	STOP: ≥48	STOP: ≥48	STOP: ≥48	STOP: ≥96
CrCl ≤50–79 mL/min	STOP: ≥72	STOP: ≥48	STOP: ≥48	STOP: ≥48	STOP: ≥96
CrCl ≤30–49 mL/min	STOP: ≥96	STOP: ≥48	STOP: ≥48	STOP: ≥48	Not indicated
CrCl ≤15–29 mL/min	Not indicated	STOP: ≥48	STOP: ≥48	STOP: ≥48	Not indicated
CrCl ≤15 mL/min	Consider measuring drug activity to determine absence of drug effect			Not indicated	
RESTART	≥48 to 72 h after intervention				

- **Minor-bleeding-risk interventions: dental, cataract, glaucoma, endoscopy without biopsy or resection, superficial surgery**
- **Low-bleeding-risk interventions: endoscopy with biopsy, prostate biopsy, bladder biopsy, pacemaker or implantable cardioverter-defibrillator implantation, noncoronary angiography, electrophysiological study/catheter ablation**
- **High-bleeding-risk intervention: major surgery, spinal puncture or placement of spinal/epidural catheter, other situations in which complete hemostasis is required.**

Major Drug Interactions

- **Drugs that inhibit or induce CYP3A4 liver enzymes and/or permeability glycoprotein (P-gp) transporters have significant interactions with DOACs(Apixaban and Rivaroxaban)**

- **Dabigatran is not metabolized by CYP 3A4 enzymes**

Drug Interaction Examples	
Strong CYP3A4 inhibitors+combined P-gp inhibitor	Itraconazole, ketoconazole, ritonavir
Moderate CYP3A4 inhibitors+combined P-gp inhibitor	Clarithromycin, diltiazem
Strong CYP3A4 inducer+combined P-gp inducer	Carbamazepine, rifampin, St. John's wort
Strong CYP3A4 inducers	Phenytoin
P-gp inhibitors	Amiodarone, clarithromycin, cyclosporine, dronedarone, erythromycin ivacaftor, ketoconazole, nifedipine, quinidine, ranolazine, ticagrelor, tolvaptan, verapamil
P-gp inducers	Rifampin

Major Drug Interactions

	Drug Interaction	Effect of DOAC	Recommendations
Dabigatran	P-gp inhibitors	Increase in concentration	Reduce dose or avoid depending on renal function
	P-gp inducers	Significant reduction in concentration	Avoid use
	Antacids	Moderate reduction in concentration	No dose adjustments required; consider spacing regiments by 2 h
Apixaban	Strong CYP3A4 inhibitor+P-gp inhibitor	Significant increase in concentration	Reduce dose or avoid use
	Moderate CYP3A4 inhibitor+P-gp inhibitor	Moderate increase in concentration	No dose adjustments required; use with caution Avoid use in patient with severe renal insufficiency
	Strong CYP3A4 inducer or P-gp inducer	Significant reduction concentration	Avoid use
Rivaroxaban	Strong CYP3A4 inhibitor+P-gp inhibitor	Significant increase in concentration	Avoid use
	Moderate CYP3A4 inhibitor+P-gp inhibitor	Moderate increase in concentration	No precaution necessary Avoid use in patient with severe renal insufficiency
	Strong CYP3A4 inducer or P-gp inducer	Significant reduction concentration	Avoid use
Edoxaban	P-gp inhibitors	Increase in concentration	AF: Do not reduce dose VTE treatment: Reduce dose
	P-gp inducers	Significant reduction in concentration	Avoid use with rifampin
Betrixaban	P-gp inhibitors	Increase in concentration	Avoid: CrCl <30 mL/min
	P-gp inducers	Significant reduction in concentration	Not addressed

Take Home Message

- Use in right indication
  - High risk patients of Atrial fibrillation
  - Patients unstable INR
  - First line venous thrombosis/embolism
  - Cancer patients
  - Orthopedic prophylaxis
  - Good compliances

- Don't use wrong dose / under dose
- Don't use with mechanical valves, moderate to severe mitral stenosis
- Don't use in very obese patients
- Don't use in pregnancy and breast feeding

THANK YOU