Direct Oral Anticoagulants in Atrial Fibrillation

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What will we cover?

1. Initiating anticoagulation
2. SEL DOAC recommendations
3. DOAC monitoring and safety
4. Case studies

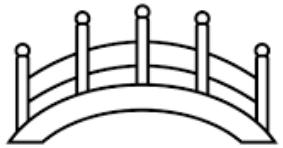
There are several advantages to using DOACs

No INR monitoring

No dietary interactions

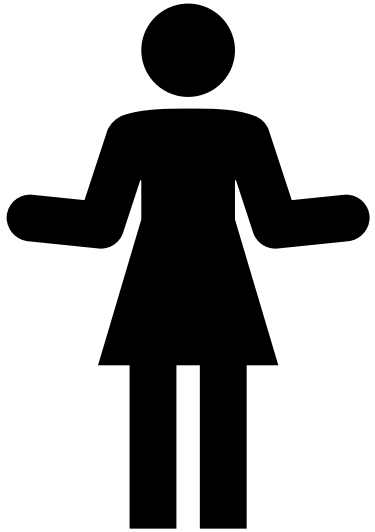
Fewer drug interactions

Short half life

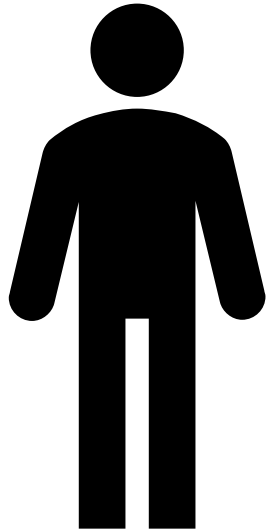


No bridging with LMWH

NICE recommends CHA_2DS_2-VASc score for initiation



CHA_2DS_2-VASc =>2



CHA_2DS_2-VASc =>1

CHA_2DS_2-VASc risk score

Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (CAD, CArD, PAD)	1
Age 65-74	1
Sex category (female)	1

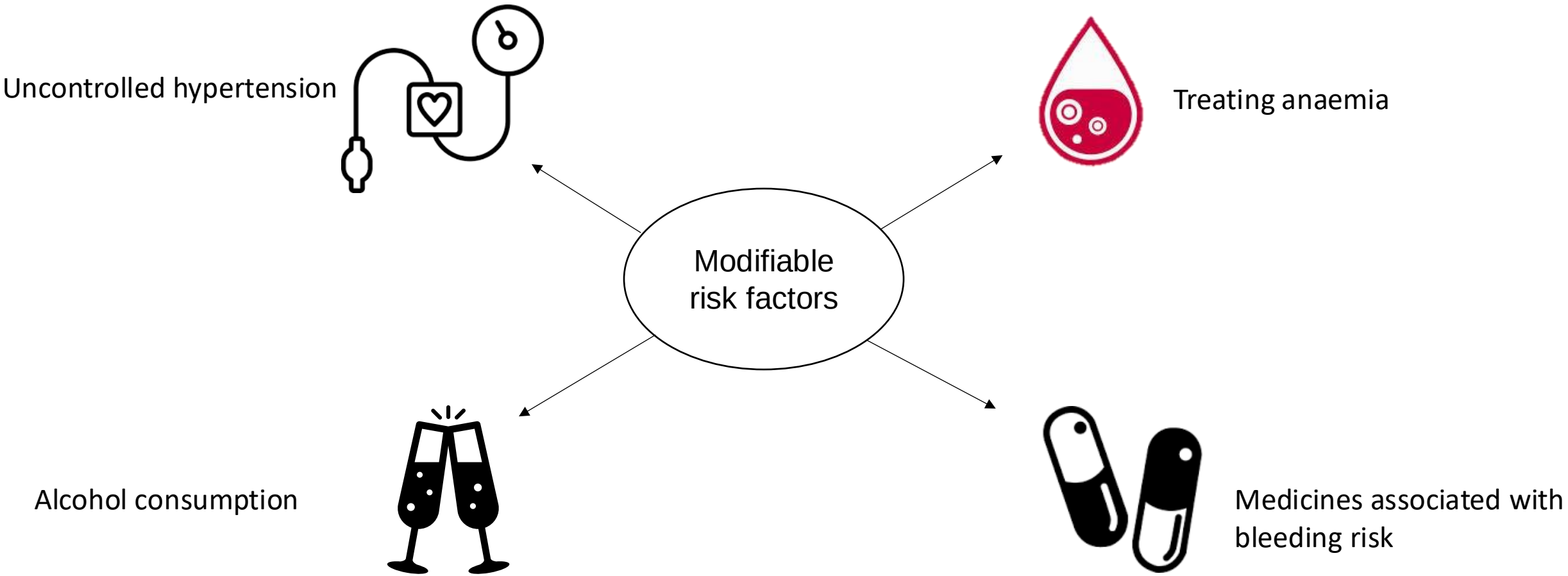
Score	Annual stroke rate, %
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

ORBIT bleeding risk score

Older than 74 years	1
Reduced haemoglobin Males: Hb<130 g/L, HCT< 0.4 L/L Females: Hb<120 g/L, HCT< 0.36L/L OR History of anaemia	2
Bleeding history GI bleeding Intracranial bleeding Haemorrhagic stroke	2
Insufficient renal function GFR<60 mL/min/1.73m^2	1
Treatment with antiplatelet	1

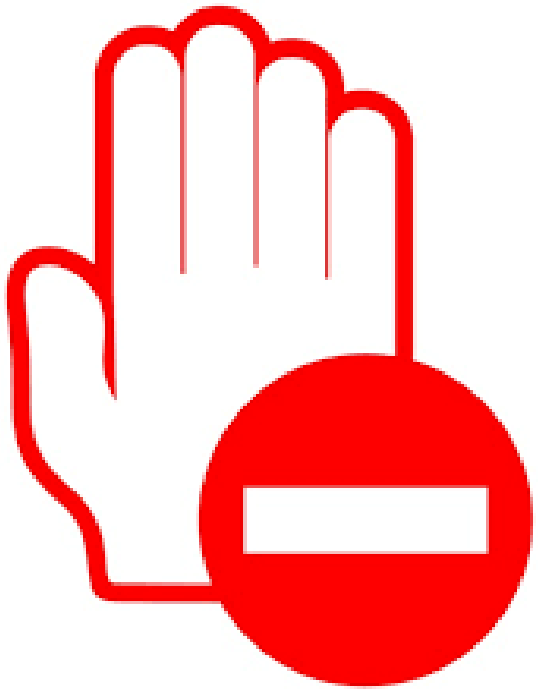
ORBIT score	Risk level	Number of major bleeds per 1000 AF patients treated with anticoagulant, per year
0-2	Low	24
3	Medium	47
4-7	High	81

ORBIT score is not a reason to withhold anticoagulation

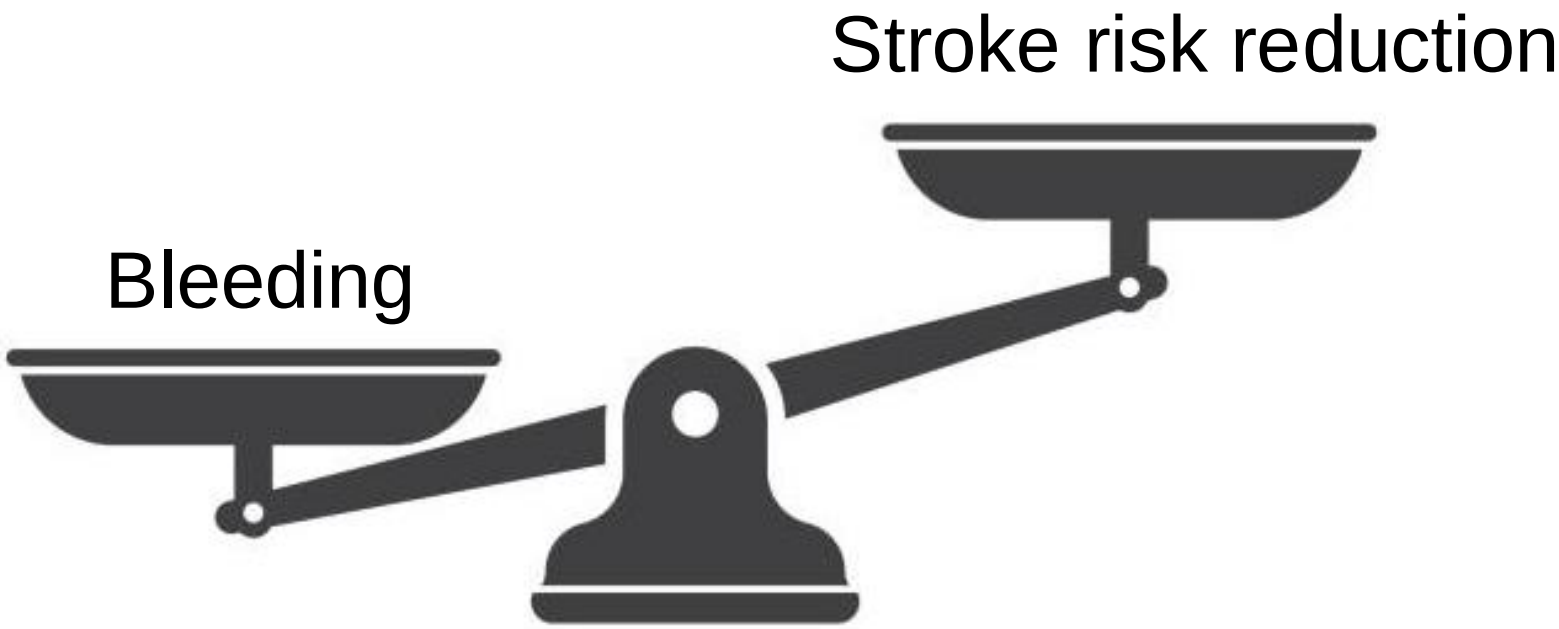


Be aware of contraindications

Mitral stenosis
APLS
Significant medication interactions
CrCl <15ml/min or dialysis
Cardioembolic stroke



Decision to start needs to be shared with the patient



In SEL generic apixaban and rivaroxaban are the preferred agents

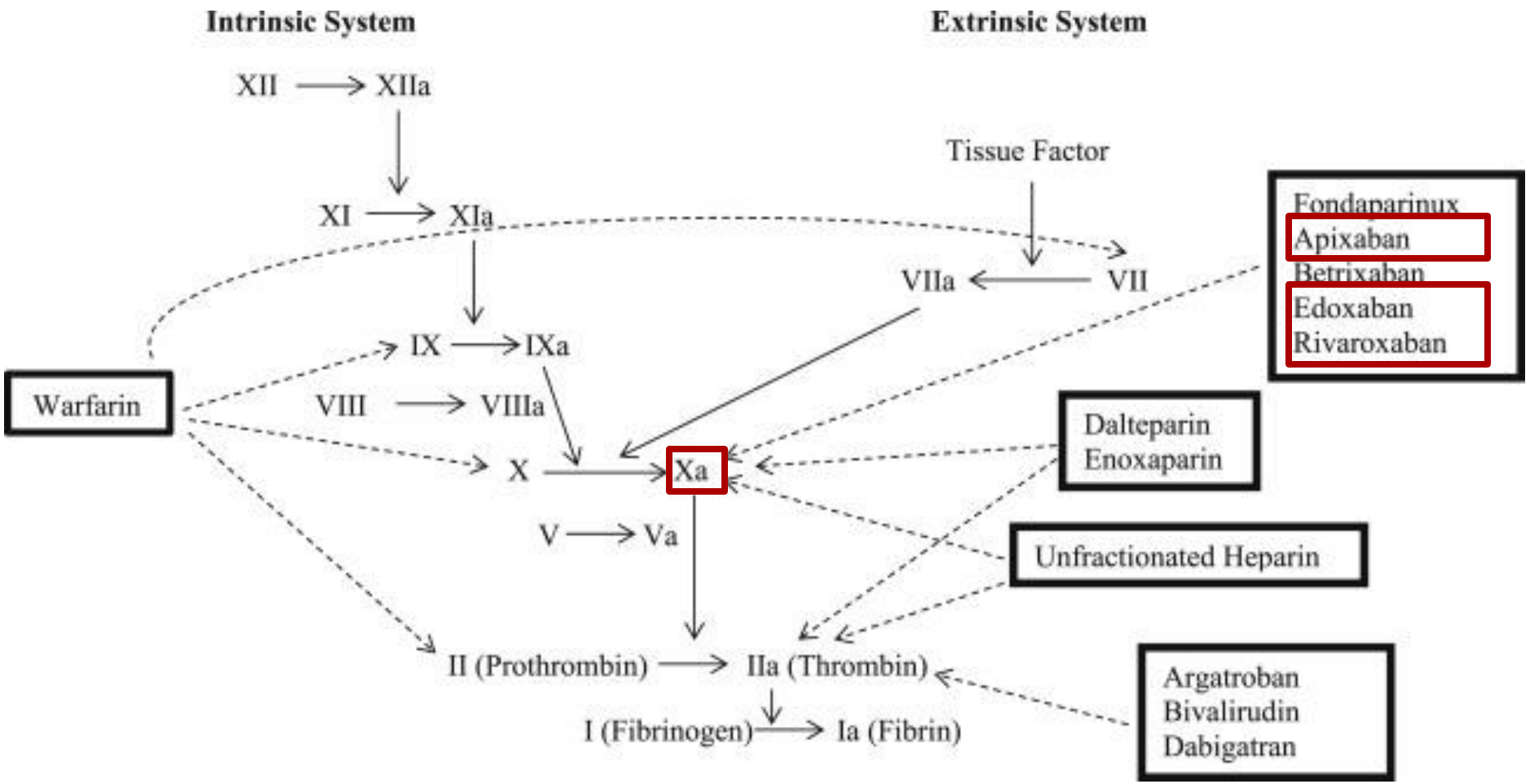
But…

Only consider switching if there are **clinical concerns** or **tolerability issues**

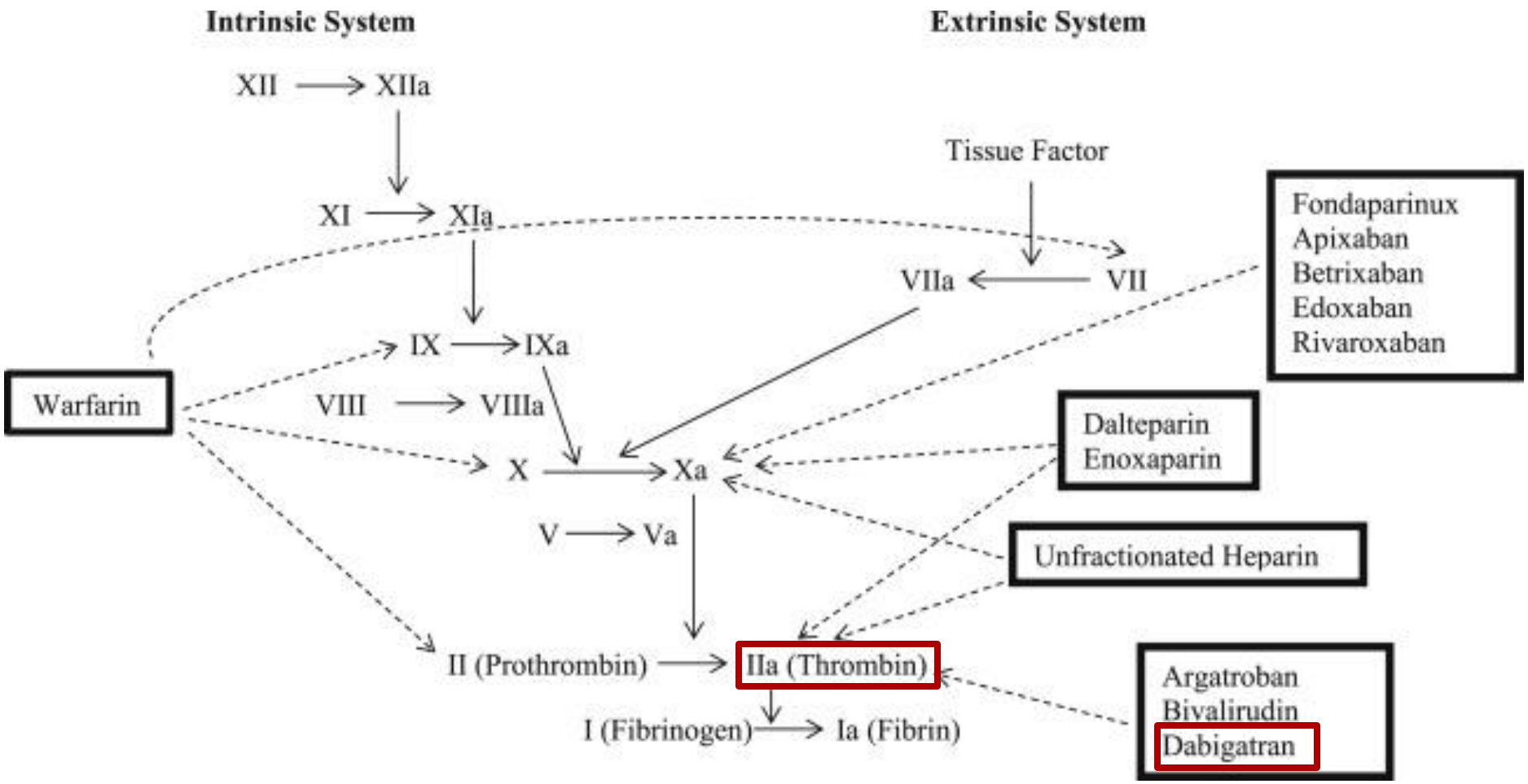
Dosing for each DOAC is different

DOAC	Edoxaban	Rivaroxaban	Apixaban	Dabigatran
Dose	60mg once daily	20mg once daily	5mg twice daily	150mg twice daily
Reduced dose	30mg once daily if: Weight <61kg *or* CrCl< 50ml/min *or* co-prescribed with ciclosporin, dronedarone, erythromycin *or* ketoconazole.	15mg once daily if: CrCl< 50mL/min	2.5mg twice daily if at least two of the following: Age ≥ 80 years Weight ≤ 60 kg Cr ≥ 133 micromol/l *or* CrCl 15 - 29 ml/min.	110mg twice daily if: Age > 80 years Prescribed verapamil Consider if: age 75-80 years *or* CrCl <50mL/min *or* increased risk of bleeding (including gastritis, oesophagitis, gastro-oesophageal reflux).
Contraindicated	CrCl <15ml/min	CrCl <15ml/min	CrCl <15ml/min	CrCl <30 ml/min

Apixaban, edoxaban and rivaroxaban work on factor Xa



Dabigatran is a thrombin II inhibitor

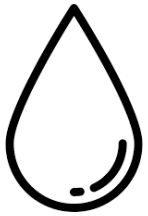


Apixaban AF trial (Aristotle)

Randomised, double-blind, double dummy

Superior to warfarin for stroke or systemic embolism

18,201 patients
(9,120 to apixaban and 9,081 to warfarin)



Superior to warfarin for major bleeding

5mg twice daily (dose reduced 2.5mg twice daily)

Apixaban AF trial (Aristotle)

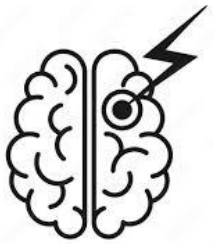
Table 2. Efficacy Outcomes.*

Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

* Analyses were performed on data from the intention-to-treat population and included all events through the cutoff date for efficacy outcomes of January 30, 2011; comparisons of the primary outcome and of death from any cause were analyzed as part of hierarchical sequence testing (starting with testing the primary outcome for noninferiority, then the primary outcome for superiority, then major bleeding, and finally death from any cause), to control the type I error.

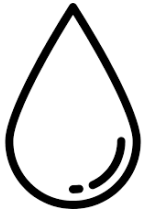
Edoxaban AF trial (Engage)

Randomised, double-blind, double dummy



Non-inferior to warfarin for stroke or systemic embolism

21,105 patients



Superior to warfarin for major bleeding

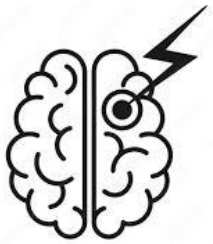
30mg or 60mg once daily

Edoxaban AF trial (Engage)

	ENGAGE AF-TIMI 48	
	Warfarin	**Edoxaban 60 mg**
First Stroke or SEE (Primary Efficacy Outcome, Testing for Superiority) ITT analysis, overall study period, set	**N = 7,036**	**N = 7,035**
No. of events (event rate per year)	337 (1.80)	296 (1.57)
HR edoxaban versus warfarin (99.0% CI)	0.87 (0.73 to 1.04)	
P value	0.0807	
Major Bleeding (Primary Safety Outcome) safety analysis set	**N = 7,012**	**N = 7,012**
No. of events (event rate per year)	524 (3.43)	418 (2.75)
HR (95% CI)	0.80 (0.71 to 0.91)	
P value	< **0.001***	

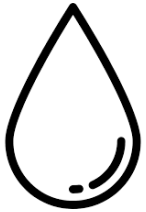
Rivaroxaban AF trial (Rocket)

Randomised, double-blind, double dummy



Non-inferior to warfarin for stroke or systemic embolism

14,264 patients



Non-inferior to warfarin for major bleeding

20mg once daily (dose reduced 15mg once daily)

Rivaroxaban AF trial (Rocket)

Table 2. Primary End Point of Stroke or Systemic Embolism.*

Study Population	Rivaroxaban			Warfarin			Hazard Ratio (95% CI)†	P Value	
	No. of Patients	No. of Events	Event Rate *no./100 patient-yr*	No. of Patients	No. of Events	Event Rate *no./100 patient-yr*		Noninferiority	Superiority
Per-protocol, as-treated population‡	6958	188	1.7	7004	241	2.2	0.79 (0.66–0.96)	<0.001	
Safety, as-treated population	7061	189	1.7	7082	243	2.2	0.79 (0.65–0.95)		0.02
Intention-to-treat population§	7081	269	2.1	7090	306	2.4	0.88 (0.75–1.03)	<0.001	0.12
During treatment		188	1.7		240	2.2	0.79 (0.66–0.96)		0.02
After discontinuation		81	4.7		66	4.3	1.10 (0.79–1.52)		0.58

* The median follow-up period was 590 days for the per-protocol, as-treated population during treatment; 590 days for the safety, as-treated population during treatment; and 707 days for the intention-to-treat population.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group.
‡ The primary analysis was performed in the as-treated, per-protocol population during treatment.
§ Follow-up in the intention-to-treat population continued until notification of study termination.

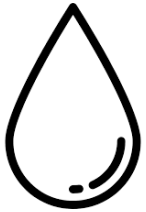
Dabigatran AF trial (RE-LY)

Randomised, double-blind

18,113 patients

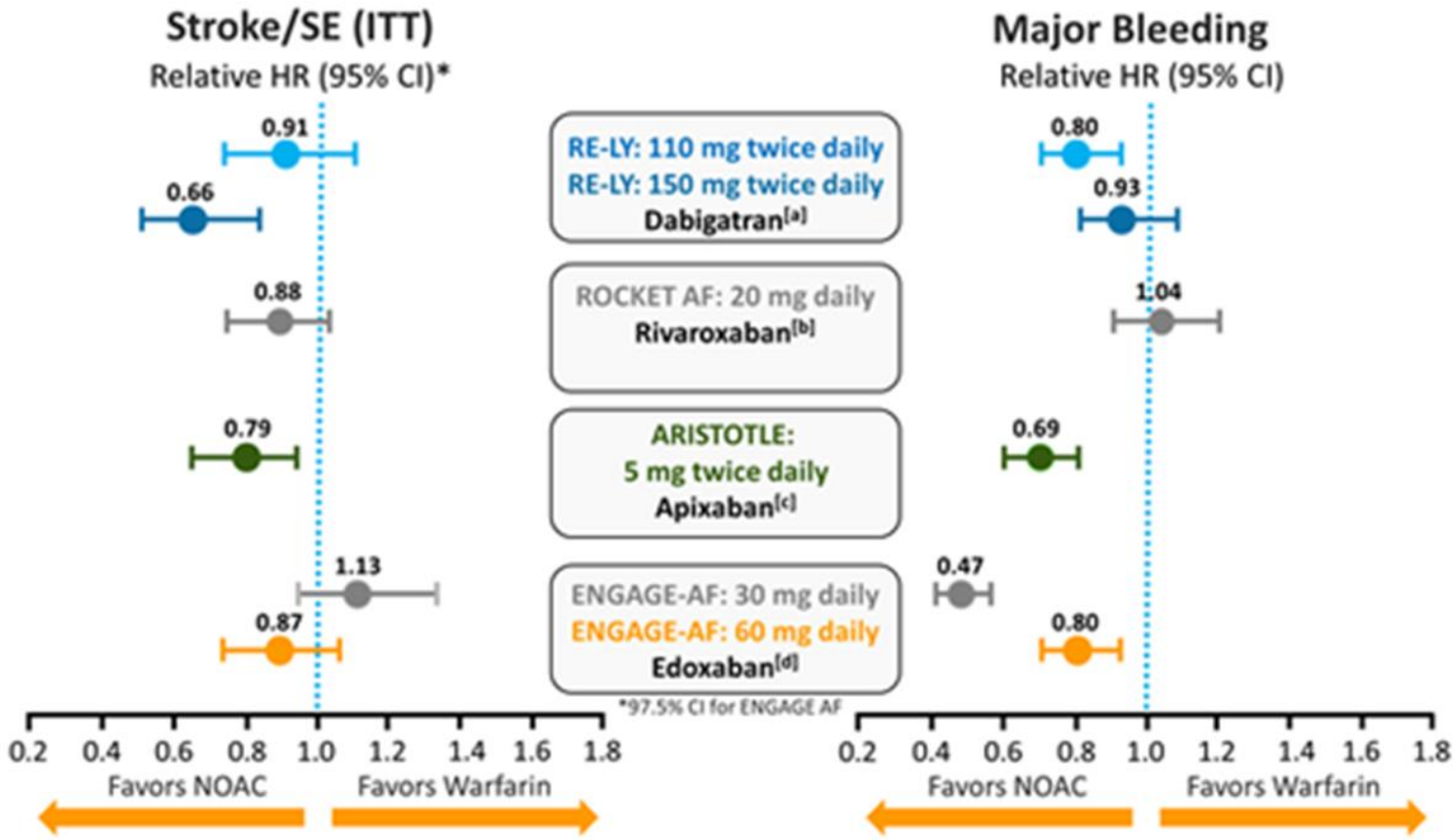
150mg twice daily (dose reduced 110mg twice daily)

Superior to warfarin for stroke or systemic embolism (150mg)



Superior to warfarin for major bleeding (110mg)

Summary of the trials

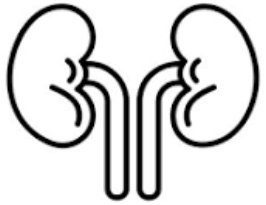


a. Connolly SJ, et al. *N Engl J Med.* 2009;361:1139-1151; b. Patel MR, et al. *N Engl J Med.* 2011;365:883-891;
c. Granger CB, et al. *N Engl J Med.* 2011;365:981-992; d. Giugliano RP, et al. *N Engl J Med.* 2013;369:2093-2104.

Comparisons to warfarin

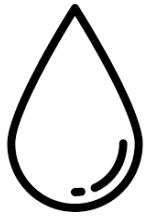
	Apixaban	**Edoxaban**	**Rivaroxaban**	**Dabigatran**
GI bleeding	Less	More	More	More
Food requirement	None	None	Yes	None
Side effects	-	-	Dizziness and headaches	Dyspepsia
Renal Clearance	25%	50%	33%	80%
Compliance	Twice daily	Once daily	Once daily	Once daily
Dosette Box	Yes	Yes	Yes	No

Cautions



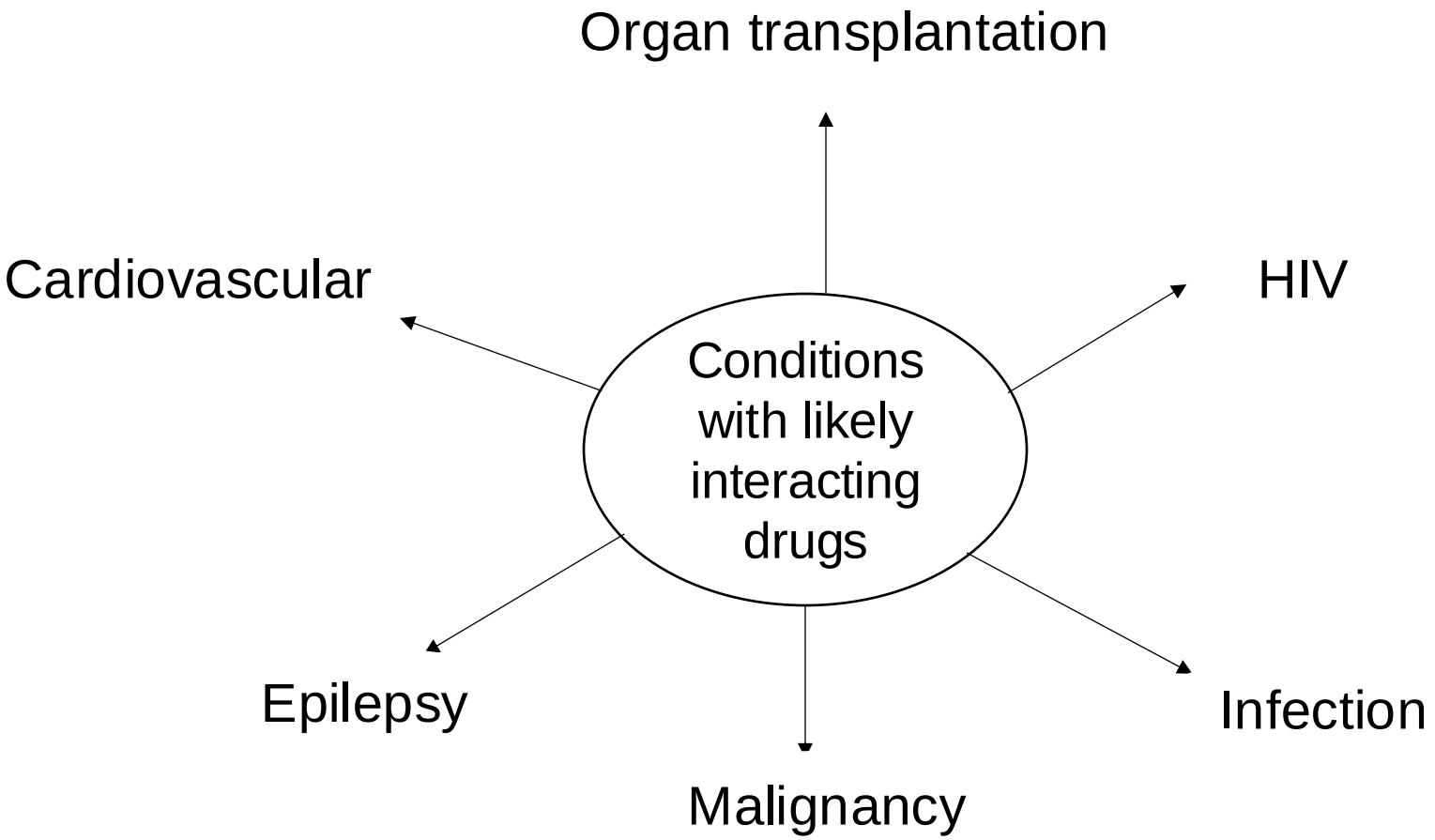
Avoid edoxaban in CrCl >95ml/min

Use rivaroxaban or apixaban in patients >120kg



Preference for apixaban in patients with a high bleeding risk

Pharmacokinetic Interactions



Pharmacodynamic Interactions

Medication	Action
NSAIDs	Avoid
Antiplatelets	Check indication Stop if no PVD or MI/cardiac surgery in last year Max duration of DAPT usually 3 months Not for ticagrelor or prasugrel
SSRIs	Consider PPI

Switching from warfarin to DOAC

INR	
≤ 2	Start DOAC immediately
2 – 2.5	Start DOAC immediately or next day
2.5 - 3	Postpone DOAC, Recheck INR in 1 - 3 days
≥ 3	Postpone DOAC, Recheck INR in 3 – 5 days

Monitoring is required at regular intervals

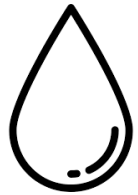
Every 3, 6 or 12 months

Indication

Medication history

Medications

Blood tests



Bleeding risk

DOAC counselling is a priority

Patient Information Checklist
Reason for DOAC
How to take
Duration of treatment
Bleeding and when to seek medical attention
Avoid aspirin or NSAIDs
Inform healthcare professionals including dentist about DOAC
Missed doses
Provide alert card and patient information leaflet
Monitoring and follow up

Case study 1 – Mrs W (New AF)

Age: 81 years
Weight: 88kg

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PMH
HTN (current BP 120/90)
T2DM
Hiatus hernia
Mild heart failure (LVEF 49%)

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Medication
Perindopril 5mg once daily
Bisoprolol 5mg once daily
Omeprazole 20mg once daily
Aspirin 75mg once daily

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Biochemistry
Cr 128 micromol/L
CrCl 42 ml/min
eGFR 35
AST 19 IU/L
Hb 130 g/L
Plts 180 x109/L

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eGFR 35
AST 19 IU/L
Hb 130 g/L
Plts 180 x109/L

Other information
Uses dosette box
No alcohol

Case study 1 – Mrs W (New AF)

Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (CAD, CArD, PAD)	1
Age 65-74	1
Sex category (female)	1

Score	Annual stroke rate, %
0	0
1	1.3
2	2.2
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6	9.8
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Reduced haemoglobin Males: Hb<130 g/L, HCT< 0.4 L/L Females: Hb<120 g/L, HCT< 0.36L/L OR History of anaemia	2
Bleeding history GI bleeding Intracranial bleeding Haemorrhagic stroke	2
Insufficient renal function GFR<60 mL/min/1.73m^2	1
Treatment with antiplatelet	1

ORBIT score	Risk level	Number of major bleeds per 1000 AF patients treated with anticoagulant, per year
0-2	Low	24
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Other information
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Case study 1 – Mrs W (New AF)

Apixaban 5mg twice daily

and

Stop aspirin

Case study 2 – Mr F (New AF)

Age: 79 years
Weight: 127kg

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PMH
IHD
Hypercholesterolemia
T2DM
Obesity

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Obesity

Medication
Atorvastatin 80mg once daily
Metformin 1g twice daily
Bisoprolol 5mg once daily
Ramipril 5mg once daily

Case study 2 – Mr F (New AF)

Age: 79 years
Weight: 127kg

PMH
IHD
Hypercholesterolemia
T2DM
Obesity

Medication
Atorvastatin 80mg once daily
Metformin 1g twice daily
Bisoprolol 5mg once daily
Ramipril 5mg once daily

Biochemistry
Cr 98 umol//L
CrCl 76 ml/min (adjusted body weight)
eGFR >90
AST 24 IU/L
Hb 128 g/L
Plts 221 x109/L

Case study 2 – Mr F (New AF)

Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/TE	2
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Age 65-74	1
Sex category (female)	1

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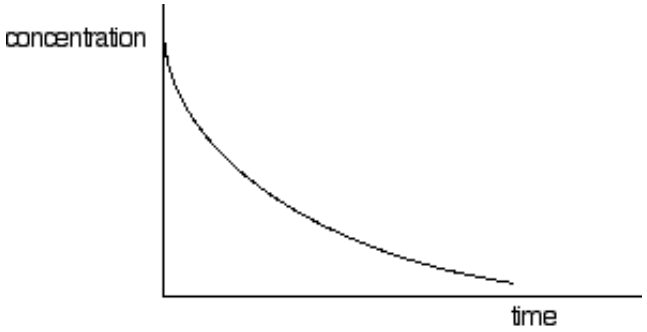
ISTH updated guidance in 2021 for high body weight in VTE

Suggest standard doses of rivaroxaban or apixaban



No need for peak or trough drug-specific DOAC levels

We have carried out work in high body weight patients

J Thromb Haemost. 2020 Sep;18(9):2296-2307. doi: 10.1111/jth.14948.

Fixed dose rivaroxaban can be used in extremes of bodyweight: A population pharmacokinetic analysis

Victoria Speed [1 2], Bruce Green [3], Lara N Roberts [1], Sarah Woolcombe [4], John Bartoli-Abdou [1], Sarah Barsam [1], Rosalind Byrne [1], Emma Gee [1], Julia Czuprynska [1], Alison Brown [1], Sinead Duffy [1], Bipin Vadher [1], Rachna Patel [1], Valerie Scott [1], Anna Gazes [1], Raj K Patel [1], Roopen Arya [1], Jignesh P Patel [1 2]

Affiliations + expand

PMID: 32511863 DOI: 10.1111/jth.14948

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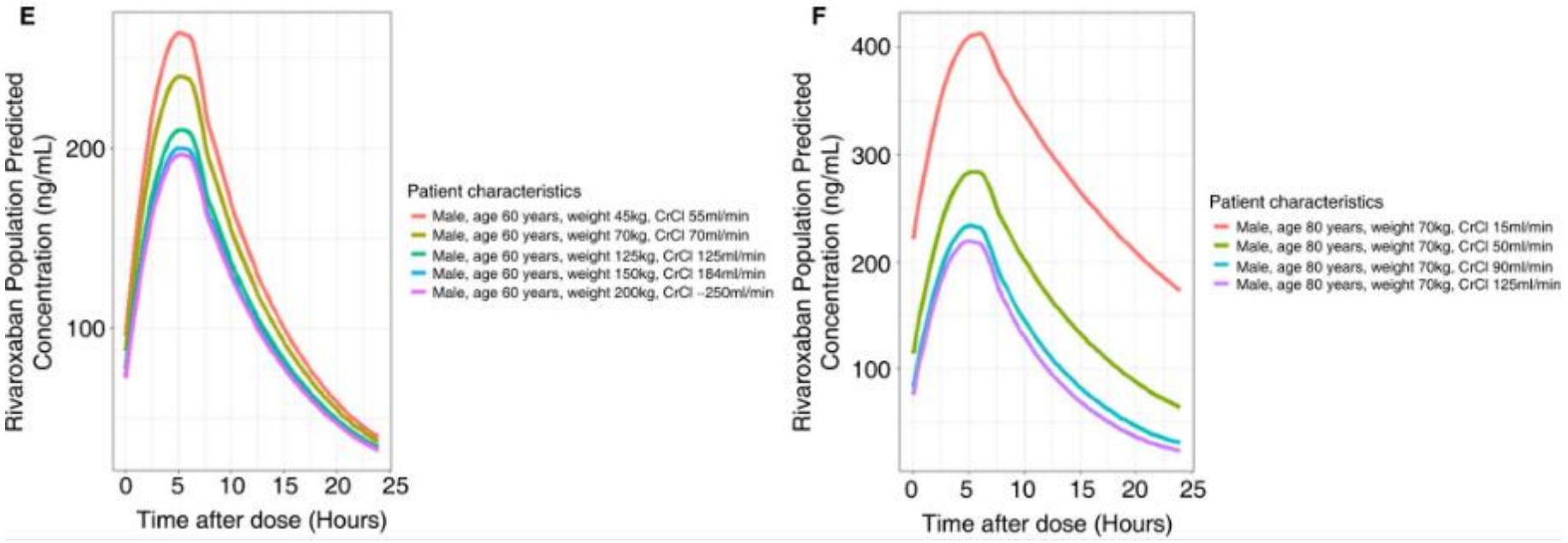

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Age: 79 years
Weight: 127kg

PMH
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Hypercholesterolemia
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Obesity

Medication
Atorvastatin 80mg once daily
Metformin 1g twice daily
Bisoprolol 5mg once daily
Ramipril 5mg once daily

Biochemistry
Cr 98 umol//L
CrCl 76 ml/min (adjusted body weight)
eGFR >90
AST 24 IU/L
Hb 128 g/L
Plts 221 x109/L

Case study 2 – Mr F (New AF)

Rivaroxaban 20mg once daily

Or

Apixaban 5mg twice daily

Useful references

DOAC position statement August 2024.pdf

Liverpool HIV Interactions (hiv-druginteractions.org)

Cancer Drug Interactions from Radboud UMC and University of Liverpool (cancer-druginteractions.org

Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges | Journal of the American Heart Association (ahajournals.org)

Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation (wiley.com)

Any questions?