

Safe use of DOACs: Perils, pitfalls and solutions

Roopen Arya

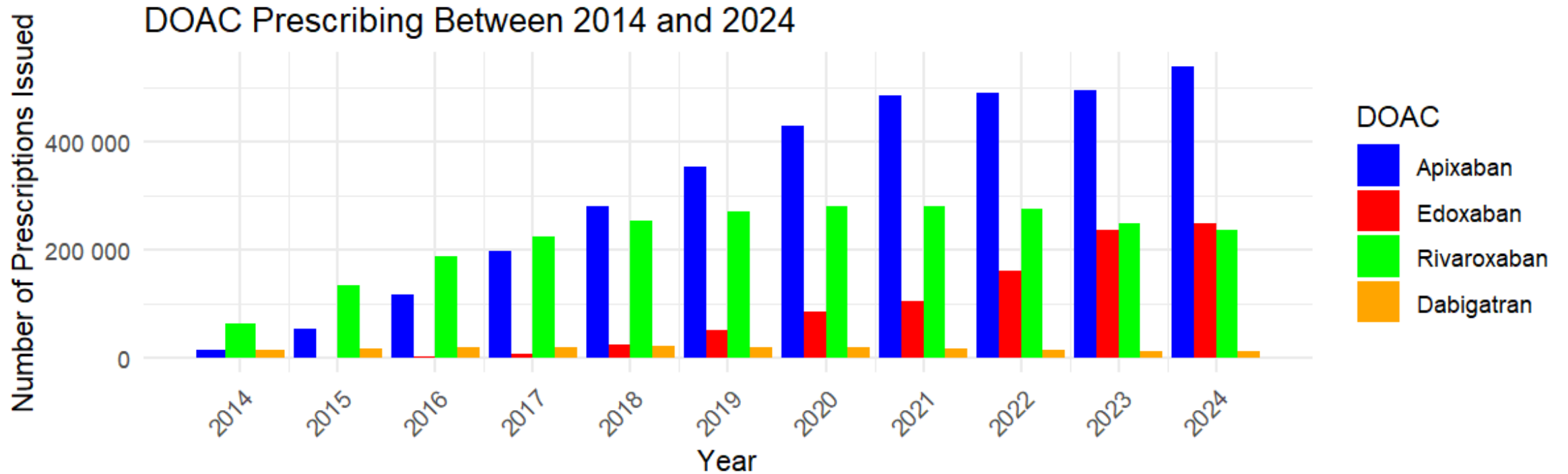
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Disclosures for Roopen Arya









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DOAC Prescribing



Source: English Prescribing Dataset hosted by the NHSBSA (Primary Care Only)

Indications for DOACs

	 AF*	 VTE	 Mechanical Heart Valves	 Rheumatic AF	 Thrombotic APS	 ESUS	 TAVR‡	 LVAD
	6	† 9,14	42		39	49,50	46	
Apixaban	Apixaban vs Warfarin	Apixaban vs Warfarin	Apixaban vs Warfarin	?	Apixaban vs Warfarin	Apixaban vs Aspirin	Apixaban vs Vitamin K Antagonist or antiplatelet	?
Rivaroxaban	Rivaroxaban vs Warfarin	† Rivaroxaban vs Warfarin, Aspirin	?	Rivaroxaban vs Vitamin K Antagonist	Rivaroxaban vs Warfarin	Rivaroxaban vs Aspirin	Rivaroxaban vs Aspirin, Clopidogrel	?
Edoxaban	Edoxaban vs Warfarin	Edoxaban vs Warfarin	?	?	?	?	‡ Edoxaban vs Aspirin and Clopidogrel, Vitamin K Antagonist	?
Dabigatran	Dabigatran vs Warfarin	† Dabigatran vs Warfarin	Dabigatran vs Warfarin	?	?	Dabigatran vs Aspirin	?	Dabigatran vs Phenprocoumon and Aspirin

National data from NRLS on harm associated with DOACs (2017-2019, England & Wales)

- 15,730 incidents, 25 deaths + 270 moderate/55 severe harm
- Active failures accounted for 88%
 - Duplication of anticoagulant therapies
 - Patients being discharged without DOACs
 - Non-consideration of renal function
 - DOACs not recommenced post-surgery

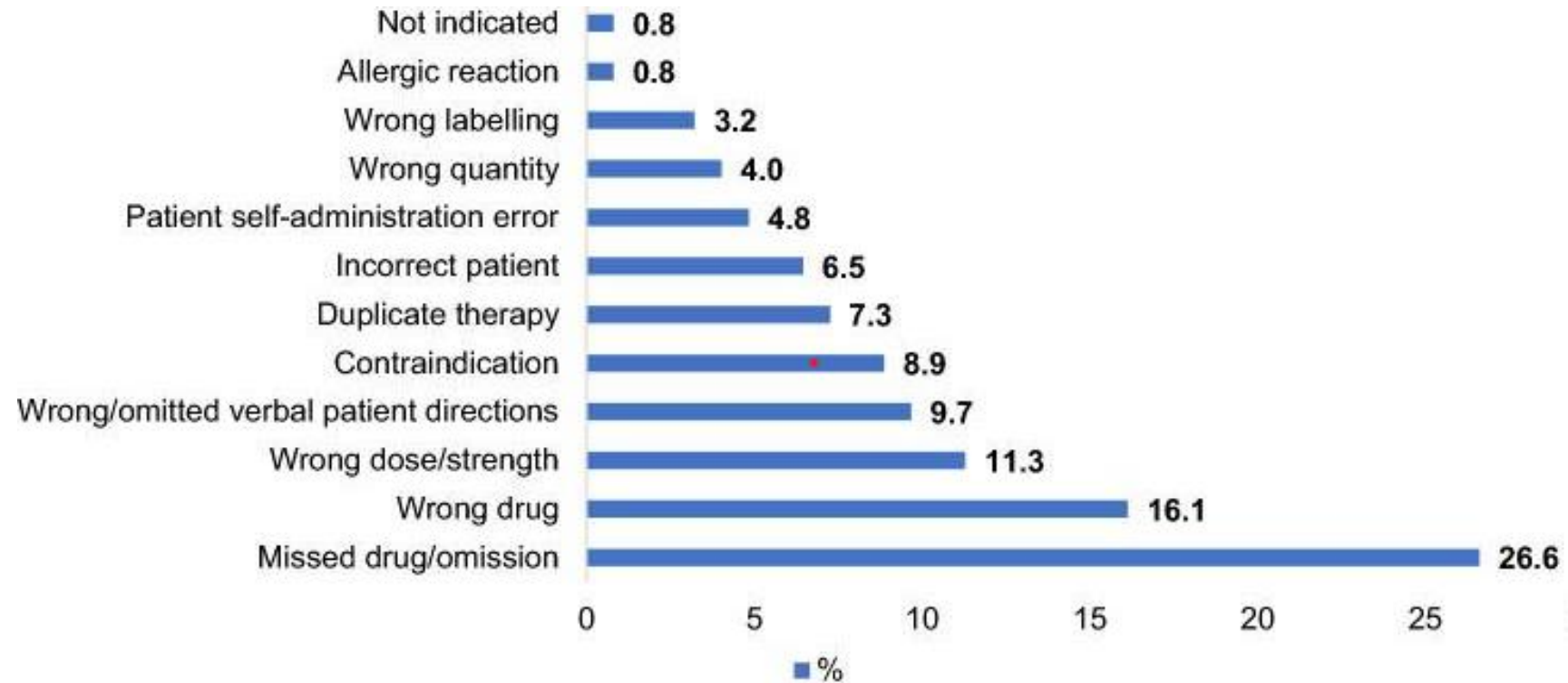
NRLS data on DOAC-related harm

- Apixaban > Rivaroxaban > Edoxaban > Dabigatran
- Indications: Atrial fibrillation > DVT > PE
- Setting: cardiology ward > acute medical ward > community
- Stage: Prescribing > Administration > Dispensing > Follow up

Conclusion:

DOAC-related incidents are common and cause significant harm

DOAC-related medication incidents (local data)



Conclusion: Prescribers' active failure contributed to majority of the incidents.

Recommend: Reinforce guideline adherence, provide prescriber education, harness pharmacists' roles, and mandate renal function information in prescriptions.

Inpatient Prescriptions Of DOACS Are Often Inconsistent With Label or Guideline Recommendations

Prevalence and Rationales for “Inappropriate” Prescribing

Prevalence



Underdosing: 4.7% - 26.1%

Overdosing: 1.4% - 8.7%

Contraindicated: 0% - 18.9%

Rationales and Predictors



Incorrectly applying dose reduction criteria

- Blindly continuing home dose / dosing error
- Decreased body weight / decreased renal function / advanced age
- Prescription of dabigatran or apixaban
- Treatment indication atrial fibrillation



(Perceived) increased bleeding risk

- History of bleeding / active bleeding
- Drug-drug interactions
- Frailty / dementia / fall risk / palliative setting
- Fluctuating renal function
- Anemia (of unknown cause)
- Perioperative care

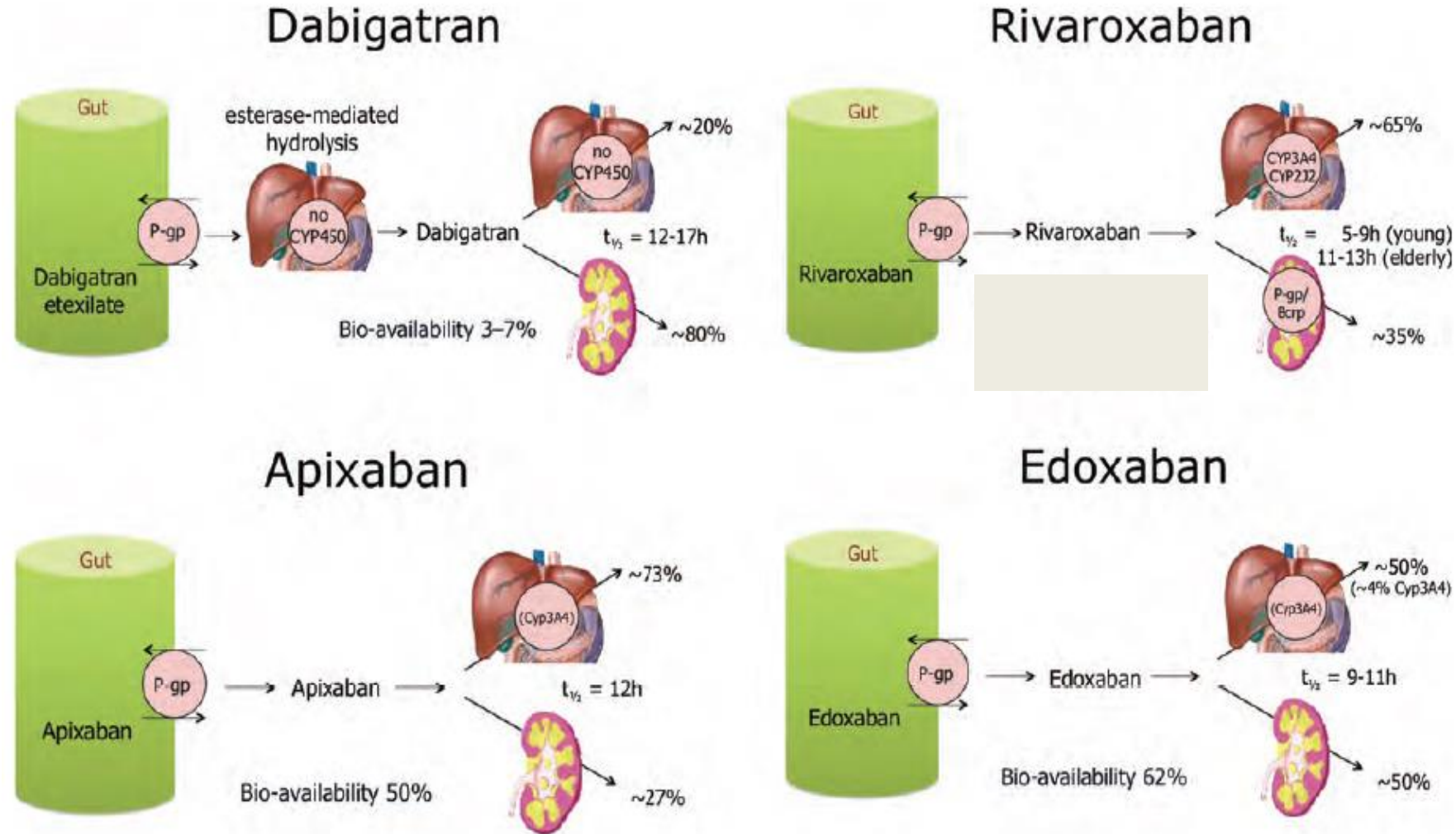
Challenges for the safe use of DOACs

- Different dosing regimens for different DOACs
- Dosing at extremes of body weight, renal and liver function
- Drug-drug interactions
- Reversal in the event of bleeding

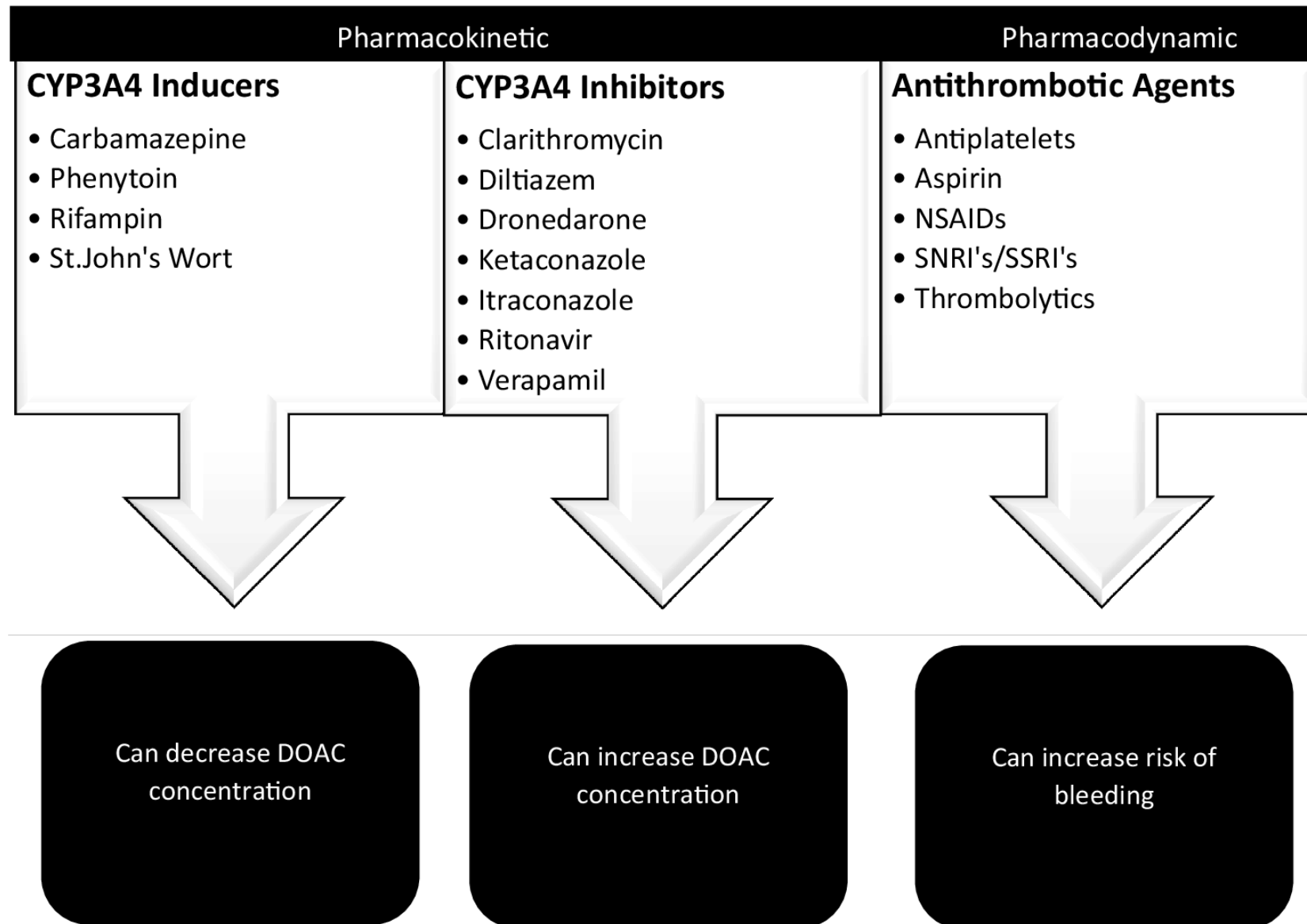
Challenges for the safe use of DOACs

- Monitoring
- Failures at the interface between secondary care and primary care
- Temporary discontinuation of DOACs for procedures and surgery
- Dwindling anticoagulation clinic support

DOAC metabolism and excretion



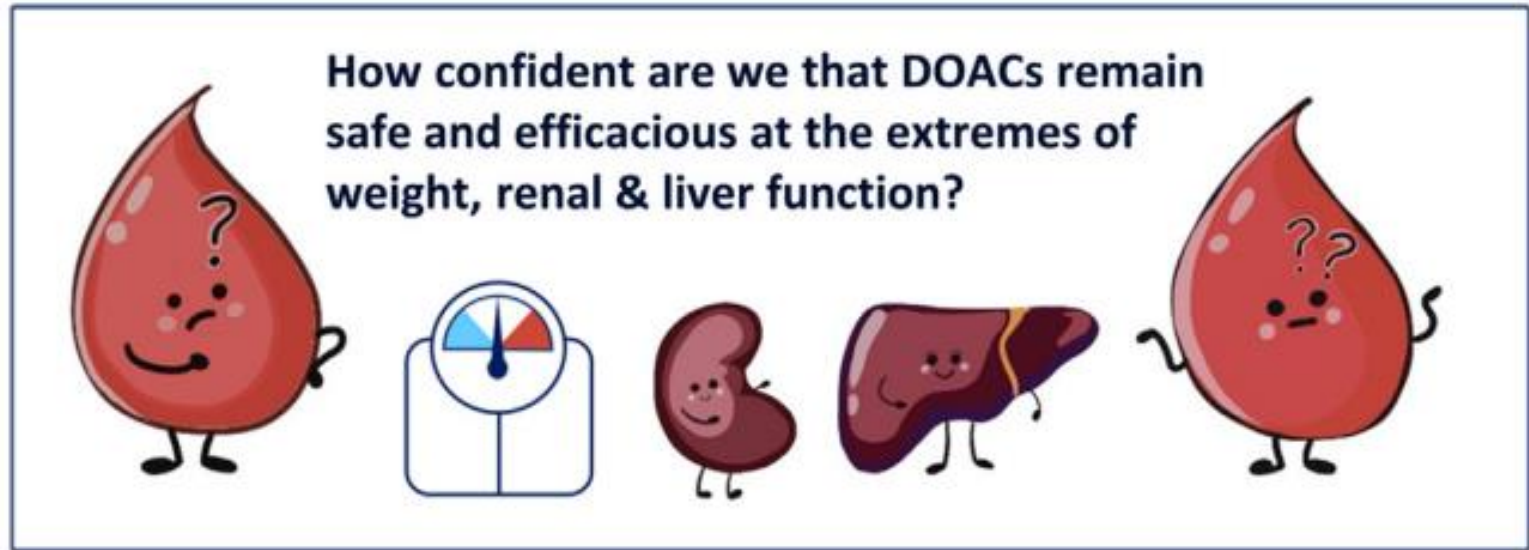
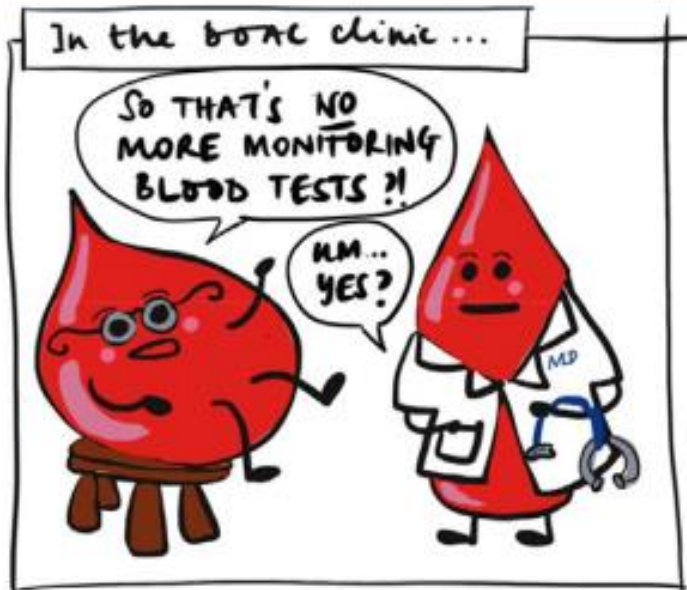
Drug- Drug Interactions of Direct Oral Anticoagulants



Everyone can have a DOAC now..... right?



Does the fixed-dose anticoagulant approach apply at extremes of body weight, renal and liver function?



DOACs: Clinical Trials vs Real-World

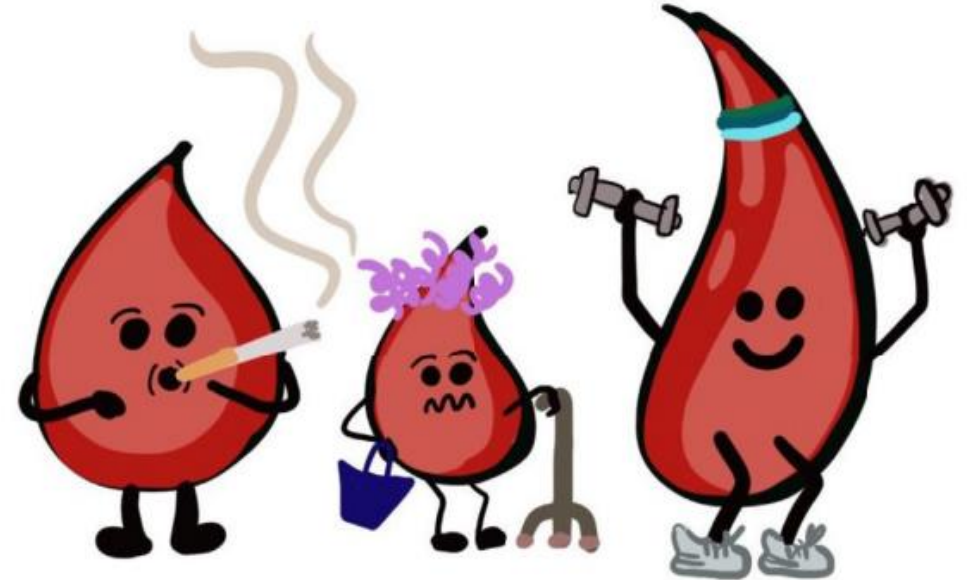
Step 1. Review clinical trial outcome data

In the licensing studies - how many patients received the DOAC and how did they get on?



Step 2. Review real world outcome data

In clinical practice - how many patients received the DOAC and how did they get on?





High
bodyweight



CrCL 15-30ml/min
And dialysis



Low
bodyweight



Hyperfiltration



Moderate
renal
impairment



Hepatic
impairment

Renal impairment

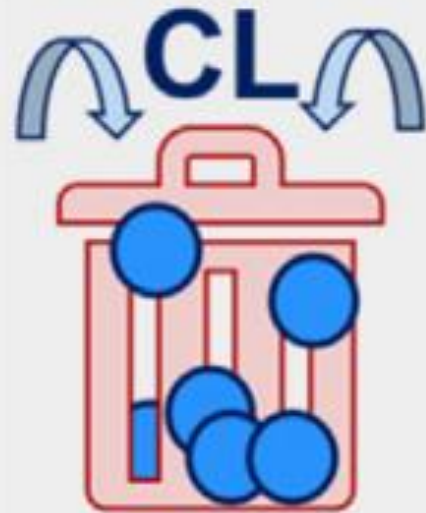


Thrombosis



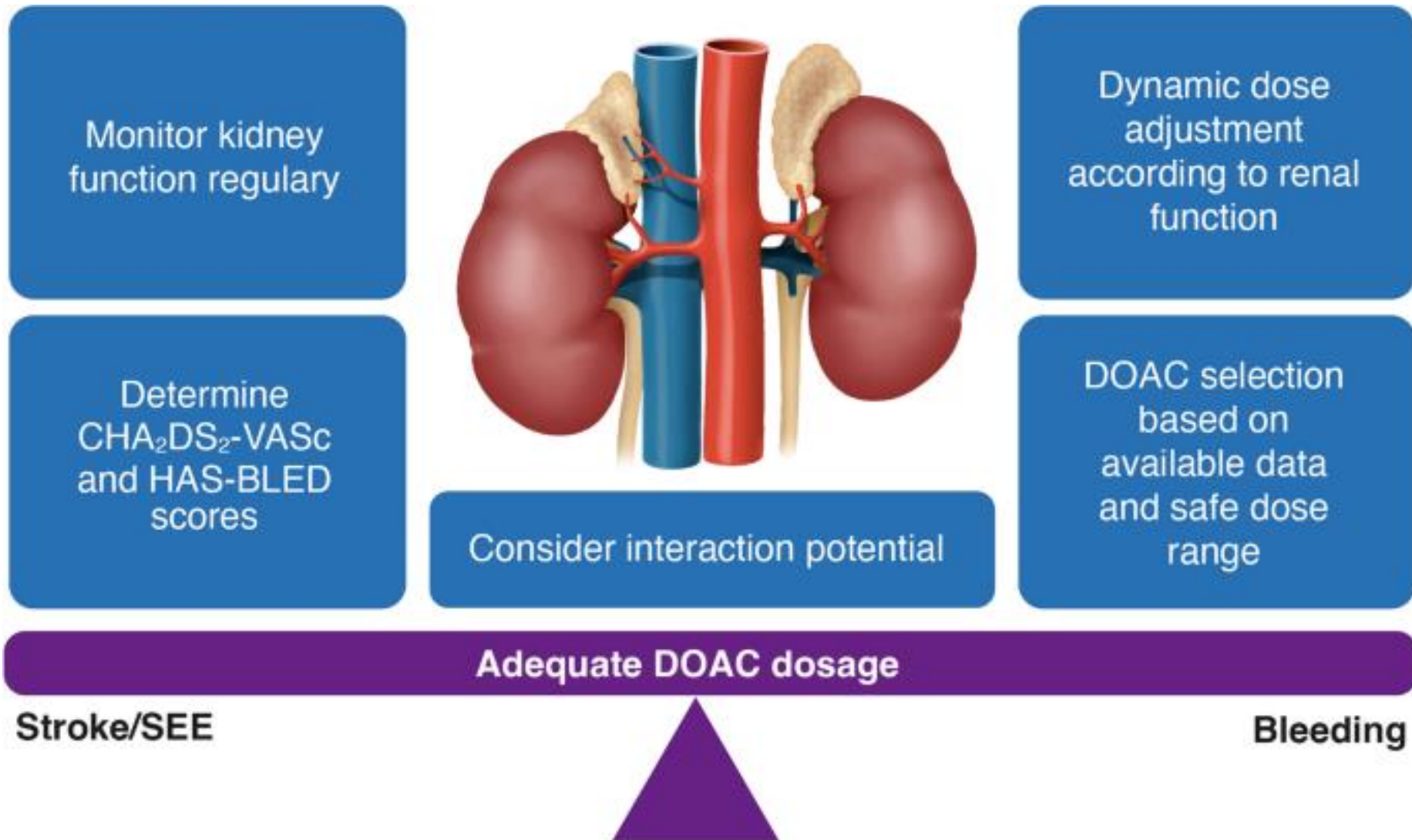
Bleeding



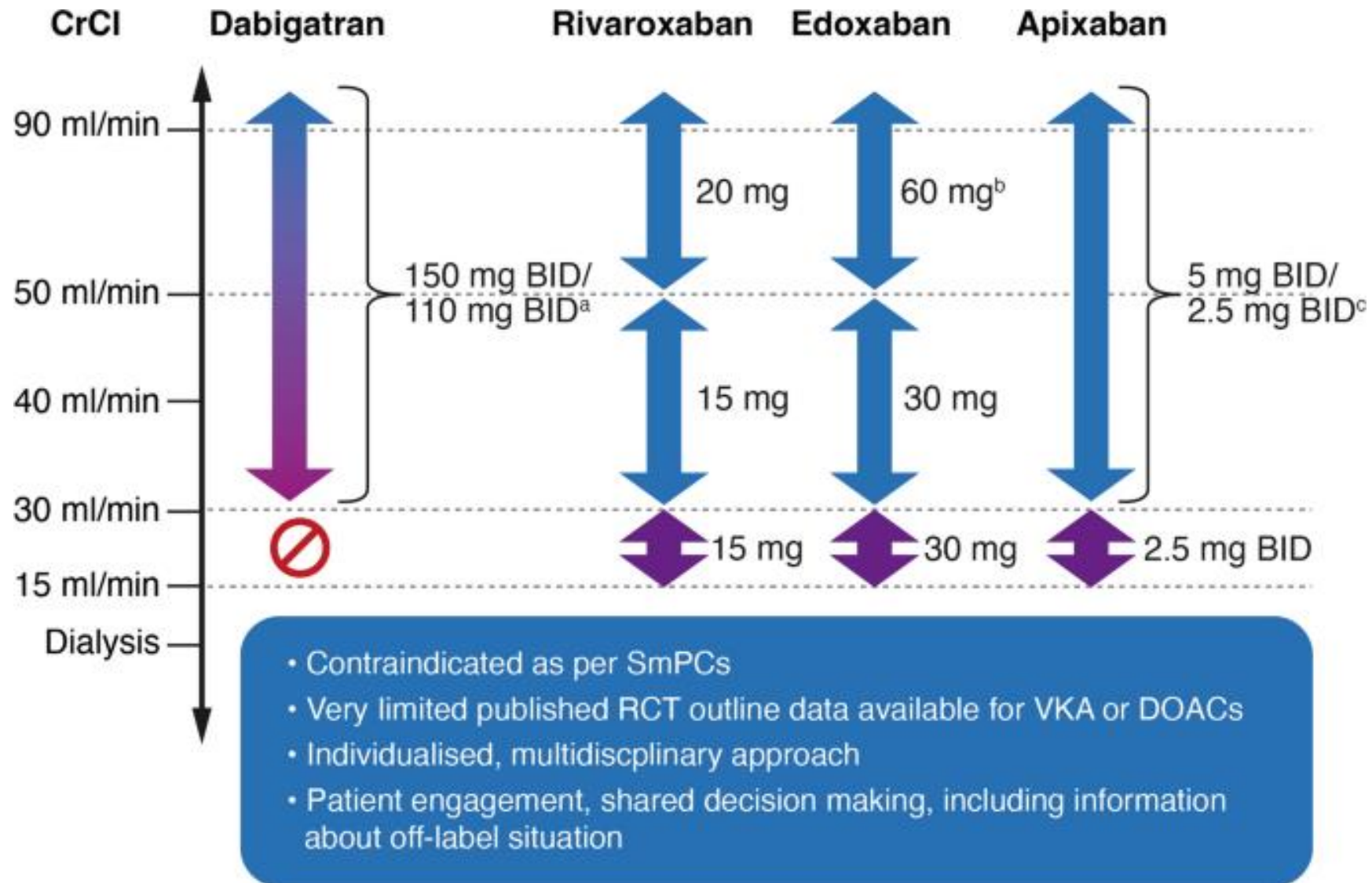


- \downarrow renal clearance will lead to \uparrow elimination $t_{1/2}$
- This will result in increased \uparrow peak and \uparrow trough concentrations, particularly with repeated doses, and \uparrow overall DOAC exposure (AUC)

DOACs and renal function



Dosing DOACs in patients with renal impairment



How to measure renal function

CrCl calculated by Cockcroft-Gault formula²³

$$\text{CrCl} = (140 - \text{age}) \times \text{body weight} / \text{SCr} \times 72$$

Result for women $\times 0.85$

GFR calculated by MDRD estimates amount of blood filtered per minute²⁴

$$\text{GFR} = 175 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \quad (\text{no weight required})$$

Result for women $\times 0.742$; for black skin $\times 1.212$

if eGFR by MDRD is >60 ml/min, the result is too imprecise, since the formula was evaluated in patients with advanced CKD

The CKD-EPI formula estimates the GFR in the borderline area of incipient renal insufficiency more accurately than the MDRD formulas²⁵

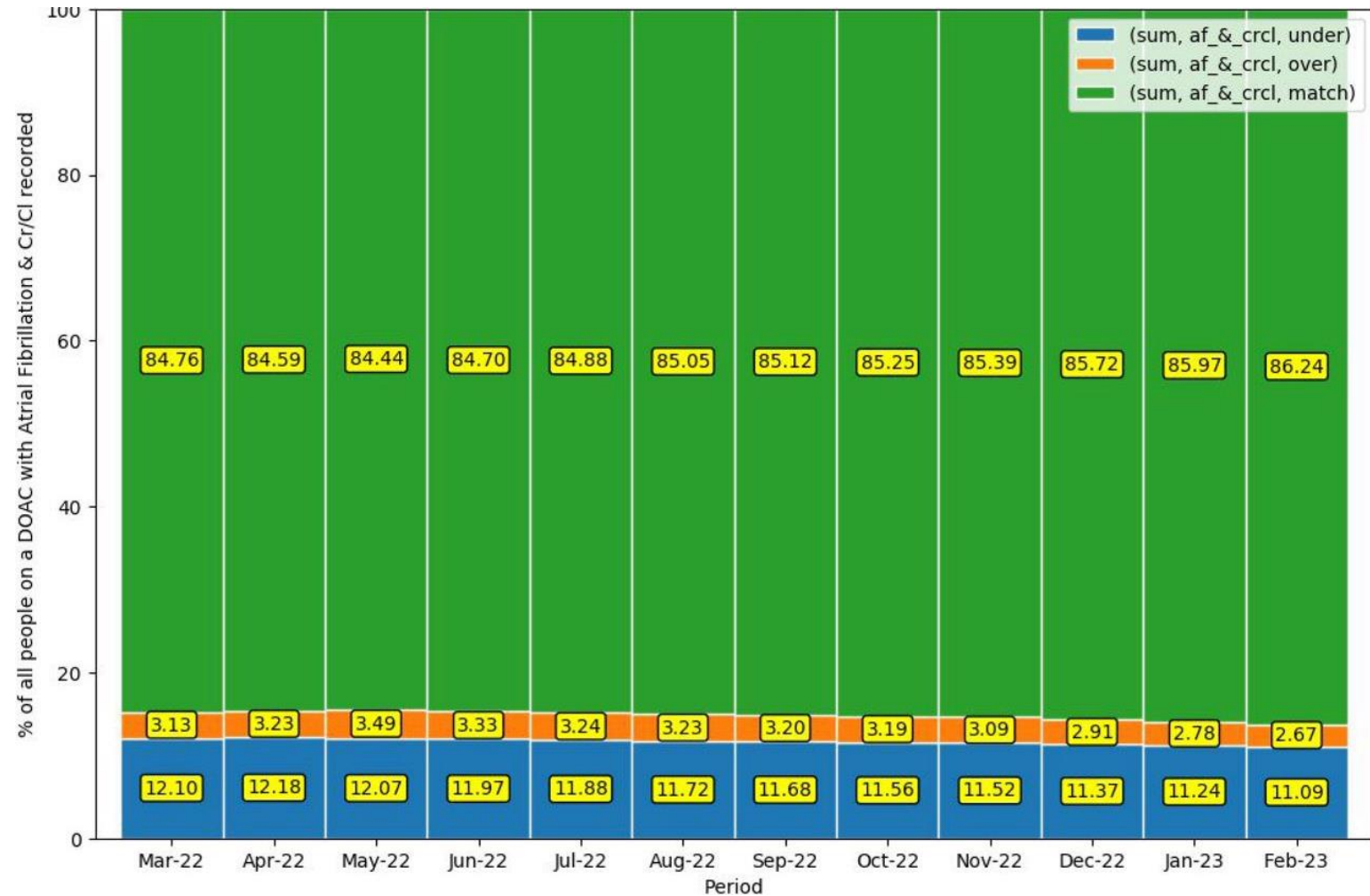
$$\text{GFR} = 141 \times \min(\text{SKr}/\kappa, 1)^{\alpha} \times \max(\text{SKr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \quad \text{normalised to BSA } 1.73 \text{ m}^2$$

Result for women $\times 0.742$; for black skin $\times 1.212$

eGFR according to CKD-EPI is of limited value in children/adolescents, and in very old and/or overweight/underweight people

Safety of DOAC prescribing: OpenSAFELY-TPP analysis

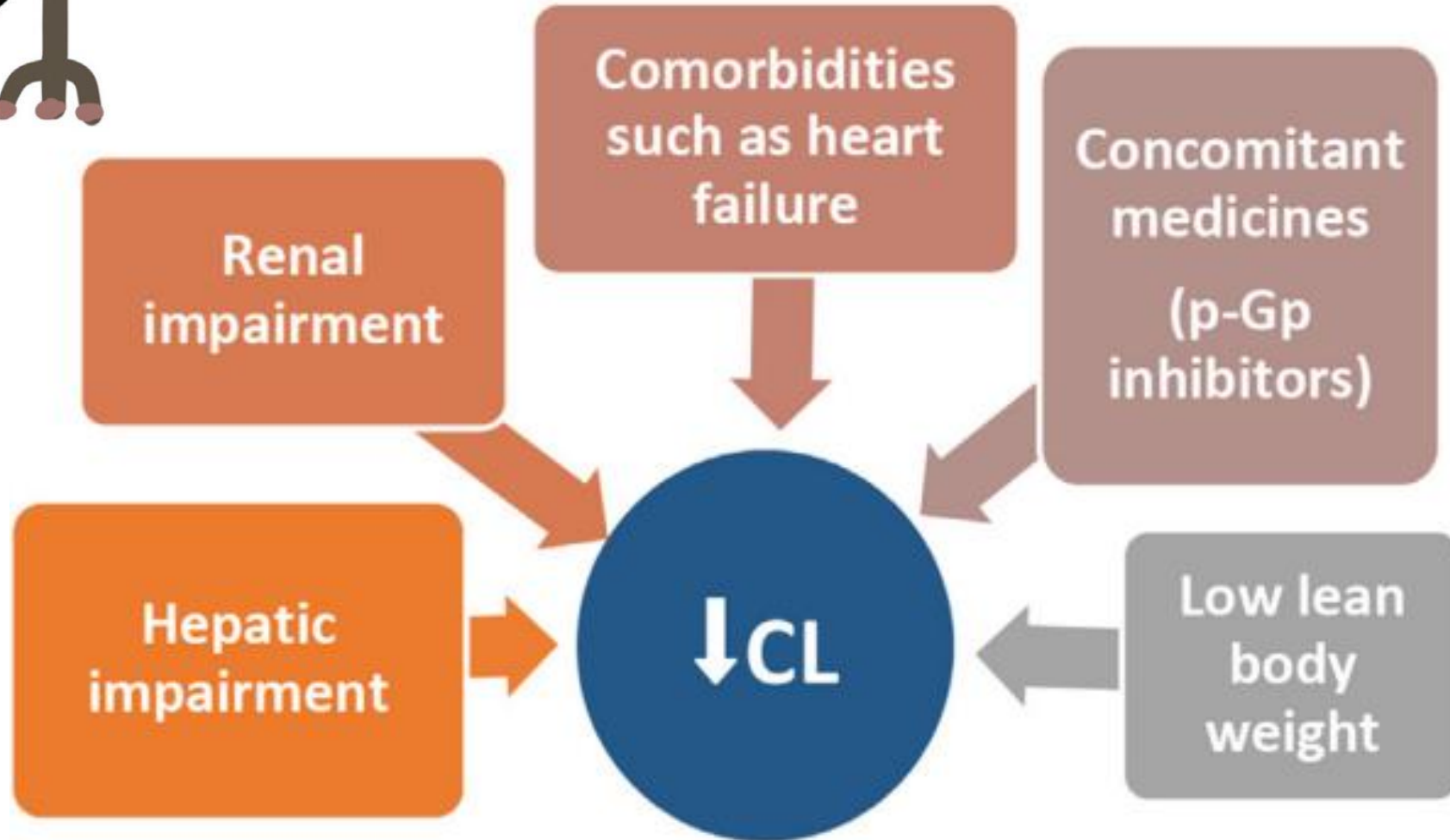
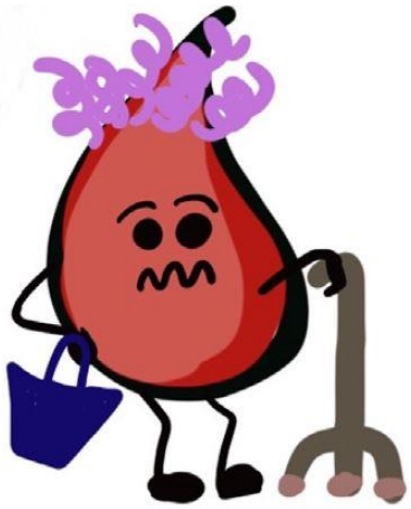
% people prescribed a DOAC with AF and with CrCl recorded where recommended dose does not match the prescribed dose



Conclusion: CrCl is not recorded for many patients on DOACs.

Frailty

40% AF patients estimated to be frail



Low bodyweight



Thrombosis



Bleeding



There is concern that low bodyweight leads to over exposure due to changes in volume of distribution and clearance.

Low body weight (Speed 2024)



Four hospital trusts in England

Any indication

Patients <50kg with a DOAC plasma concentration

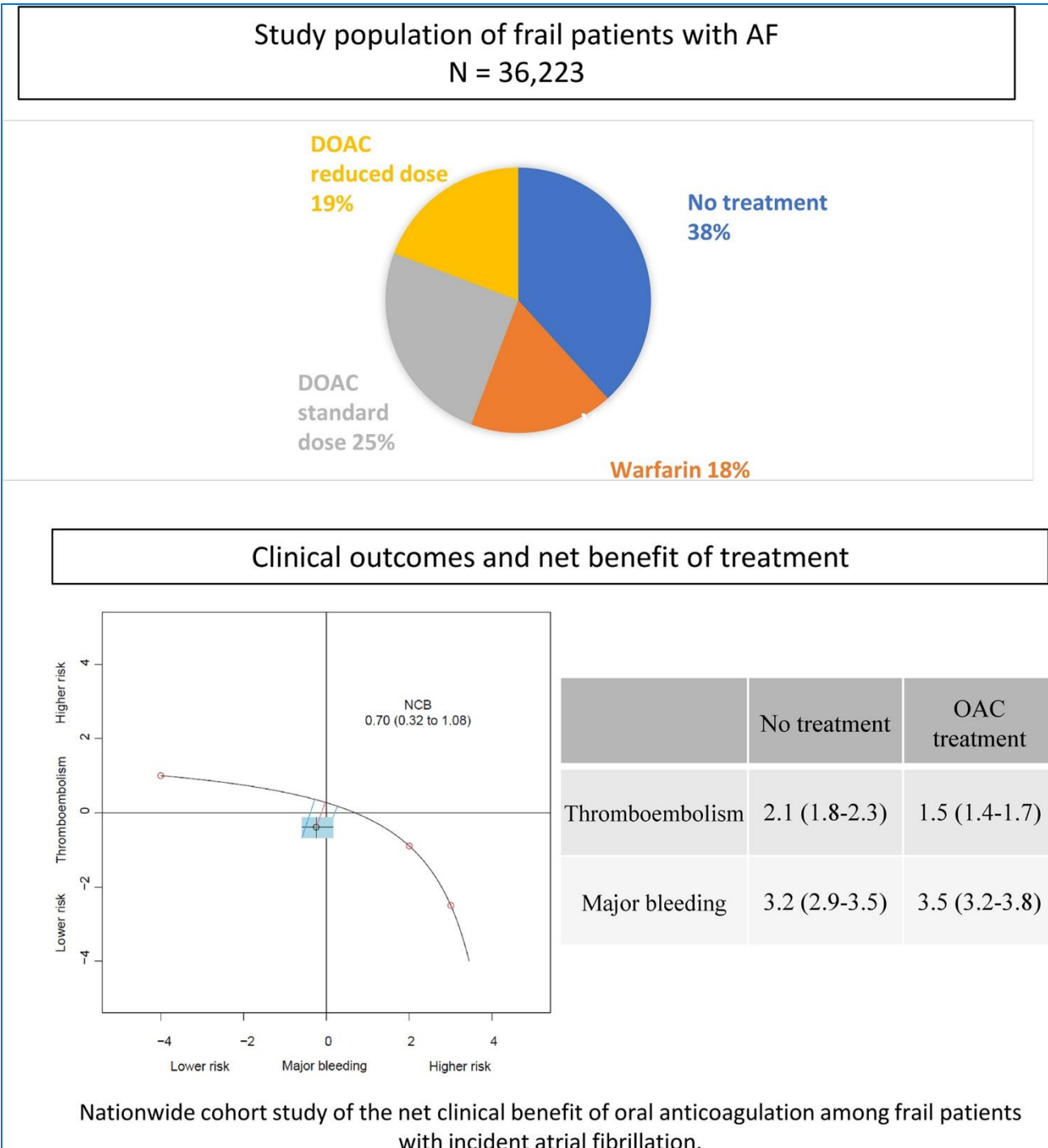
131 patients <50kg, 2/3 >80 years, 91% female, 1/3 CrCL <30ml/min

3.3% major bleeds

5.3% CRNMB

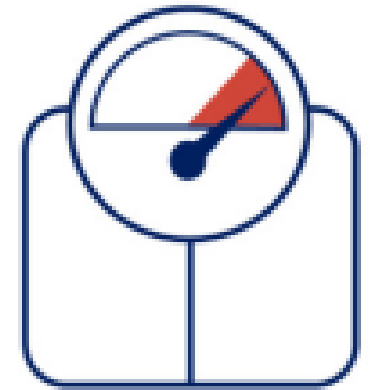
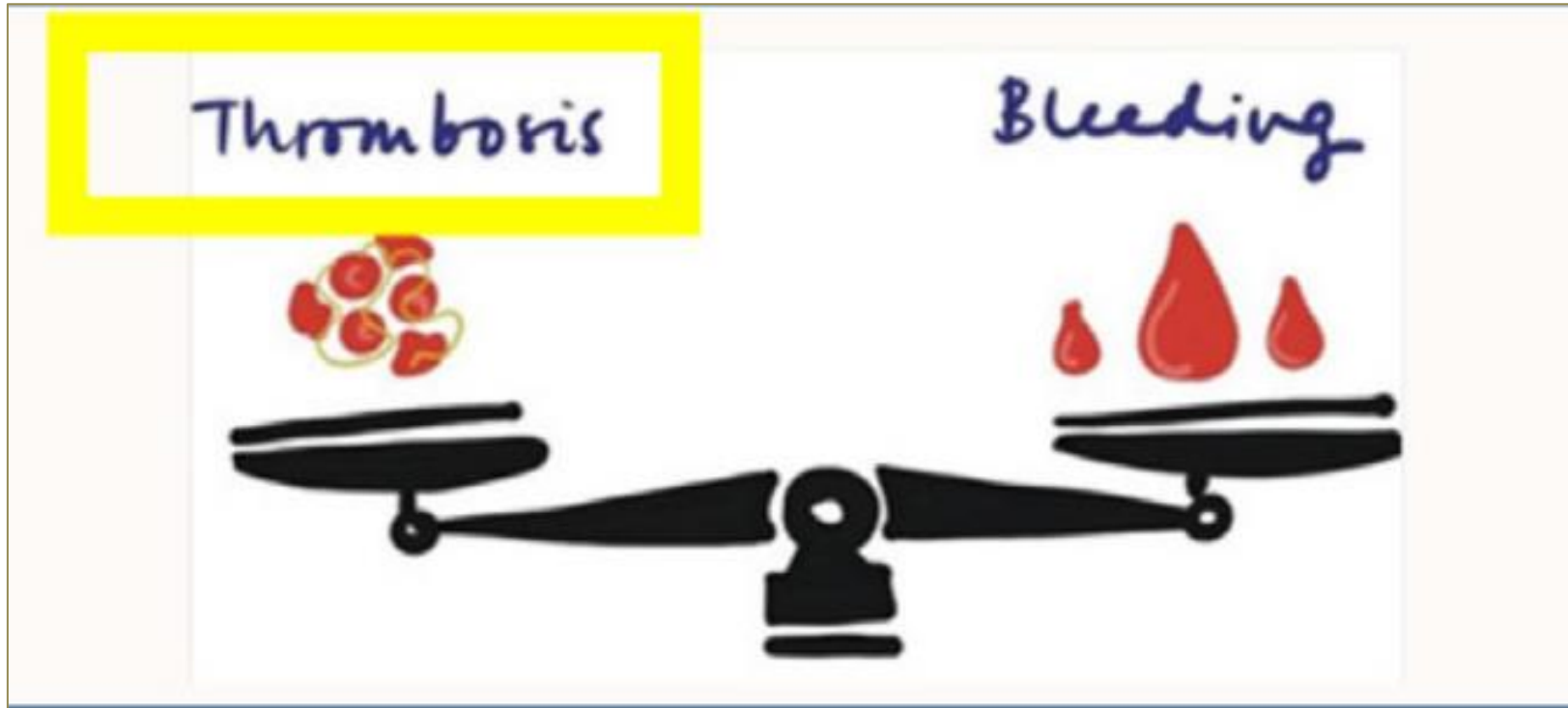
Speed, V et al 2024. Factor Xa Inhibitor Plasma Concentrations and Clinical Outcomes in Patients Weighing ≤ 50 kg—Experience from Four UK Centers. Thrombosis and Haemostasis, 124(02), 177-180.

Net Clinical Benefit of Oral Anticoagulation Among Frail Patients With Atrial Fibrillation: Nationwide Cohort Study



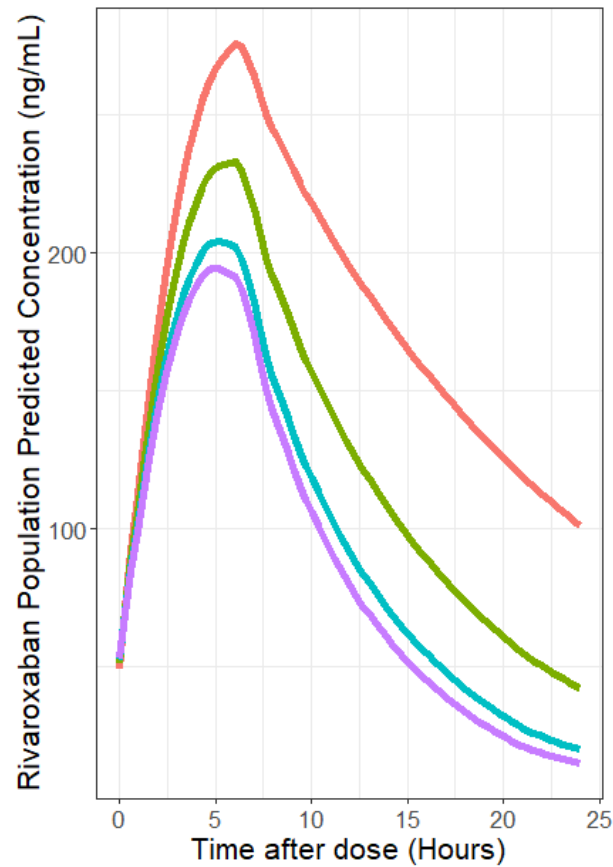
Søgaard et al, Stroke 2024

High bodyweight patients in the clinic



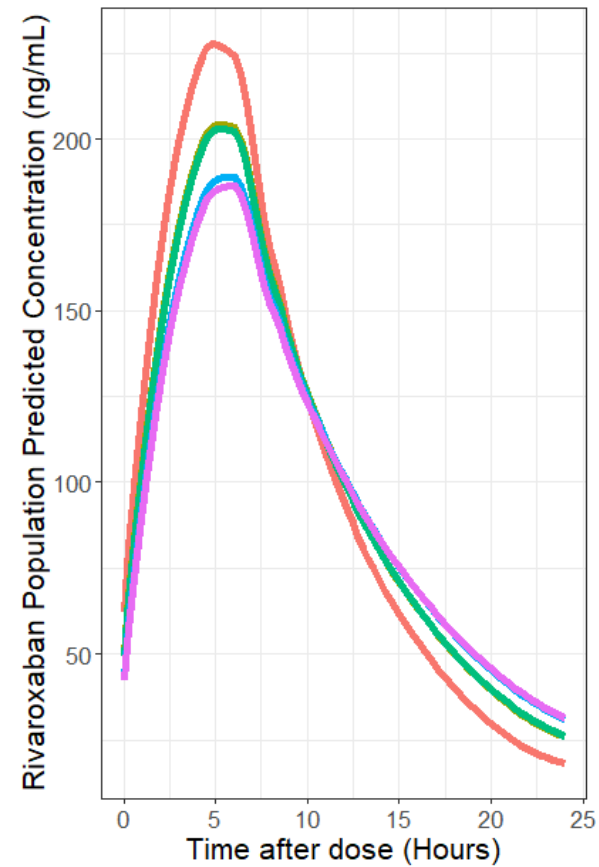
There is concern that high bodyweight leads to under-exposure due to changes in volume of distribution and clearance.

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



Patient characteristics

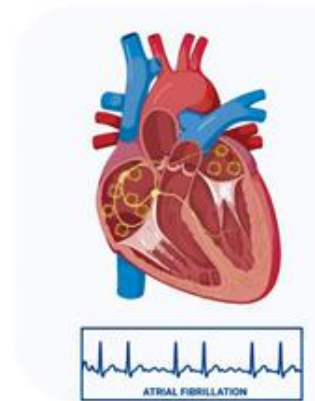
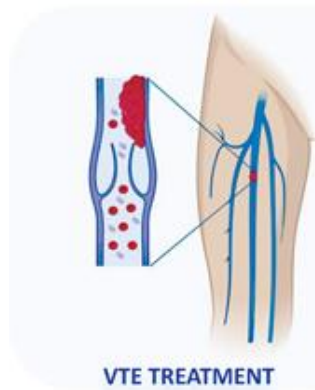
- Male, age 70 years, weight 70kg, CrCl 15ml/min
- Male, age 70 years, weight 70kg, CrCl 50ml/min
- Male, age 70 years, weight 70kg, CrCl 90ml/min
- Male, age 70 years, weight 70kg, CrCl 125ml/min



Patient characteristics

- Male, age 70 years, weight 45kg, CrCl ~90ml/min
- Male, age 70 years, weight 70kg, CrCl ~90ml/min
- Male, age 70 years, weight 125kg, CrCl ~90ml/min
- Male, age 70 years, weight 150kg, CrCl ~90ml/min
- Male, age 70 years, weight 200kg, CrCl ~90ml/min


Choice of DOAC at extremes of weight



**UNDERWEIGHT
PATIENTS**

**BMI <18.5
kg/m²**

 **APIXABAN
5 mg BID**


 **EDOxabAN
30 mg OD**


 **APIXABAN
5 mg BID**


 **EDOxabAN
30 mg OD**


OBESSE PATIENTS

**BMI ≥30
kg/m²**

 **APIXABAN
5 mg BID**

 **RIVAROXABAN
20 mg OD**

 **APIXABAN
5 mg BID**

 **RIVAROXABAN
20 mg OD**

How can we make DOAC use safer?

Sharing information



Direct Oral Anticoagulation Therapy

What is a Direct Oral Anticoagulant?

Blood clots are usually treated with drugs that reduce the ability of the blood to clot (anticoagulants). Anticoagulants do not break down or dissolve an existing clot but they do prevent it from growing bigger and reduce the risk of further clots forming. Warfarin is an anticoagulant that is often prescribed and a newer group of anticoagulants that have been recommended for some patients are known as 'Direct Oral Anticoagulants' (DOAC's). In the UK DOACs include Rivaroxaban (Xarelto®), Apixaban (Eliquis®), Dabigatran (Pradaxa®) and Edoxaban (Lixiana®).

How do I know how much to take?

Each patient is individual and so the dose prescribed may vary from patient to patient depending on why you require the anticoagulant. The healthcare professional who prescribes your medication will be able to advise you on the dose best suited for your medical needs.

How do I take my DOAC?

It is very important to take the medication regularly and at the same time each day. If you forget to take one dose, read the instructions that come with the tablets to guide you on what to do. You must read the pharmacy label and take the tablets exactly as directed. Take each dose of your DOAC anticoagulation therapy with a glass of water.

What side effects might I have from a DOAC?

The main side effect of an anticoagulant may be unexpected bleeding or bruising.

If you experience any of the following, you must contact your GP or clinic as soon as possible:

- Prolonged nose bleeds (lasting more than 10 minutes)
- Prolonged bleeding from cuts
- Blood in vomit or sputum (spit), nose bleed, bleeding gums.
- Blood in urine (urine coloured pink or brown)
- Headaches
- It is common for women to experience heavy or increased bleeding during their period. If you are concerned about the increased bleeding contact your doctor or clinic.
- Some patients experience nausea, diarrhoea and/or heartburn. If these symptoms persist, contact your GP or clinic.
- Seek immediate medical help if you suffer major trauma or a blow to the head or are unable to stop bleeding.

How long will I need to take a DOAC?

The length of treatment depends on your medical history and the condition requiring treatment. Your doctor will discuss this with you when you start the anticoagulation treatment. It is usual for most people who have suffered from a deep vein thrombosis or pulmonary embolism to continue to take anticoagulation for at least three months. For some, treatment will continue longer or indefinitely.

What happens if I need dental treatment or an operation whilst I am taking a DOAC?

Tell your healthcare professional team before any operation or dental treatment. They will decide the management of your DOAC before and after your procedure and should give you a verbal and written detailed information sheet about what you will need to stop. Each case is individually assessed. It is important to follow the instructions of the healthcare professional to avoid any cancellation or severe bleeding due to your DOAC.

Will I need blood tests to monitor my DOAC?

DOACs do not require routine blood test monitoring. It is recommended that your kidney function is checked prior to starting treatment and at least annually while on treatment. If you develop issues with your kidneys such as kidney infection or abnormal kidney blood tests you should contact your clinic or doctor as your dose may need to be adjusted.

What if I forget a dose?

It depends on which DOAC you are taking. Apixaban (Eliquis®): Take the tablet remember and take the following tablet then continue as normal.

Dabigatran (Pradaxa®): A forgotten dose up to 6 hours prior to the next due dose should be omitted if the remaining time prior to the next due dose. Do not take make up for missed doses.

Edoxaban (Lixiana®): Take the dose remember. Do not take more than one tablet to make up for a forgotten dose. Take the following day and then carry on taking day.

Rivaroxaban (Xarelto®): If you are on one 20 mg tablet once a day or once a day and have missed a dose, take remember. Do not take more than one tablet to make up for a forgotten dose. Take the following day and then carry on taking day.



SCI ANI

Anticoagulants and your Periods

2:39

SA Anticoagulants and your periods

Science Animated · 12K views · 6 months ago

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DOACs (Direct Oral Anticoagulants) monitoring

Published 5 July 2021 · Last updated 27 July 2022

Topics: Apixaban · Dabigatran etexilate · Edoxaban · 2 more ▾

Using this page · Individualise medicines monitoring

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- Notes
 - What to assess at a review appointment

Before starting

Required

- Baseline
 - Baseline clotting screening
 - Body weight
 - Full blood count
 - Liver function tests
 - Serum creatinine (for creatinine)
 - Urea and electrolytes

Monitoring renal function

[Cockcroft and Gault is recommended](#) for ca rate can overestimate renal function and inc

Sharing information



Frequently asked questions (FAQs) concerning Direct Acting Anticoagulants (DOACs) for primary care practitioners in South East London

This guidance has been written by anticoagulation specialists in answer to common questions received by anticoagulation teams and medicines optimisation teams in South East London from healthcare practitioners (HCPs) concerning patients taking DOACs.

The aim of this guidance is to provide information to assist HCPs with queries concerning DOACs and advice concerning when a referral and/or further investigation is appropriate for their patient.

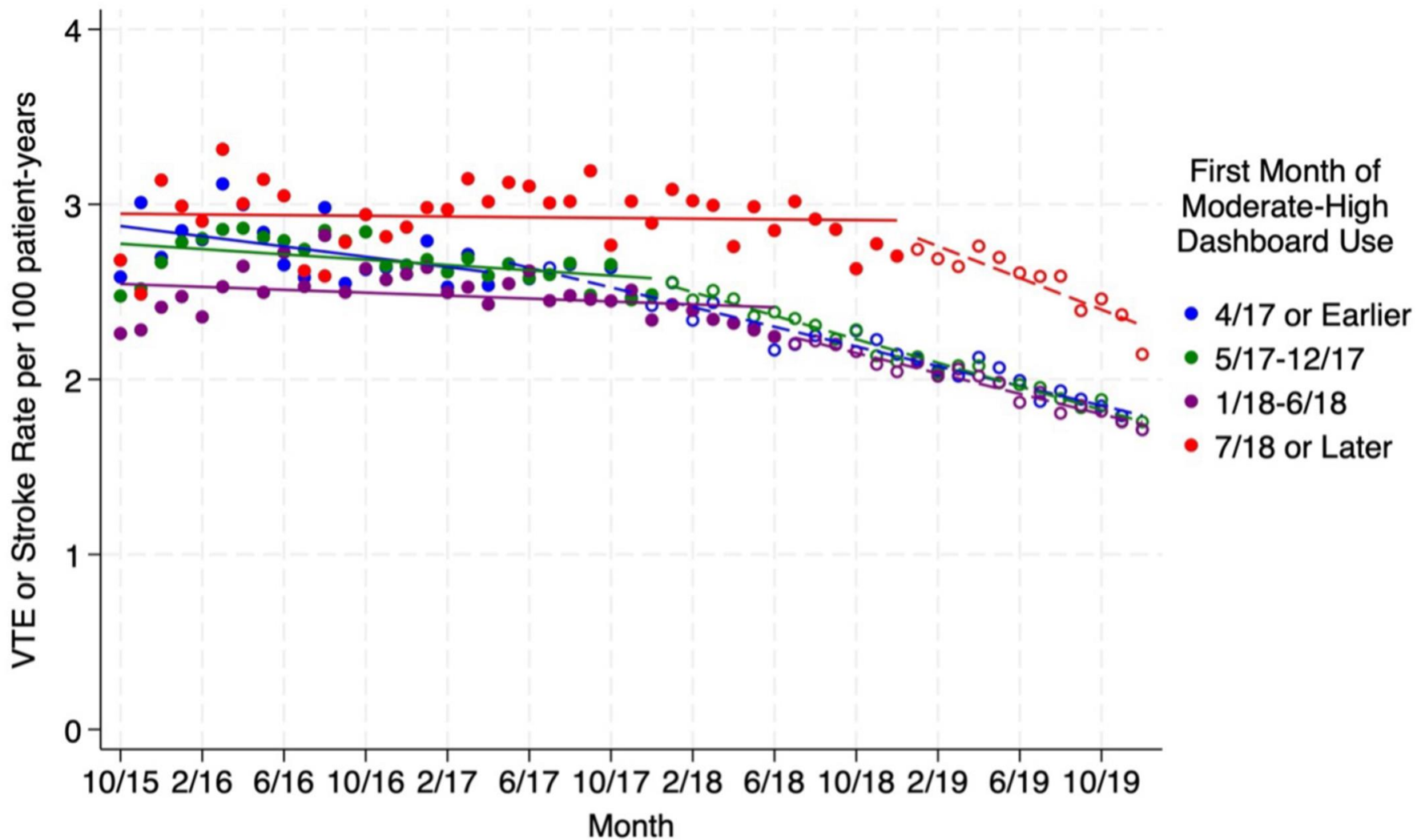
Original approval date: September 2020 **Last reviewed & updated:** January 2024, minor updates approved August 2024

Next review date: January 2026 (or earlier if indicated)

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South East London Integrated Medicines Optimisation Committee (SEL IMOC). A partnership between NHS organisations in South East London Integrated Care System: NHS South East London (covering the boroughs of Bexley/Bromley/Greenwich/ Lambeth/Lewisham and Southwark) and GSTFT/KCH /SLaM/ Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust

Innovative solutions: Pharmacist use of a population management dashboard results in improved outcomes



Anticoagulation Stewardship

- Education and awareness initiatives
- Clear end-to-end guidance on safe use of DOACs
- Robust systems for monitoring and follow-up that address interfaces between primary and secondary care
- Provision of safe anticoagulation transitioning
- IT solutions and innovations
- Multi-professional anticoagulation and thrombosis teams