DOACS
Therapeutic considerations made easy

Dr Sangeeta Atwal
Consultant Haematologist
Kingston Hospital
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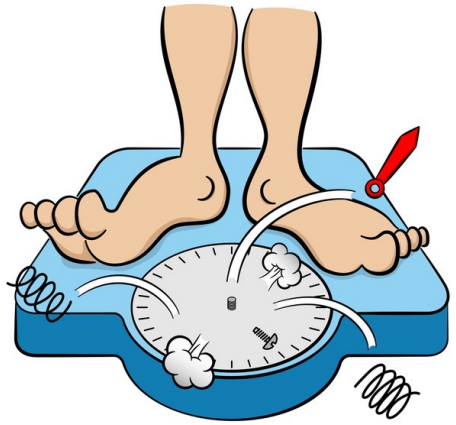
CLINICAL CASE 1

A 53-year-old man presented with pleuritic chest pain and shortness of breath, and imaging confirmed bilateral pulmonary embolism. He has no history of VTE but has restricted mobility due to progressive multiple sclerosis. His weight is 149 kg, with a body mass index (BMI) of 45 kg/m^2. His complete blood count and kidney function are unremarkable. What anticoagulant should be recommended?

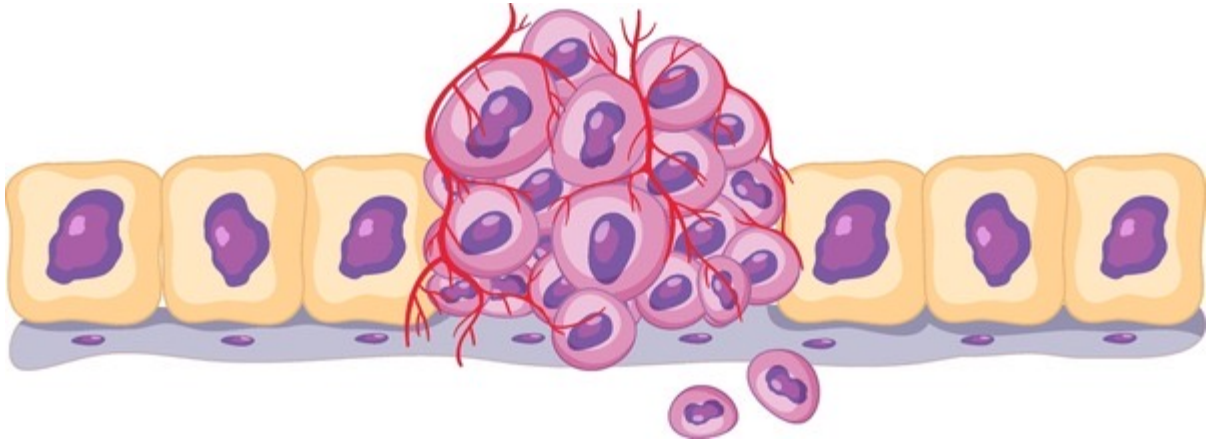


CLINICAL CASE 1 (Continued)

After an informed discussion, standard-dose rivaroxaban was started. He tolerated rivaroxaban well for 2 months without bleeding or thrombotic complications but unfortunately developed septic shock from bacteremia and acute renal failure. After resuscitation, he was stabilized, but his renal function remained significantly compromised with creatinine clearance (CrCl) of 25 mL/min. How should one manage his anticoagulation?

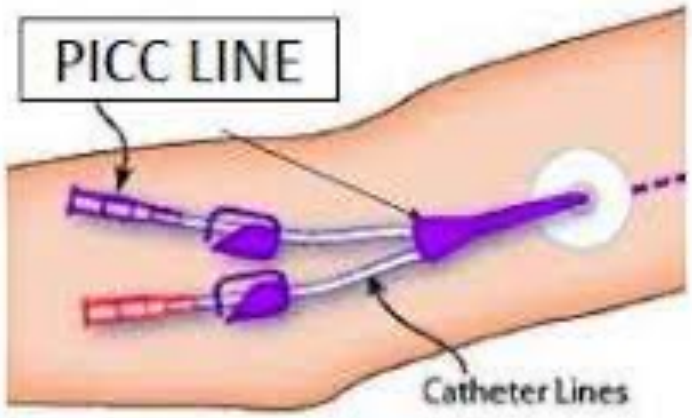
CLINICAL CASE 2

A 62-year-old woman presented with fatigue, paler, and left leg swelling and redness. She was found to have iron-deficiency anemia and a deep vein thrombosis (DVT) in the left lower extremity. Further workup revealed a gastric mass, with biopsy confirming adenocarcinoma. She is referred to discuss anticoagulation options.



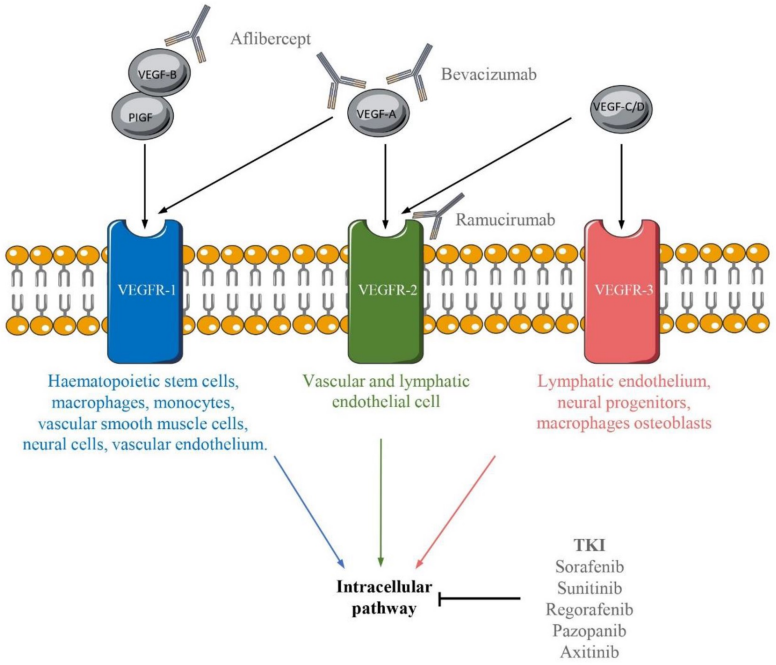
CLINICAL CASE 2 (Continued)

Her oncologist recommended intravenous chemotherapy and a peripherally inserted central catheter (PICC) to facilitate delivery of chemotherapy. The patient is apprehensive about the risks of thrombosis associated with a central venous catheter (CVC).



CLINICAL CASE 2 (Continued)

Her cancer progressed, and her oncologist recommended changing therapy to vascular endothelial growth factor (VEGF) inhibitors. The oncology pharmacist is concerned about potential drug-drug interactions with her anticoagulant.

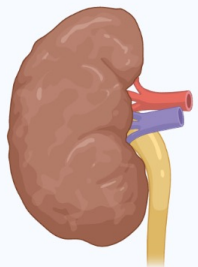


Commonly asked questions about oral FXa inhibitors

1 Obesity

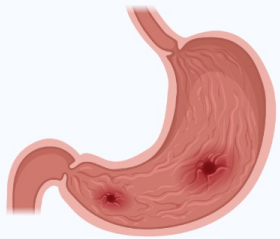
Rivaroxaban or apixaban can be used for weight > 120 kg or BMI > 40 kg/m^2

2 Renal impairment



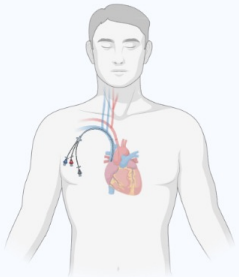
Caution DOAC use in patients with CrCl < 15-30 ml/min

3 GI cancer



Avoid DOACs in patients with unresected luminal GI cancers due to higher risk of GI bleeding

4 Catheter-related thrombosis



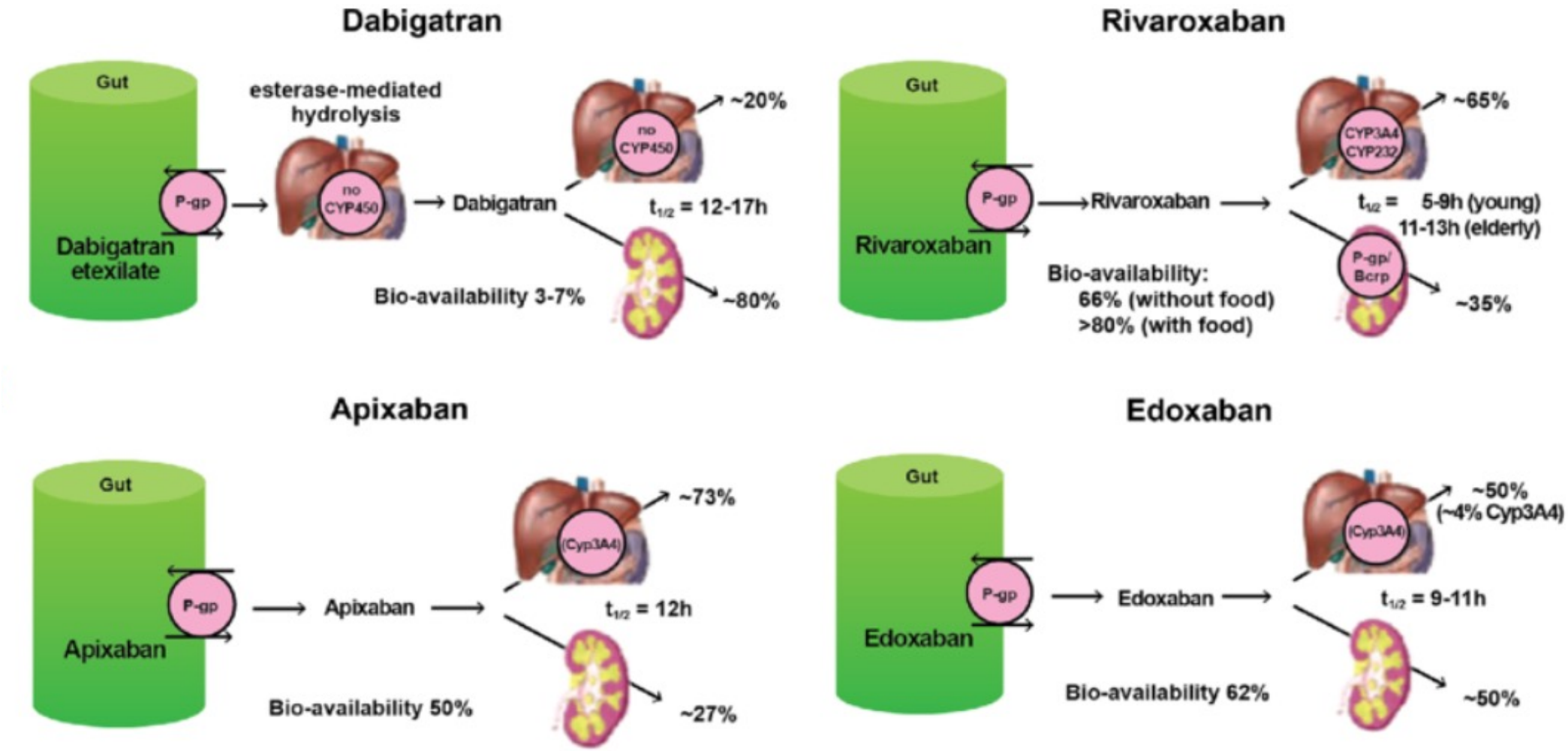
Management is individualized in a similar way as for proximal lower extremity DVT and PE, although data are limited

5 Drug-drug interactions

Consider PK and PD drug-drug interactions when starting an anticoagulant

Summary of practice suggestions for the 5 frequently asked questions

Issues/questions	Our practice
Obesity	▪ We use standard-dose rivaroxaban or apixaban for VTE treatment in patients with weight >120 kg or BMI >40 kg/m^2. While we do not routinely monitor anti-Xa levels, we do consider it in patients with weight >150 kg or BMI >50 kg/m^2 (when available), although this practice remains investigational.
Renal impairment	▪ We avoid using DOACs in patients with CrCl <15-30 mL/min. However, apixaban might be used with close monitoring in situations where no safer alternative anticoagulants are available. ▪ Tinzaparin can be used (when available) in patients with CrCl >20 mL/min.
Gastrointestinal malignancy	▪ We avoid DOACs in patients with unresected luminal GI cancers due to the higher risk of GI bleeding.
Catheter-related thrombosis	▪ We tailor anticoagulant for catheter-related thrombosis in patients with cancer similarly as for proximal lower extremity DVT and PE based on patient characteristics, type of cancer, and anticancer treatments.
Drug-drug interactions	▪ We consider DDIs whenever an anticoagulant is prescribed by utilizing resources such as Lexicomp, Micromedex, package inserts, and pharmacists.



Routes of absorption, metabolism and elimination of the direct oral anticoagulants. Reprinted with permission from [68]

Dosing recommendations of oral factor Xa inhibitors for VTE from different regulatory agencies

Drug	Renal clearance, %	Standard dose for VTE	FDA	Health Canada	EMA
Rivaroxaban	33	15 mg twice daily for 21 days, then 20 mg daily	▪ Avoid use if CrCl <15 mL/min	▪ Avoid use if CrCl <15 mL/min	▪ Avoid use if CrCl <15 mL/min ▪ Use with caution for CrCl 15-29 mL/min ▪ For CrCl <50 mL/min, a reduction from 20 mg to 15 mg daily can be considered if risk of bleeding outweighs recurrent VTE
Apixaban	27	10 mg twice daily for 7 days, then 5 mg twice daily	▪ No dose adjustment for any CrCl	▪ Avoid use if CrCl <15 mL/min ▪ Use with caution for CrCl 15-29 mL/min	▪ Avoid use if CrCl <15 mL/min ▪ Use with caution for CrCl 15-29 mL/min
Edoxaban	50	LWMH for ≥5 days, then 60 mg daily	▪ Not recommended if CrCl <15 mL/min ▪ CrCl 15-50 mL/min: 30 mg daily	▪ Avoid use if CrCl <30 mL/min ▪ Weight ≤60 kg, CrCl 30-50 mL/min, or coadministration with P-gp inhibitors: 30 mg daily	▪ Avoid use if CrCl <15 mL/min ▪ Weight ≤60 kg, CrCl 15-50 mL/min, or coadministration with P-gp inhibitors: 30 mg daily

Management of Bleeding in Patients Receiving the Direct Oral Anticoagulants Rivaroxaban, Apixaban, Edoxaban and Dabigatran

BLEEDING IN-PATIENT TAKING RIVAROXABAN, APIXABAN, EDOXABAN or DABIGATRAN

↓

Discontinue treatment

↓

Assess clinical effects of bleeding and resuscitate patient as appropriate

Use local haemostatic measures to control bleeding

- Mechanical compression

Check: FBC, U&E and clotting screen for PT, APTT, TT. Send Group and Save sample.

Minor bleeding

↓

Consider delaying next dose.

Reconsider indication.

Moderate to severe or life-threatening bleeding

↓

Contact on-call consultant haematologist for non-GI bleeding or on-call consultant gastroenterologist for GI bleeding

Give fluid replacement to maintain urine output.

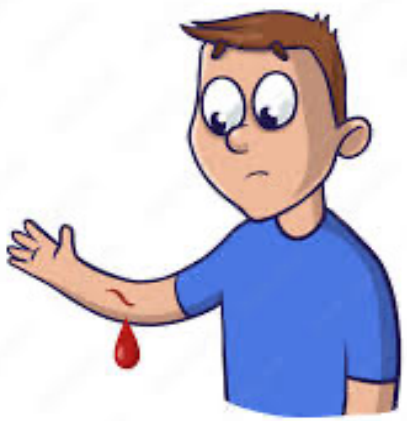
Use blood product support to keep: Hb>8.0g/dl, platelets > 80 x 10^9/l

For patients taking **Dabigatran,** consider the reversal agent **Idarucizumab (Praxbind)** click here for more information**.** This is available from blood transfusion in pathology only after discussion with a consultant haematologist.

For serious and life-threatening **gastro-intestinal bleeds ONLY** (to consider in bleeds associated with haemodynamic compromise or Hb decrease >20g/l or Hb < 80g/l) in patients taking **apixaban and rivaroxaban**, consider using the reversal agent **Andexanet Alfa.** This is available from blood transfusion in pathology only after Consultant approval (by BOTH GI on call Consultant and GIM Consultant). Click here for more information on dosing and authorisation

For serious and life-threatening **non- GI bleeding** in patients taking **apixaban, rivaroxaban or edoxaban**, consider (in escalating steps)

- Tranexamic acid IV 1g (over 10 minutes) and repeat if bleeding persists (up to TDS)
- Prothrombin Complex Concentrate (i.e. Octaplex): see guideline
- rFVIIa 90 micrograms/kg with further dose after 2 hours (haematology recommendation only)



VTE-Bleed score

	Points in score
Active cancer	2
Male patient with uncontrolled hypertension	1
Anemia	1.5
History of bleeding	1.5
Kidney dysfunction (CrCl 30 to 60 mL/min)	1.5
Age ≥60 years	1.5

This score was developed from an evaluation of over 2500 individuals with venous thromboembolism in the RE-COVER trials who were assigned to receive dabigatran and verified in over 2500 individuals from the same trials assigned to warfarin. A score of 2 points or higher was associated with a high bleed risk and 0 to 1.5 points with a low bleed risk.

Bleeding outcomes in the gastrointestinal cancer subgroup in randomized controlled trials comparing DOACs with dalteparin for acute cancer-associated VTE

Trials	Hokusai-VTE Cancer[34]	Select-D[35]	ADAM-VTE[32]	Caravaggio[31]	CASTA-DIVA[33]
Total N	1046	406	300	1155	158
DOACs	Edoxaban	Rivaroxaban	Apixaban	Apixaban	Rivaroxaban
GI cancer	305 (29.2)	177 (43.6)	105 (35)	375 (32.5)	46 (29.1)
Upper GI cancer	54 (5.2)	41 (10.1)	11 (3.7)	54 (4.7)	3 (1.9)
Major bleeding (DOAC vs dalteparin)	21/165 (12.7) vs 5/140 (3.6) HR 4.0 (95% CI, 1.5-10.6)	8/91 (8.8) vs 5/86 (5.8)	0/48 (0) vs 0/57 (0)	9/188 (4.8) vs 9/187 (4.8)	NR
CRNMB (DOAC vs dalteparin)	NR	7/91 (7.7) vs 1/86 (1.2)	NR	19/188 (10.1) vs 7/187 (3.7)	NR

Values are presented as number (%) unless otherwise indicated.

CRNMB, clinically relevant nonmajor bleeding; NR, not reported.

Efficacy and Safety of DOACs in Morbidly Obese Patients

Quick Takes

- The use of direct oral anticoagulants (DOACs) in patients with nonvalvular atrial fibrillation (AF) weighing ≥120 kg was not associated with an increased risk of thromboembolic events or bleeding compared to those patients weighing 60-120 kg.
- The results of this study add to the growing body of literature demonstrating that DOACs are a reasonable alternative for patients with non-valvular AF who are obese, specifically those with a body weight exceeding 120 kg.

Study Questions:

Are DOACs safe and effective in obese patients weighing ≥120 kg?

Methods:

This was a single-center retrospective study in patients weighing ≥120 kg with nonvalvular AF who were taking apixaban, rivaroxaban, or dabigatran between January 1, 2011 and September 30, 2018. A total of 348 patients >18 years of age were included and were matched to patients weighing 60-120 kg based on age, sex, ethnicity, and prescribed oral anticoagulant. Additional baseline characteristics collected included creatinine clearance, weight, BMI, and CHA_2DS_2-VASc score. Patients were followed for 1 year after their initial encounter. The primary outcome was the incidence of stroke, deep vein thrombosis, pulmonary embolus, or myocardial infarction. The primary safety outcome was a composite of the incidence of major or clinically relevant non-major bleeding as defined by the International Society of Thrombosis and Hemostasis.

Efficacy and Safety of DOACs in Morbidly Obese Patients

Results:

The median weight and BMI for patients included in the ≥120 kg group were 132.1 kg and 41 kg/m^2, respectively, while the median weight and BMI in the <120kg group was 93 kg and 29.4 kg/m^2, respectively. The median age was 63 years with 78% being male. Approximately 80% were Caucasian. Apixaban was the most commonly prescribed anticoagulant at 55%, with rivaroxaban being the next most frequent agent at 27%, and dabigatran at 19%. The primary endpoint occurred in 2.5% of patients in the ≥120 kg group versus 3.1% in the <120 kg group (p = 0.632). The incidence of the composite safety outcome occurred in 5.3% in patients in the ≥120 kg group compared to 6.6% in the <120 kg group (p = 0.503).

Conclusions:

This retrospective review demonstrated that apixaban, rivaroxaban, and dabigatran are safe and effective in patients with nonvalvular AF weighing ≥120 kg.

Perspective:

Several retrospective studies have been published that have demonstrated similar findings in the obese population. This was one of the largest retrospective studies conducted to date. Of note, the occurrence of the primary endpoint did not correlate to extreme body weight as the median weight of the primary outcome occurrence was 128.3 kg, while the range of patients enrolled was 126-143.4 kg. These results add to the growing body of literature for the use of DOACs in obese patients (≥120 kg) with nonvalvular AF. However, the number of patients with severe obesity (BMI >50 kg/m^2 or weight >150 kg) were underrepresented and additional evaluation is likely needed in this patient population.

DOACs at extremes of body weight

Rivaroxaban and apixaban can be used at standard doses for VTE and AF in patients who weigh ≤ 150kg or BMI ≤50 - see ISTH 2021 update on DOACs in obesity.

DOAC anti-xa levels are not routinely available at Worthing and St Richard's Hospitals

DOACs at extremes of body weight (VTE and AF)	**Patient weight**			
DOAC	**<50kg**	**50kg-120kg or BMI ≤40 kg/m^2**	**>120kg and ≤150kg or BMI >40 and ≤50kg/m^2**	**>150kg or BMI >50 kg/m^2**
Rivaroxaban	DOACs not routinely recommended, limited evidence, increased bleeding risk especially with renal impairment. Anti-xa levels can be considered. Discuss with anticoagulation and VTE team or oncall haematologist for advice.	Standard BNF dosing for all DOACs. For patients with **high clot burden or high risk PE, give 5-7 days of treatment low molecular weight heparin** before considering switch to DOAC.	More supportive data exist for rivaroxaban than apixaban in this weight range therefore rivaroxaban is recommended to be used first line. Anti-xa levels not required. For patients with **high clot burden or high risk PE, give 5-7 days of treatment low molecular weight heparin** before considering switch to rivaroxaban.	All patients should be discussed with haematology consultant. Rivaroxaban at standard doses can be considered with trough anti-xa levels. For patients with **high clot burden or high risk PE, give 5-7 days of treatment low molecular weight heparin** before considering switch to rivaroxaban.
Apixaban			Apixaban is second line choice as more limited data than rivaroxaban to support use in this weight range. Anti-xa levels not required. For patients with **high clot burden or high risk PE, give 5-7 days of treatment low molecular weight heparin** before considering switch to apixaban.	Do not use
Edoxaban			Do not use	Do not use
Dabigatran			Do not use	Do not use

Long-term VTE prophylaxis in obese patients

- Long term VTE prevention Patients with weight > 120kg or BMI >40kg/m2 who need longterm anticoagulation for VTE prevention should continue on 20mg once daily Rivaroxaban as there is insufficient evidence to support dose reduction to long term prevention dose Rivaroxaban 10mg once daily in these patients.

Drug Interactions

Class	Drugs	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Strong P-gp inhibitors(also CYP3A4 inhibitors)	Ciclosporin Dronaderone Itraconazole Ketoconazole Posaconazole Tacrolimus Voriconazole	Combination contraindicated	Strong recommendation not to use		Reduce dose to 30mg daily if on ciclosporin, dronaderone, erythromycin or ketoconazole
Other strong P-gp inhibitors(also CYP3A4 inhibitors)	Amiodarone Clarithromycin Quinidine Verapamil	Caution. If on verapamil give 110mg twice daily	Avoid use particularly in renal impairment	Caution	Caution
Protease inhibitors (P-gp inhibitors and CYP3A4 inhibitors)	Ritonavir Telaprevir	Concomitant use not recommended	Strong recommendation not to use		No data
Strong P-gp and CYP3A4 inducers	Carbamazepine Phenobarbital Phenytoin Primidone Rifampicin St John's Wort	Combination should be avoided			Use with caution
Other anticoagulants	E.g. LMWH, warfarin, UFH, fondaparinux	Combination contraindicated except when switching therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter			
Others	Aspirin Clopidogrel NSAID's	Caution. Combination not recommended. A careful risk-benefit assessment should be made prior to initiation if required.			
	Prasugrel Ticagrelor	Combination not recommended			
	SSRI's and SNRI's	Caution. Monitor for signs of bleeding			

Apixaban: Direct Factor Xa Inhibitor

DRUG-DRUG INTERACTIONS (DDIs)

Pharmacokinetic DDIs occur only with combined alterations to *both* CYP3A4 and P-glycoprotein transporters (**DUAL inhibitors/inducers**).

Dual inhibitors increase risk of bleeding:

Diltiazem, naproxen, ketoconazole, itraconazole, ritonavir, and *possibly* clarithromycin*

** Clarithromycin has only recently been described to alter Apixaban metabolism, in conflict to package insert*

Dual inducers increase risk of VTEs:

Rifampin, phenytoin, carbamazepine, and St. John's wort

⚠ Clinical relevance – older/younger patients, risk of bleeding/thrombosis – especially aspirin, risk with other COVID drugs, updates to package insert!

Table 1. Drug Interactions with Dabigatran[2,4,10,11]

Interacting Medication	Risk/Management
P-gp inducers *rifampin*	Increases risk of stroke or systemic embolism. Avoid combination and consider alternative agents for anticoagulation.
P-gp inhibitors and CrCl 30-50 mL/min *ketoconazole, dronedarone*	Increases bleeding risk. Consider dose reduction to 75 mg twice daily or the use of an alternative agents for anticoagulation.
P-gp inhibitors and CrCl 15-30 mL/min *amiodarone, verapamil, ketoconazole, dronedarone, diltiazem, clarithromycin*	Increases bleeding risk. Avoid combination and consider alternative agents for anticoagulation.
Antiplatelets/NSAIDs *aspirin, clopidogrel, naproxen, diclofenac, celecoxib, etc.*	Increases bleeding risk. Weigh risk and benefits prior to concomitant therapy and monitor closely for bleeding during therapy.

Table 3. Drug Interactions with Apixaban[8,10,11,13]

Interacting Medication	Risk/Management
Strong dual inducers of CYP3A4 and P-gp *rifampin, carbamazepine, phenytoin, St. John's wort*	Increases risk of stroke or systemic embolism. Avoid combination and consider alternative agents for anticoagulation.
Strong dual inhibitors of CYP3A4 and P-gp *ketoconazole, itraconazole, HIV protease inhibitors, clarithromycin*	Increases bleeding risk. If starting dose is 5 mg twice daily, consider reducing dose to 2.5 mg twice daily. If starting dose is 2.5 mg twice daily, consider using alternative agents to avoid excessive bleeding risks.
Antiplatelets/NSAIDs *aspirin, clopidogrel, naproxen, diclofenac, celecoxib, etc.*	Increases bleeding risk. Weigh risks and benefits prior to concomitant therapy and monitor closely for bleeding during therapy.

Table 2. Drug Interactions with Rivaroxaban[7,10-12]

Interacting Medication	Risk/Management
Strong dual CYP3A4 and P-gp inducers *carbamazepine, phenytoin, rifampin, St. John's wort*	Increases risk of stroke or systemic embolism. Avoid combination and consider alternative agents for anticoagulation.
Strong dual CYP3A4 and P-gp inhibitors *conivaptan, HIV protease inhibitors, itraconazole, ketoconazole*	Increases bleeding risk. Avoid combination and consider alternative agents for anticoagulation.
Weak-moderate CYP3A4 inhibitors and P-gp inhibitors with CrCl 15-50 mL/min *amiodarone, chloramphenicol, cimetidine, diltiazem, erythromycin, verapamil*	Increases bleeding risk. Consider alternative agents for anticoagulation and only combine if benefit outweighs risk.
Antiplatelets/NSAIDs *aspirin, clopidogrel, naproxen, diclofenac, celecoxib, etc.*	Increases bleeding risk. Weigh risks and benefits prior to concomitant therapy and monitor closely for bleeding during therapy.

CHA_2DS_2 – VASc Score for Atrial Fibrillation Stroke Risk

CHF	+1
Hypertension	+1
Age ≥75	+2
Diabetes	+1
Stroke/TIA/VTE	+2
Vascular Disease	+1
Age 65-74	+1
Sex (female)	+1

Score	Risk of stroke	
0	0.2%	Low
1	0.6%	Moderate
2	2.2%	High
3	3.2%	
4	4.8%	
5	7.2%	
6	9.7%	
7	11.2%	
8	10.8%	
9	12.2%	

1(male): oral anticoagulant should be considered

≥2: oral anticoagulant is recommended

HAS-BLED score

Condition	Points
H - Hypertension	1
A - Abnormal renal or liver function (1 point each)	1 or 2
S - Stroke	1
B - Bleeding	1
L - Labile INRs	1
E - Elderly (> 65 years)	1
D - Drugs or alcohol (1 point each)	1 or 2

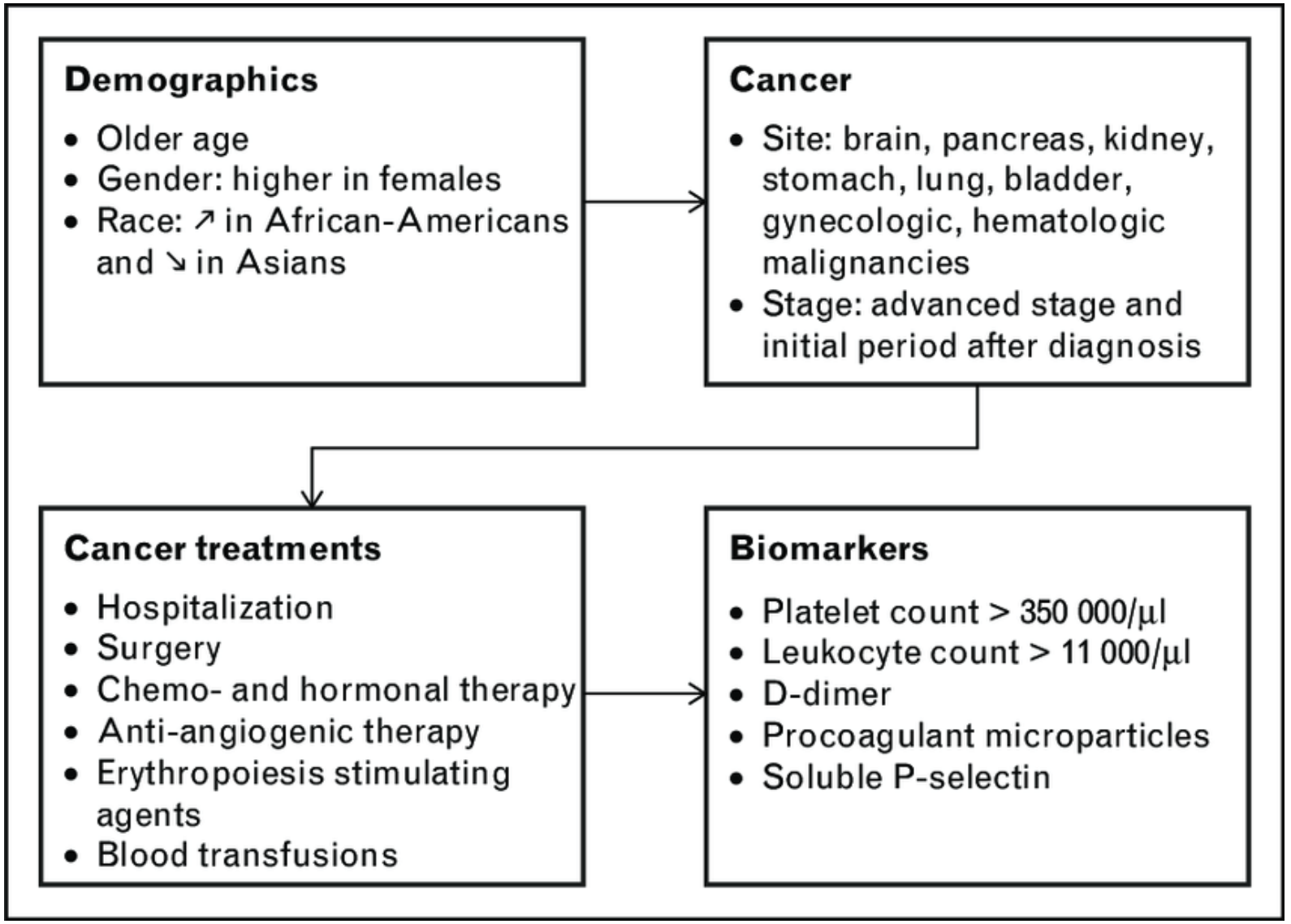
HAS-BLED score	Bleeds per 100 patient-years
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.5

Note: HAS-BLED has been validated for warfarin, but not for the new anticoagulants.

Pisters R et al. Chest 2010;138(5):1093-1100.

	Risk predictors	Scoring system	Risk stratification
ORBIT	Older age (≥ 74 years) Reduced hemoglobin/anemia Bleeding history Insufficient kidney function Treatment with antiplatelet	1 point for each risk factor	Low risk 0–2 Intermediate risk 3 High risk ≥ 4
HAS-BLED	Hypertension Abnormal renal and/or liver function Stroke Bleeding history Labile INR Elderly (≥ 65 years) Drugs or alcohol concomitant	1 point for each risk factor	Low risk 0–1 Intermediate risk 2 High risk ≥ 3

Risk of VTE in Cancer patients



VTE RISK PREDICTION TOOL (KHORANA)

Patient characteristic (site of cancer)	Risk score*
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynaecological, bladder, testicular)	1
Prechemotherapy platelet count 350×10^9/l or more	1
Haemoglobin level less than 110 g/l or use of red cell growth factors	1
Prechemotherapy leucocyte count more than 11×10^9/l	1
BMI 35 kg/m^2 or more	1

The Khorana risk assessment tool is the best way of assessing risk for VTE in cancer patients.

* 0 points = low risk; 1–2 points = intermediate risk and ≥3 points = high risk

Source: AA Khorana et al. *Blood* (2008) 111:4902–07, published with permission from American Society of Hematology

DOAC perioperative management scheme

DOAC	Procedural bleeding risk	Perioperative DOAC management									
		Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day +1	Day +2	Day +3	Day +4
Direct Xa Inhibitors *and* Dabigatran (CrCl ≥ 50mL/min)	Low	✓	✓	✓	✓	OMIT	Day of procedure Do not administer any DOAC	✓	✓	✓	✓
	High	✓	✓	✓	OMIT	OMIT		OMIT	Resume day +2 or day +3		✓
Dabigatran (CrCl < 50mL/min)	Low	✓	✓	✓	OMIT	OMIT		✓	✓	✓	✓
	High	✓	OMIT	OMIT	OMIT	OMIT		OMIT	Resume day +2 or day +3		✓

✓ = DOAC may be taken or administered

Adapted from Douketis et al, JAMA Intern Med. 2019;179(11):1469-78

The Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) study

Prospectively enrolled 3007 patients with atrial fibrillation receiving anti-coagulation with a DOAC (apixaban 41.8%, rivaroxaban 36%, dabigatran 22.2%), who were planned to have an elective procedure/surgery that required anti-coagulation interruption.

Patients undergoing a low bleeding risk procedure omitted the DOAC for one day prior to the procedure (i.e. last dose to be taken at least 36 hours prior to procedure) Those undergoing a high bleeding risk procedure omitted the DOAC for two days (i.e. last dose to be taken at least 60 hours prior to procedure).

Due to its almost exclusive renal elimination, patients on dabigatran who had a creatinine clearance (CrCl) of <50 ml/min had double the period of preprocedural interruption (i.e. two days and four days for low and high bleeding risk procedures respectively).

DOACs were resumed one day after a low bleeding risk procedure and 2–3 days after a high bleeding risk procedure.

Bridging with heparin was not employed prior to the procedure, although postprocedural use of prophylactic heparin was permitted in patients at high risk of venous thromboembolism until DOAC resumption.

The Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) study

Procedures classified as high risk included 230 patients (7.6%) who had neuraxial anaesthesia.

Both 30-day rates of major bleeding (apixaban 1.35%, dabigatran 0.90%, rivaroxaban 1.85%) and arterial thromboembolic events (apixaban 0.16%, dabigatran 0.60%, rivaroxaban 0.37%) were low.