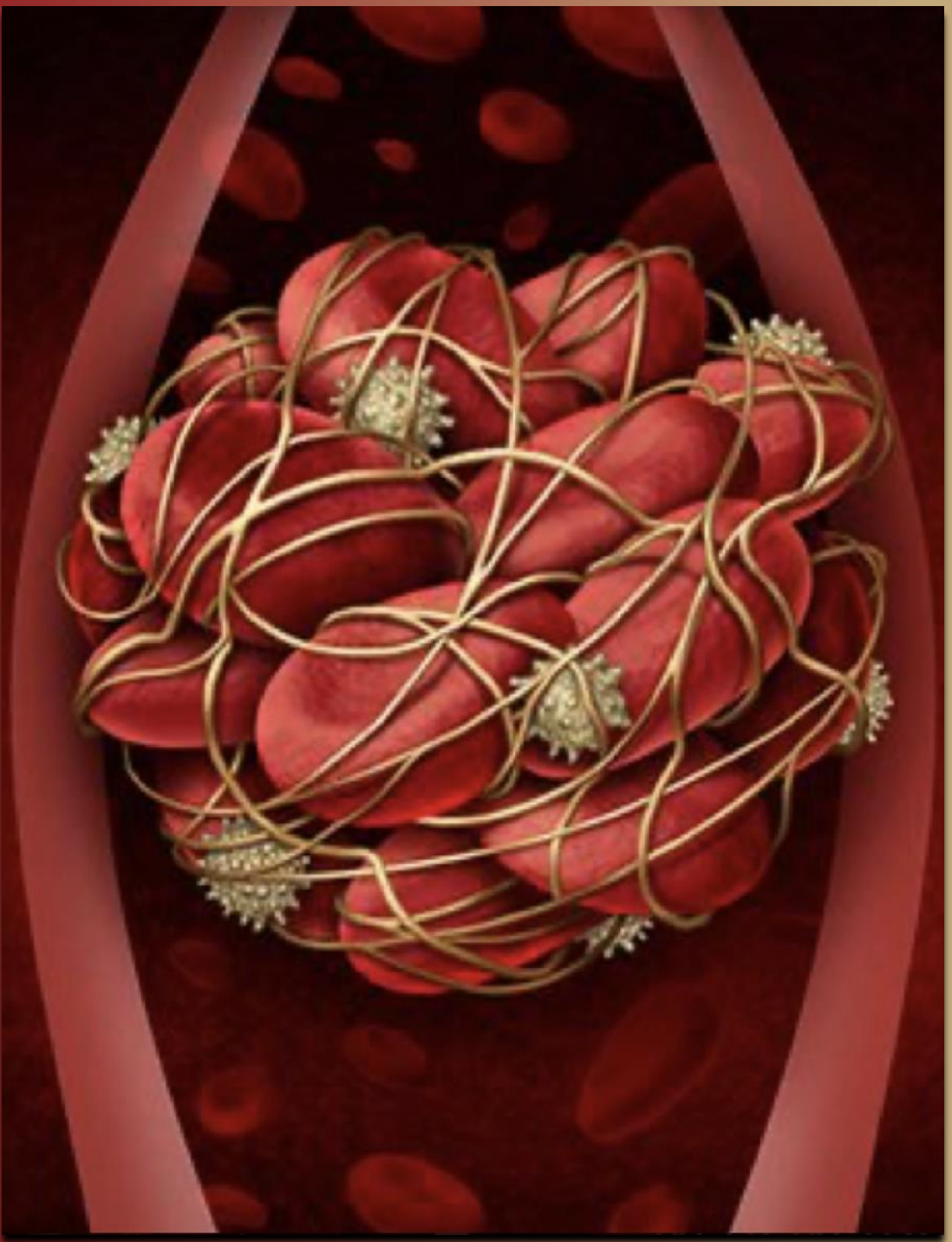
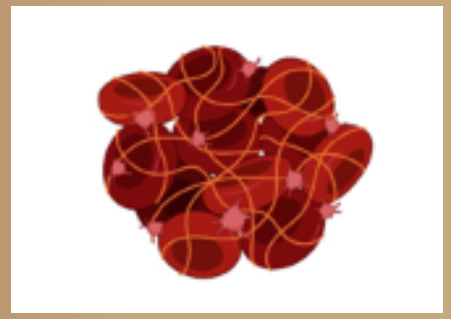


Oral Anticoagulant agents

Dr. Maryam Aghakouchakzadeh;
Pharm D; Clinical Pharmacist
Tehran Heart Center

August 2024

Different types of clot



Red clot

Low speed blood flow (*e.g. venous*)

Fibrin rich

White clot

High speed blood flow (*e.g. coronary artery*)

Platelet rich

Antithrombotic agents

- Antiplatelets
- **Anticoagulants**
  - **Oral**
  - Parenteral
- Fibrinolytics

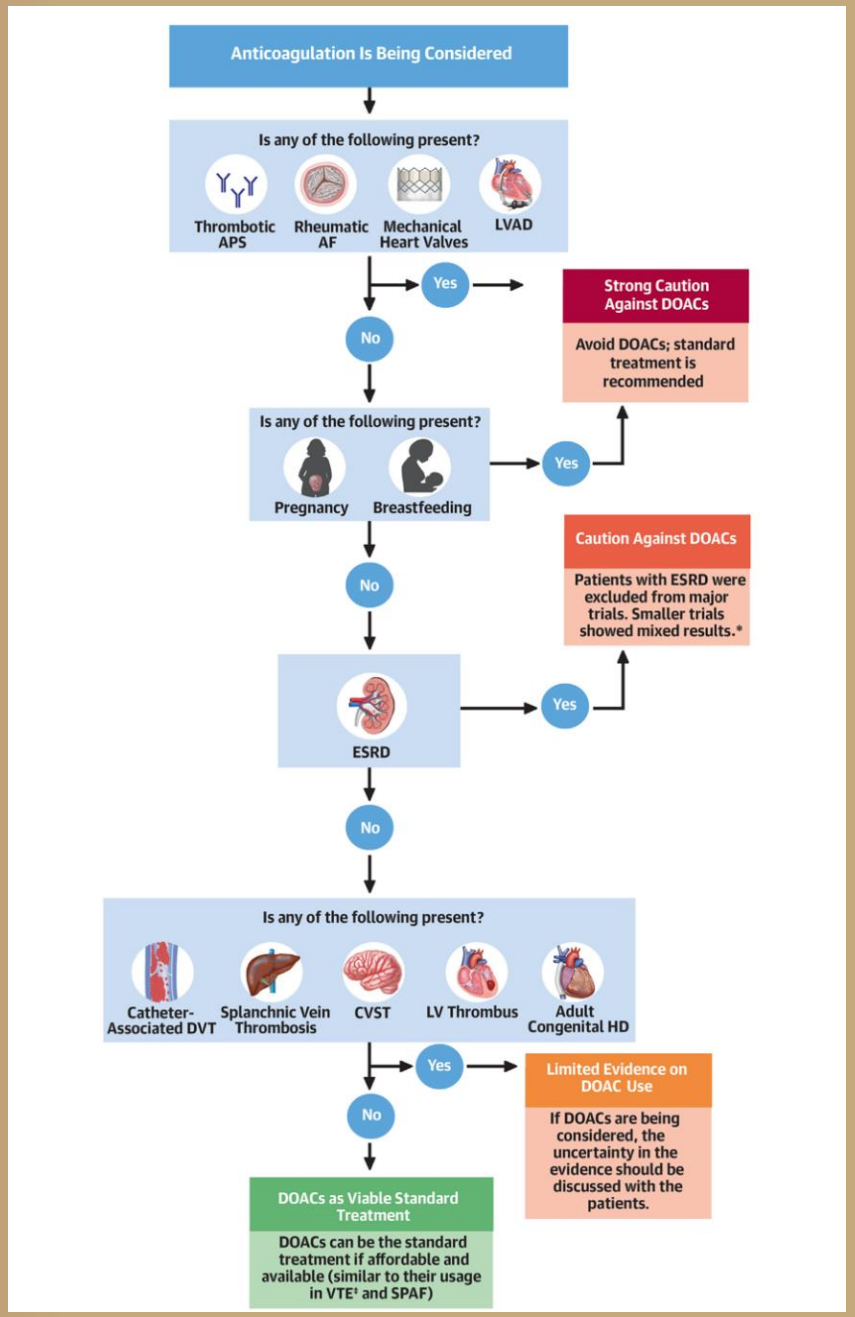
- **Oral Anticoagulants**
  - **Vitamin k Antagonists**
    - **warfarin**
  - **DOACs (NOACs)**
    - **Direct Thrombin Inhibitors**
      - **Dabigatran**
    - **Xa inhibitors**
      - **Apixaban, Rivaroxaban,** Edoxaban, Betrixaban

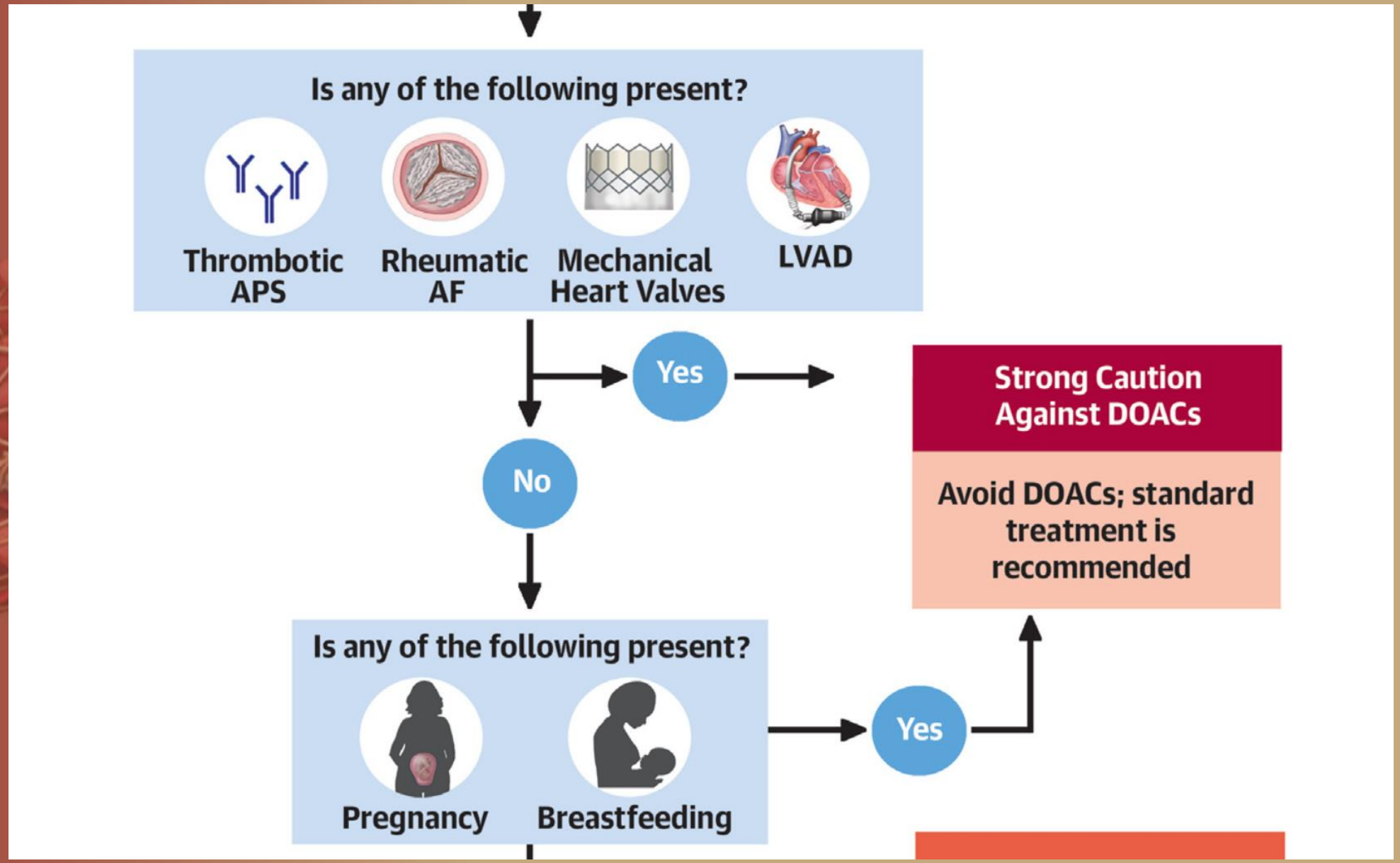
Case 1

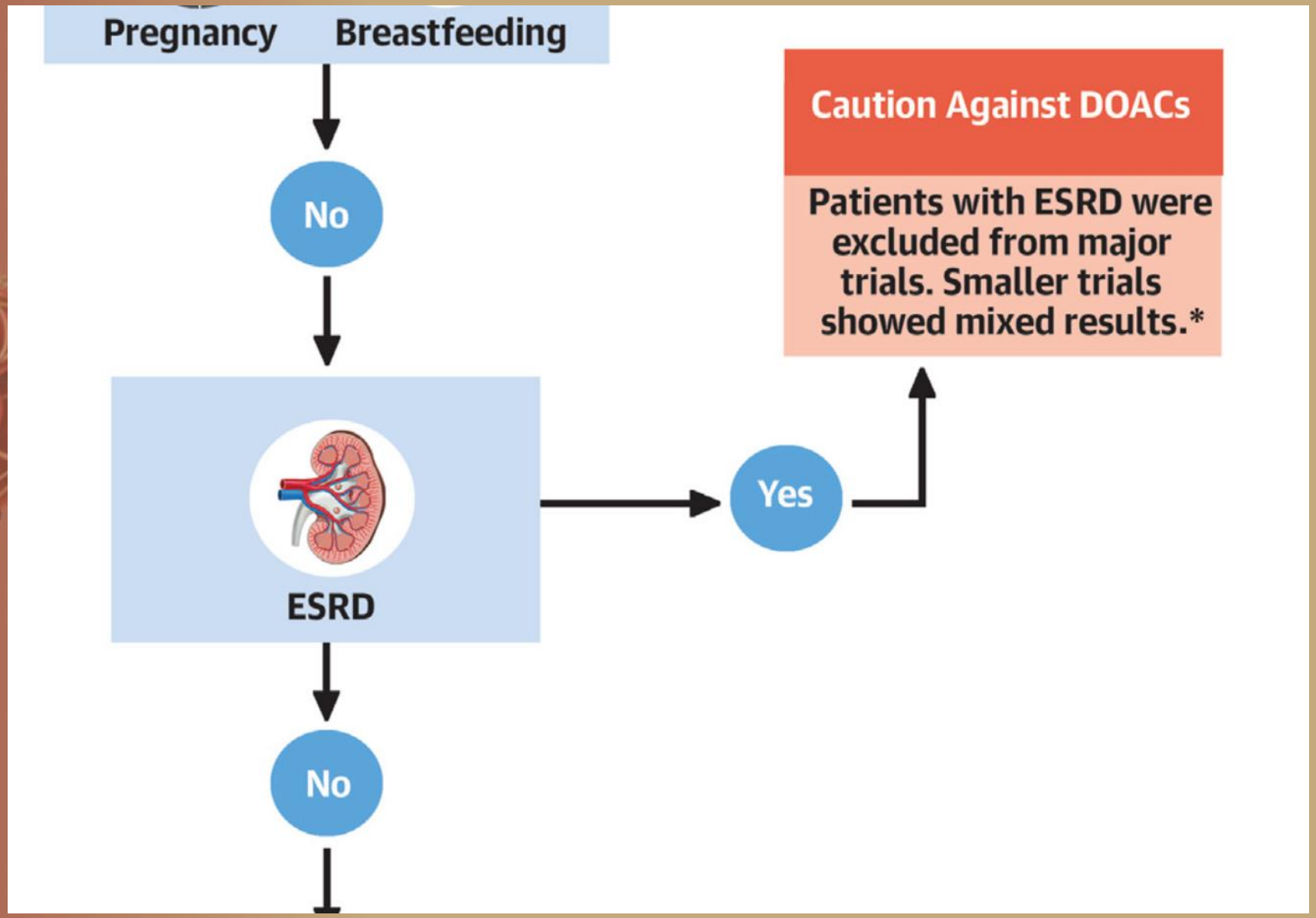
- 47 y/o lady has come to your pharmacy to fill her prescription:

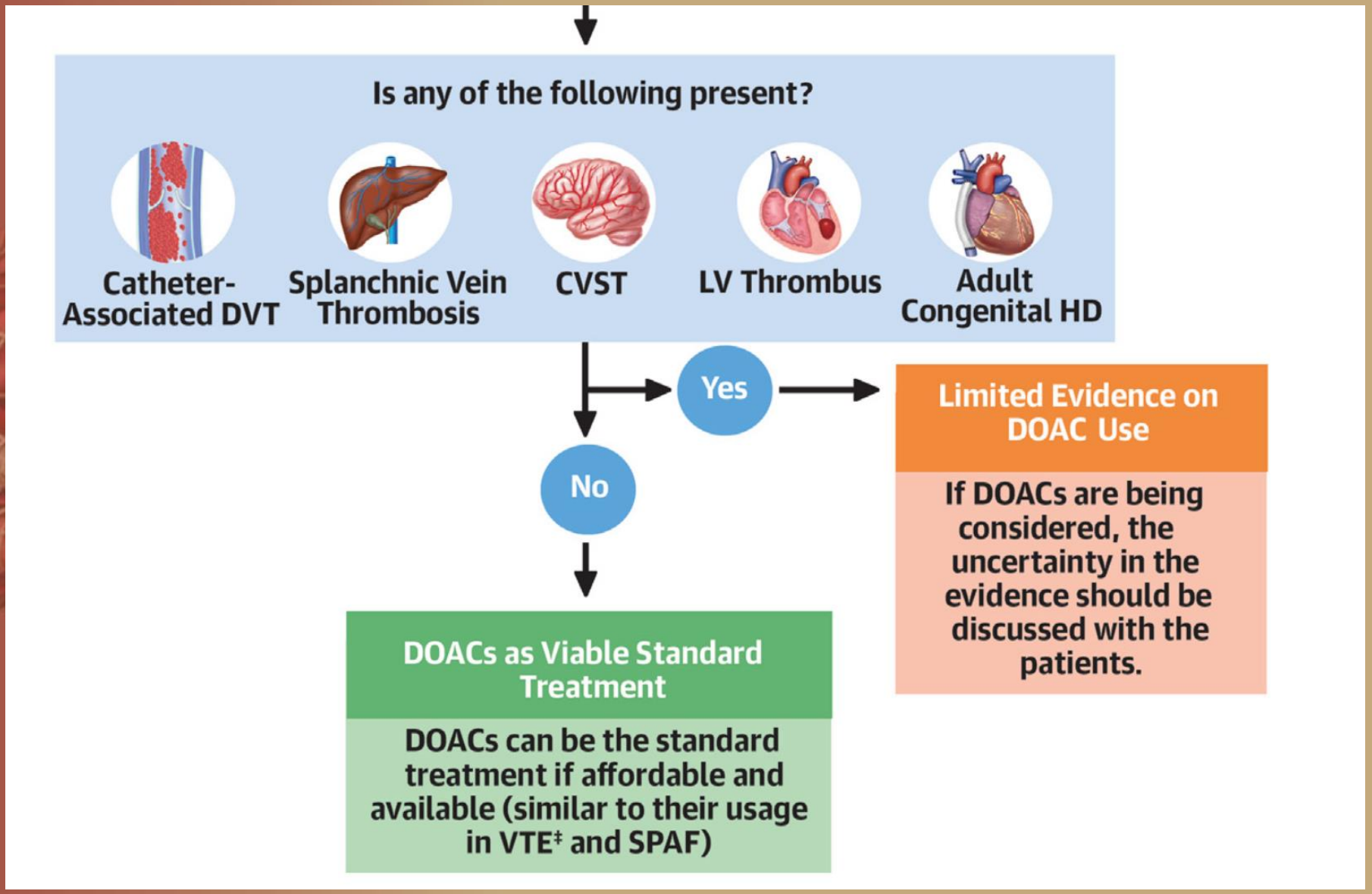
- Tab. Warfarin 5 mg daily
- Tab. Sertraline 50 mg daily
- Tab. Pantoprazole 40 mg daily

- she said: I heard about a blood thinner without necessity of INR monitoring
- What's your recommendation?


Anticoagulation Is Being Considered
Is any of the following present?
Thrombotic APS
Rheumatic AF
Mechanical Heart Valves
LVAD
Yes
Strong Caution Against DOACs
Avoid DOACs; standard treatment is recommended
No
Is any of the following present?
Pregnancy
Breastfeeding
Yes
Caution Against DOACs
Patients with ESRD were excluded from major trials. Smaller trials showed mixed results.*
No
ESRD
Yes
No
Is any of the following present?
Catheter-Associated DVT
Splanchnic Vein Thrombosis
CVST
LV Thrombus
Adult Congenital HD
Yes
Limited Evidence on DOAC Use
If DOACs are being considered, the uncertainty in the evidence should be discussed with the patients.
No
DOACs as Viable Standard Treatment
DOACs can be the standard treatment if affordable and available (similar to their usage in VTE‡ and SPAF)


Is any of the following present?
Thrombotic APS
Rheumatic AF
Mechanical Heart Valves
LVAD
Yes
No
Strong Caution Against DOACs
Avoid DOACs; standard treatment is recommended
Is any of the following present?
Pregnancy
Breastfeeding
Yes


Pregnancy
Breastfeeding
No
ESRD
No
Yes
Caution Against DOACs
Patients with ESRD were excluded from major trials. Smaller trials showed mixed results.*


Is any of the following present?
Catheter-Associated DVT
Splanchnic Vein Thrombosis
CVST
LV Thrombus
Adult Congenital HD
Yes
No
Limited Evidence on DOAC Use
If DOACs are being considered, the uncertainty in the evidence should be discussed with the patients.
DOACs as Viable Standard Treatment
DOACs can be the standard treatment if affordable and available (similar to their usage in VTE‡ and SPAF)

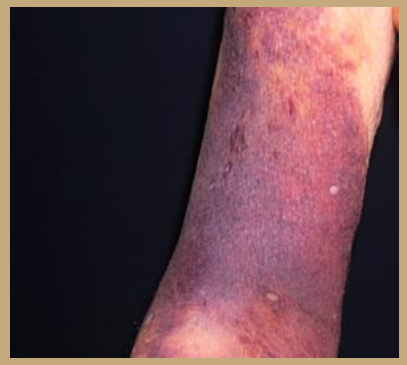
Warfarin

- Vitamin k antagonist
- Tab. 5 mg

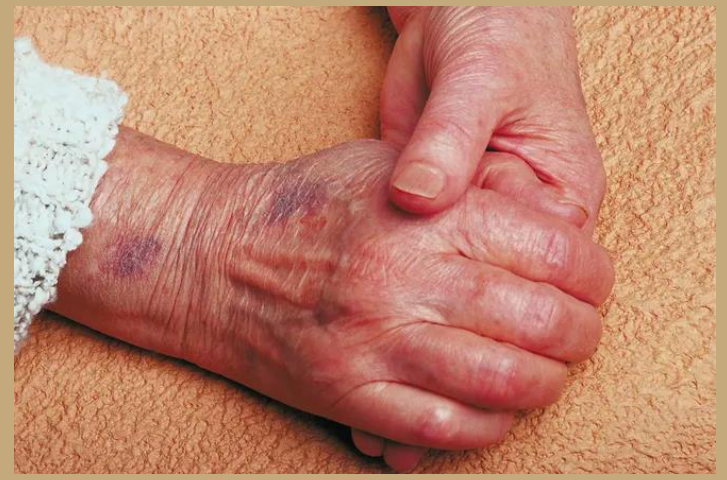
Indication	INR Goal	Minimum Duration
Prophylaxis of VTE (DVT, PE)	2–3	~1–4 weeks depending on patient status and risk factors
Treatment of first VTE with transient risk factors	2–3	3–6 months
First episode of unprovoked VTE	2–3	3–6 months Consider extended treatment if first episode of VTE is PE or proximal DVT with no bleeding risk factors.
Second episode of unprovoked VTE	2–3	Indefinitely
VTE and cancer	2–3	Indefinitely or until cancer resolved[a]
VTE prophylaxis after hip or knee arthroplasty, hip fracture surgery	2–3	Up to 35 days after surgery
AF (persistent or paroxysmal)/atrial flutter	2–3	Long term
Following placement of left atrial appendage occlusion device	2–3	45 days from procedure or until adequate seal of left atrial appendage is confirmed
Any mechanical valve in mitral position	2.5–3.5	Long term
Bileaflet mechanical valve or tilting disk valve in aortic position in sinus rhythm	2–3	Long term
Caged ball valve in aortic position	2.5–3.5	Long term
Mechanical On-X® valve in aortic position	2–3	3 months
	1.5–2	After initial 3 months of therapy
Mechanical aortic heart valves with additional risk factors (AF, previous VTE, LV dysfunction, hypercoagulable conditions)[b]	2.5–3.5	Long term
Bioprosthetic valve in aortic or mitral position[c]	2–3	3 to 6 months
Bioprosthetic valves with additional risk factors (AF, previous VTE, LV dysfunction, hypercoagulable conditions)[d]	2–3	Long term

Monitoring Parameters

- PT
- INR
- CBC



- Bleeding presentations



Kidney and Hepatic impairment

- **No dosage adjustment**
- **Increasing risk of bleeding** in patients with GFR < 60 mL/min, ESKD (HD), hepatic impairment
- CRRT: Avoid use

Warfarin-Drug interactions

Inducers

Decrease INR

Inhibitors

Increase INR

Table 1 Warfarin–drug interactions by drug group

Anti-infectives	Cardiovascular drugs	Analgesics, anti-inflammatories, and immunologics
Potentiation (increase INR)		
Amoxicillin/clavulanate	Acetylsalicylic acid	Acetaminophen
Amoxicillin	**Amiodarone**	Acetylsalicylic acid
Amoxicillin/tranexamic rinse	Atorvastatin	Allopurinol
Azithromycin	Bezafibrate	Celecoxib
Cefamandole	**Clofibrate**	Dextropropoxyphene
Cefazolin	**Diltiazem**	Indomethacin
Chloramphenicol	Disopyramide	Interferon
Ciproflaxacin	Ezetimibe	Leflunomide
Clarithromycin	**Fenofibrate**	Methylprednisolone
Cotrimoxazole	Fluvastatin	Nabumetone
Doxycycline	Gemfibrozil	**Phenybutazone**
Efavirenz	Glucagon	**Piroxicam**
Etravirine	Lovastatin	Sulindac
Erythromycin	Metolazone	Tolmetin
Fluconazole	**Propafenone**	Topical salicylates
Gatifloxacin	**Propranolol**	Tramadol
Isoniazid	Quinidine	
Itraconazole	Rosuvastatin	
Levofloxacin	Simvastatin	
Metronidazole		

Table 1 Warfarin–drug interactions by drug group

Anti-infectives	Cardiovascular drugs	Analgesics, anti-inflammatories, and immunologics
Potentiation (increase INR)		
Miconazole topical gel		
Miconazole vaginal suppositories		
Moxifloxacin		
Nalidixic acid		
Nevirapine		
Norfloxacin		
Ofloxacin		
Ritonavir		
Saquinavir		
Sulfisoxazole		
Terbinafine		
Tetracycline		
Voriconazole		

CNS drugs	GI drugs	Other drugs
Potentiation (increase INR)		
Alcohol (if concomitant liver disease)	**Cimetidine**	Acarbose
Citalopram	**Omeprazole**	**Anabolic steroids**
Choral hydrate	Orlistat	CMF (cyclophosphamide/ methotrexate/fluorouracil)
Disulfiram		Danazol
Duloxetine		Doxifluridine
Entacapone		Etoposide/carboplatin
Felbamate		Fluorouracil
Fluoxetine		Gemcitabine
Fluvoxamine		Ifosphamide
Marijuana		Levamisole/Flurouracil
Methylphenidate		Levonorgestrel
Propoxyphene		Oxolamine
Phenytoin (biphasic with later inhibitor)		Paclitaxel
		Tamoxifen
Quetiapine		Tolterodine
Ropinirole		Trastuzumab
		Zafirlukast
		Zileuton

Common Warfarin Interactions
FAB-Four & G-Supplements

FAB-Four	G-Supplements
Fluconazole	Garlic
Amiodarone	Ginger
Bactrim	Gingko biloba
Flagyl	Ginseng
	Green tea

Increased Bleeding Risk

Monitor INR & Bleeding Symptoms

Table 1 Warfarin–drug interactions by drug group

Anti-infectives	Cardiovascular drugs	Analgesics, anti-inflammatories, and immunologics	CNS drugs	GI drugs	Other drugs
Inhibition (decrease INR)			*Inhibition (decrease INR)*		
Cloxacillin	Bosentan	Azathioprine	**Barbiturates**	Sucrafate	Chelation therapy
Dicloxacillin	**Cholestyramine**	**Mesalamine**	**Carbamazepine**		Cyclosporine
Fosamprenavir	Telmisartan	Sulfasalazine	Chlordiazepoxide		Etretinate
Griseofulvin			Propofol		Influenza vaccine
Lopinavir/ritonavir					Menthol (cough)
Nafcillin					**Mercaptopurine**
Nafcillin/dicloxacillin					Methimazole
Nevirapine					Multivitamin supplement
Ribavirin					Raloxifene hydrochloride
Rifampin					

Supplements with vitamin K

TABLE 37-13 Vitamin K Content of Select Foods[a]

Very High (>200 mcg)	High (100-200 mcg)	Medium (50-100 mcg)	Low (<50 mcg)
Brussel sprouts	Basil	Apple, green	Apple, red
Chickpeas	Broccoli	Asparagus	Avocado
Collard greens	Chive	Cabbage	Beans
Coriander	Coleslaw	Cauliflower	Breads, grains
Endive	Cucumber (with peel)	Mayonnaise	Carrot
Kale	Canola oil	Nuts, pistachio	Cereal
Lettuce, red leaf	Green onion/scallion	Squash, summer	Celery
Parsley	Lettuce, butterhead		Coffee
Spinach	Mustard greens		Corn
Swiss chard	Soybean oil		Cucumber (without peel)
Tea, green			Dairy products
Tea, black			Eggs
Turnip greens			Fruit (varies)
Watercress			Lettuce, iceberg
			Meats, fish, poultry
			Pasta
			Peanuts
			Peas
			Potato
			Rice
			Tomato

[a]Approximate amount of vitamin K per 100 g (3.5 oz) serving.

Table 2. Vitamin K content of selected vegetables.

Description	Common measure	Vitamin K (μg) per measure
Asparagus, frozen, cooked	1 cup	144
Beans, green, cooked	1 cup	20
Beet greens, cooked	1 cup	697
Broccoli, cooked	1 cup	220
Brussels sprouts, cooked	1 cup	219
Cabbage, cooked	1 cup	73
Collards, cooked	1 cup	836
Collards, frozen, cooked	1 cup	1060
Cucumber with peel	1 large	49
Dandelion greens, cooked	1 cup	203
Endive, raw	1 cup	116
Kale, cooked	1 cup	1062
Kale, frozen, cooked	1 cup	1147
Lettuce, butterhead	2 medium leaves	15
Lettuce, iceberg	1 cup	13.3
Mustard greens, cooked	1 cup	419
Okra, frozen, cooked	1 cup	88
Onions, spring or scallions	1 cup	207
Parsley, raw	10 sprigs	164
Peas, green, frozen, cooked	1 cup	38
Rhubarb, frozen	1 cup	71
Soybeans, cooked	1 cup	33
Spinach, canned	1 cup	988
Spinach, raw	1 cup	145
Turnip greens, cooked	1 cup	529
Turnip greens, frozen, cooked	1 cup	851

Table 3. Vitamin K content in commonly used oils.

Type of oil	Vitamin K (μg/100g)*
Peanut	0.65
Corn	2.91
Safflower	9.13
Walnut	15
Sesame	15.5
Olive	55.5
Canola	141
Soybean	193

Herbs (common and Latin name)	Clinical effects	Severity	Reliabilities of evidence	Mechanisms	
				PK	PD
Cranberry *(Vaccinium macrocarpon)*	Potentiation	Major [55]	I	F [52, 53, 160]	D [40]
Soya *(Glycine max* Merr.*)*	Inhibition	Moderate [115, 116]	I	F [113, 114]	B [115]
St John's wort *(Hypericum perforatum)*	Inhibition	Major [121, 122]	I	F [41, 118, 119]	NA
Danshen *(Salvia miltiorrhiza)*	Inhibition	Moderate [133, 134]	I	F, G [131, 132, 135, 136]	A,C [40]
Coenzyme Q10 *(Theobroma cacao)*	Inhibition	Minor [47, 48]	II	NA	B [50]
Chinese angelica *(Angelica sinensis)*	Potentiation	Moderate [126]	II	F [125]	C [40]
Ginger *(Zingiber officinale* Roscoe*)*	Potentiation	Moderate [161]	II	NA	A [162]
Chamomile *(Matricaria recutita)*	Potentiation	Major [44]	III	F [41, 163, 164]	NA
Chitosan *(Swertia chirayita)*	Potentiation	Moderate [46]	III	NA	B [45]
Cannabis *(Cannabis sativa* L*)*	Potentiation	Major [165]	III	F [166]	NA
Devil's claw *(Harpagophytum procumbens)*	Potentiation	Moderate [61]	III	F [60]	NA
Ginkgo *(Ginkgo biloba)*	Potentiation	Major [83]	III	F [75–77]	NA
Garlic *(Allium sativum)*	Potentiation	Major [40]	III	F [167, 168]	A [73, 169]
Ginseng *(Panax quinquefolius/Panax ginseng)*	Inhibition	Moderate [170]	III	F [40]	A [87]
Grapefruit *(Citrus paradise)*	Potentiation	Major [94]	III	F [95]	NA
Green tea *(Camellia sinensis)*	Inhibition	Moderate [97]	III	NA	B [99]
Lycium *(Lycium barbarum)*	Potentiation	Major [139]	III	F [137]	NA
Boldo *(Peumus boldus)*	Potentiation	Minor [36]	IV	NA	C [40]
Echinacea *(Echinacea purpurea)*	Inhibition	Minor [66]	IV	F [119, 171]	NA
Fenugreek *(Trigonella foenum-graecum)*	Potentiation	Minor [36]	IV	NA	B, C [40]
Melilot *(Melilotus officinalis)*	Potentiation	Moderate [102]	IV	NA	C [40]
Parsley *(Petroselinum crispum)*	Potentiation	Moderate [104]	IV	F [103]	B [40]
Pumpkin *(Cucurbita pepo)*	Potentiation	Minor [106]	IV	NA	B [40]
Red clover *(Trifolium pretense)*	Potentiation	Major [108]	IV	F [60, 107]	NA
Saw palmetto *(Serenoa repens)*	Potentiation	Minor [106, 111]	IV	F [109]	NA

Notes. (1) As to mechanisms of herb-warfarin interaction, PD factors including the following: A: interference with platelet function; B: altering gut vitamin K synthesis or containing vitamin K; C: interference with vitamin K cycle; D: interference with coagulation cascade. PK factors including the following: E: interference with warfarin absorption; F: interference with metabolizing enzymes of warfarin; G: interference with protein binding of warfarin. (2) Other nonclinical evidenced herbs defined as doubtful in Section 3 were excluded in this table.

Table 9. Dietary supplements that can affect platelet function and anticoagulant effect.

Agent	Mechanism	Comments
Bladderwrack	Has anticoagulant effects	Increased risk of bleeding or bruising
Boldo	Constituents may have antiplatelet effects	Increased risk of bleeding or bruising
Bromelain	Decreased platelet aggregation	Increased risk of bleeding or bruising
Burdock	Decreased platelet aggregation by inhibiting platelet activation factor	Increased risk of bleeding or bruising
Caffeine	May have antiplatelet activity; not reported in humans	Increased risk of bleeding or bruising; found in black tea, green tea, guarana, mate, oolong tea
Clove	Eugenol has antiplatelet activity	Increased risk of bleeding or bruising
Cod liver oil	May inhibit platelet aggregation	Increased risk of bleeding or bruising; avoid concomitant use
Coltsfoot	May inhibit platelet aggregation	Increased risk of bleeding or bruising; avoid concomitant use
Danshen	Decreased platelet aggregation; may also have antithrombotic effects	Increased risk of bleeding or bruising; avoid concomitant use
Dong quai	May inhibit platelet aggregation	Increased risk of bleeding or bruising
Fenugreek	Constituents may have antiplatelet effects; concentration may not be clinically significant	Increased risk of bleeding or bruising
Fish Oil	Has antiplatelet effects	Increased risk of bleeding or bruising
Flax seed	Decreased platelet aggregation and increased bleeding time	Increased risk of bleeding or bruising
Gamma linolenic acid	Has anticoagulant effects	Found in borage and evening primrose oil, Increased risk of bleeding or bruising
Garlic	Has anticoagulant effects and may inhibit platelet aggregation	Increased risk of bleeding or bruising
Ginger	Inhibit thromboxane synthetase and decrease platelet aggregation	Increased risk of bleeding or bruising
Ginkgo	Decreased platelet aggregation; ginkgolide B, a component of ginkgo, is a potent inhibitor of PAF	Increased risk of bleeding or bruising
Ginseng, panax	Components may decrease platelet aggregation through PAF antagonism; not shown in humans	Increased risk of bleeding or bruising; use with caution until more is known.
Ginseng, Siberian	A component, dihydroxybenzoic acid, may inhibit platelet aggregation	Increased risk of bleeding or bruising
Melatonin	Unknown; might increase the anticoagulant or antiplatelet effect; decreased prothrombin activity observed	Increased risk of bleeding or bruising
Nattokinase	Has thrombolytic activity	Increased risk of bleeding or bruising
Onion	Decreased platelet aggregation	Increased risk of bleeding or bruising
Pantethine	Decreased platelet aggregation	Increased risk of bleeding or bruising
Policosanol	Inhibits platelet aggregation	Increased risk of bleeding or bruising
Poplar	Contains salicylates and may cause decreased platelet aggregation	Increased risk of bleeding or bruising
Resveratrol	Has antiplatelet effects	Increased risk of bleeding or bruising
Sea buckthorn	Inhibits platelet aggregation	Increased risk of bleeding or bruising
Turmeric	Decreased platelet aggregation; has antiplatelet effects	Increased risk of bleeding or bruising
Vinpocetine	Has antiplatelet effects	Increased risk of bleeding or bruising
Vitamin E	Inhibits platelet aggregation and antagonises the effects of vitamin K-dependent clotting factors	Dose-dependent and significant with doses > 800 units/day. Advise patients to avoid high doses of vitamin E; increased risk of bleeding or bruising.
Willow bark	Decreased platelet aggregation; has antiplatelet effects, but less than aspirin	Increased risk of bleeding or bruising

Pregnancy

- In first trimester with a dose ≦ 5 mg
- Discontinuation of warfarin at least 1 week prior delivery

TABLE 28 **Anticoagulation Strategies During Pregnancy.**

Antenatal Options

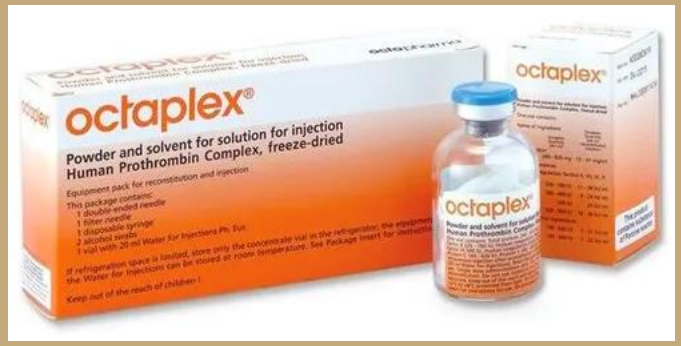
	Method 1	Method 2	Method 3	Alternative Method 4
First trimester	Warfarin ≤5 mg	LMWH	UFH	LMWH
Second trimester	Warfarin	Warfarin	Warfarin	LMWH
Third trimester	Warfarin	Warfarin	Warfarin	LMWH

Delivery Planning

	Method 1	Method 2
1 wk before	Discontinue warfarin → continuous IV UFH	Dose-adjusted LMWH
36 h before	Continuous IV UFH	Switch to continuous IV UFH
4-6 h before	Stop IV heparin	Stop IV heparin

Antidote

- Vitamin K (PO, IV)
- FFP
- PCC



Direct Oral Anticoagulants (DOACs)

- **Direct Thrombin Inhibitors:**
  - **Dabigatran**

- **Factor Xa Inhibitors:**
  - **Rivaroxaban, Apixaban**, Edoxaban, Betrixaban

Case 2

- 53 y/o gentleman has come to your pharmacy to fill his prescription:

- Tab. Rivaroxaban 20 mg daily
- Tab. Bisoprolol 5 mg daily
- Tab. Telmisartan 40 mg daily
- Tab. Rosuvastatin 20 mg daily

- He wants to go to dentistry for dental extraction and he asked when he should discontinue his blood thinner?
- What's your recommendation?

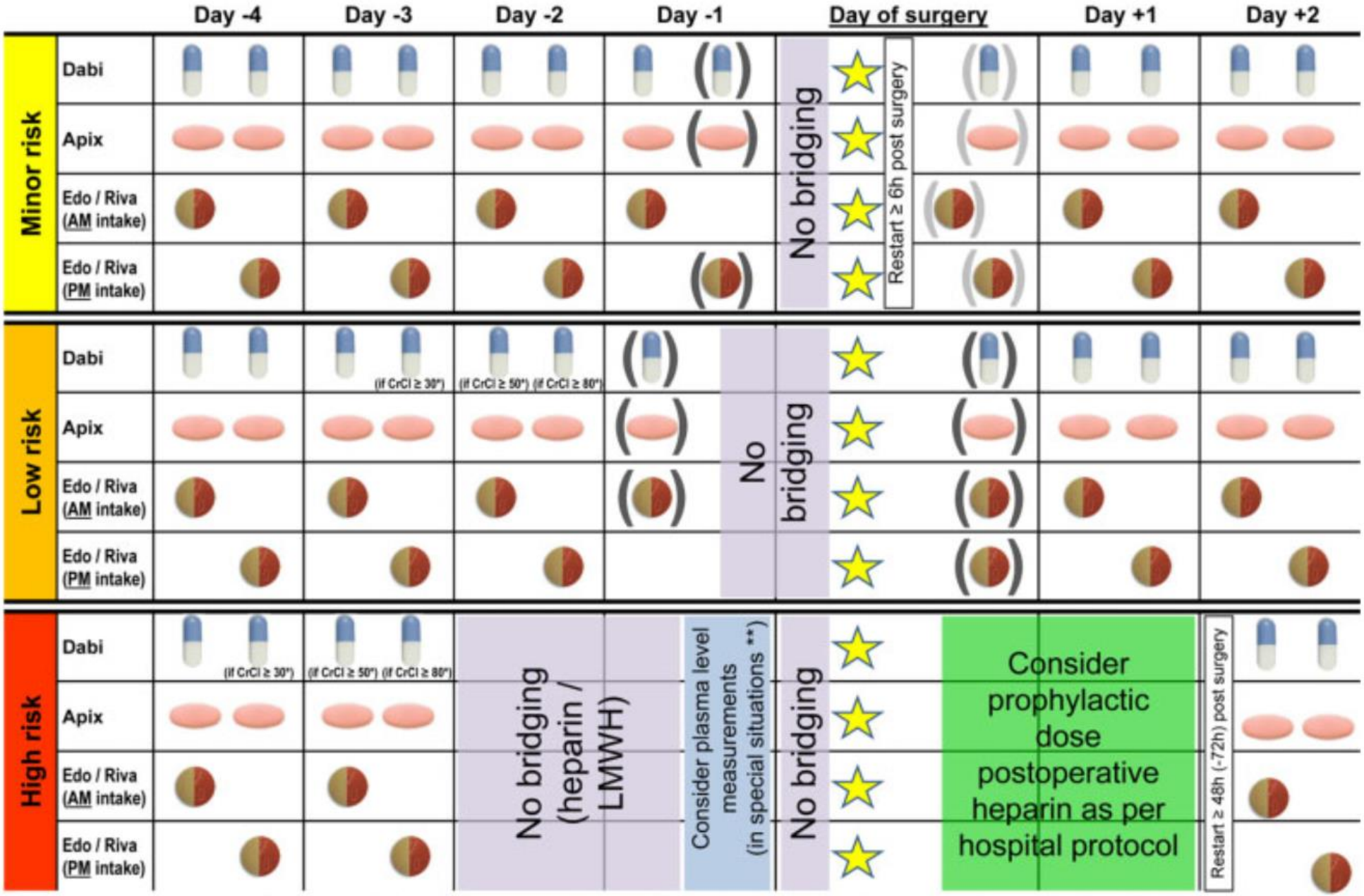
Table 12 Classification of elective surgical interventions according to bleeding risk

Minor risk interventions (i.e. infrequent bleeding and with low clinical impact)
Dental extractions (1–3 teeth), paradontal surgery, implant positioning, subgingival scalling/cleaning
Cataract or glaucoma intervention
Endoscopy without biopsy or resection
Superficial surgery (e.g. abscess incision; small dermatologic excisions, skin biopsy)
Pacemaker or ICD implantation (except complex procedures)
Electrophysiological study or catheter ablation (except complex procedures)
Routine elective coronary/peripheral artery intervention (except complex procedures)
Intramuscular injection (e.g. vaccination)
Low-risk interventions (i.e. infrequent bleeding or with non-severe clinical impact)
Complex dental procedures
Endoscopy with simple biopsy
Small orthopaedic surgery (foot, hand, arthroscopy, . . .)
High-risk interventions (i.e. frequent bleeding and/or with important clinical impact)
Cardiac surgery
Peripheral arterial revascularization surgery (e.g. aortic aneurysm repair, vascular bypass)
Complex invasive cardiological interventions, including lead extraction, (epicardial) VT ablation, chronic total occlusion PCI etc.
Neurosurgery
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Complex endoscopy (e.g. multiple/large polypectomy, ERCP with sphincterotomy etc.)
Abdominal surgery (incl. liver biopsy)
Thoracic surgery
Major urologic surgery/biopsy (incl. kidney)
Extracorporeal shockwave lithotripsy
Major orthopaedic surgery

	Dabigatran		Apixaban - Edoxaban - Rivaroxaban	
No perioperative bridging with LMWH / UFH				
Minor risk procedures: - Perform procedure at NOAC trough level (i.e., 12 h / 24 h after last intake). - Resume same day or latest next day.				
	Low risk	**High risk**	**Low risk**	**High risk**
CrCl ≥80 ml/min	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
CrCl 50-79 ml/min	**≥ 36 h**	**≥ 72 h**		
CrCl 30-49 ml/min	**≥ 48 h**	**≥ 96 h**		
CrCl 15-29 ml/min	Not indicated	Not indicated	**≥ 36 h**	
CrCl <15 ml/min	No official indication for use			

Important:

- Timing of interruption may require adaptation based on individual patient characteristics (Fig. 13)
- In patients / situations with risk of NOAC accumulation (renal insufficiency, older age, concomitant medication, see Fig. 6) pausing the NOAC 12-24 hours earlier may be considered.[207,208]
- Resume full dose of NOAC 24h after low-risk- and 48 (-72) h after high-risk interventions



Important: Timing of interruption may require adaptation based on individual patient characteristics (Fig. 13)

Dabigatran

DTI

Pradaxa®

- Cap. 75 mg
- Cap. 110 mg
- Cap. 150 mg

Dabigatran

Administration

- **Twice daily**
- **With a full glass of water without regard meals**
- If dyspepsia occurs, consider administration with meals

- Do not break, chew, or open capsules

Dabigatran

Indications

VTE prophylaxis and treatment

AF

HIT

Dabigatran	Stroke prevention in NVAF	CrCl >30 mL/minute: 150 mg bid CrCl 30–50 mL/minute: decrease to 75 mg bid or avoid if on P-gp inhibitor CrCl 15–30 mL/minute: 75 mg bid or avoid if on P-gp inhibitor CrCl <15 mL/minute or on dialysis: contraindicated
	Treatment of DVT and PE	CrCl >30 mL/minute: LMWH or UFH × 5–10 days, then dabigatran 150 mg bid CrCl <50 mL/minute and on P-gp inhibitor: avoid coadministration CrCl ≤30 mL/minute or on dialysis: dosing recommendations cannot be provided.
	Prevention of recurrent DVT and PE	(CrCL >30 mL/minute): 150 mg bid
	Prevention of VTE after total hip replacement	(CrCl >30 mL/minute): 110 mg × 1 day, then 220 mg daily

Stroke prevention in atrial fibrillation (SPAF)

	Standard dose	Comments/dose reduction
Apixaban[47]	5 mg BID	2.5 mg BID if two out of three fulfilled: weight ≤60 kg, age ≥80 years, serum creatinine ≥133 µmol/L (1.5 mg/dL) (*or* single criterion: if CrCl 15–29 mL/min)
Dabigatran[48]	150 mg BID/110 mg BID	No pre-specified dose-reduction criteria in phase III trial[a]
Edoxaban[49]	60 mg QD	30 mg QD if: weight ≤60 kg *or* CrCl 15–49 mL/min *or* concomitant therapy with strong P-Gp inhibitor (see 'Pharmacokinetics and drug-drug interactions of NOACs' section)
Rivaroxaban[46]	20 mg QD	15 mg QD if CrCl ≤15–49 mL/min

'SmPc' refers to European SmPc.
BID, twice daily; CrCl, creatinine clearance; GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant; QD, once daily.
[a]SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding.

NOAC dosing in AF patients post-ACS/PCI (see 'Patients with atrial fibrillation and coronary artery disease' section)

	Standard dose	Comments/dose reduction
Apixaban[244]	5 mg BID	Dose reduction as for SPAF
Dabigatran[247]	150 mg BID or 110 mg BID	110mg as for SPAF[403]
Edoxaban[245]	60 mg QD	Dose reduction as for SPAF
Rivaroxaban[246]	15 mg QD	Dose reduction to 10 mg QD if CrCl 30–49 mL/min

In addition to single/dual antiplatelet therapy, where applicable. See 'Patients with atrial fibrillation and coronary artery disease' section for details.
BID, twice daily; CrCl, creatinine clearance; QD, once daily; SPAF, stroke prevention in atrial fibrillation.

Treatment of DVT/PE

	Initial therapy	Remainder of treatment phase
Apixaban[498]	10 mg BID, 7 days	5 mg BID, no dose reduction
Dabigatran[499]	Heparin/LMWH	150 mg BID, no dose reduction[a]
Edoxaban[500]	Heparin/LMWH	60 mg QD, same dose reduction as for SPAF (see above)
Rivaroxaban[501,502]	15 mg BID, 21 days	20 mg QD, no dose reduction[b]

BID, twice daily; GI, gastrointestinal; LMWH, low molecular weight heparin; QD, once daily; SPAF, stroke prevention in atrial fibrillation.
[a]Per SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding [based on pharmacokinetic/pharmacodynamic (PK/PD) analyses; not studied in this setting].
[b]Per SmPc: 15 mg if risk of bleeding outweighs risk for recurrent DVT and PE (based on PK/PD analyses; not studied in this setting).

Long-term prevention of recurrent DVT/PE

	Standard dose	Comments/dose adjustment
Apixaban[503]	2.5 mg BID	
Dabigatran[504]	150 mg BID	No pre-specified dose-reduction criteria in clinical trial[a]
Edoxaban[473,500,505]	60 mg QD[b]	
Rivaroxaban[506]	10 mg QD	[c]

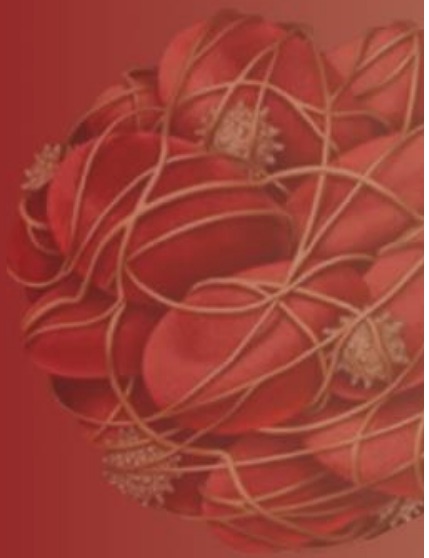
BID, twice daily; QD, once daily.
[a]SmPC: 110 mg BID if age ≥80 years, concomitant verapamil (both based on pharmacokinetics/pharmacodynamics analyses; not studied in this setting).
[b]Not specifically studied, follow-up data available up to 12 months in phase III trial.
[c]SmPc: 20 mg QD in patients at high risk of recurrence.

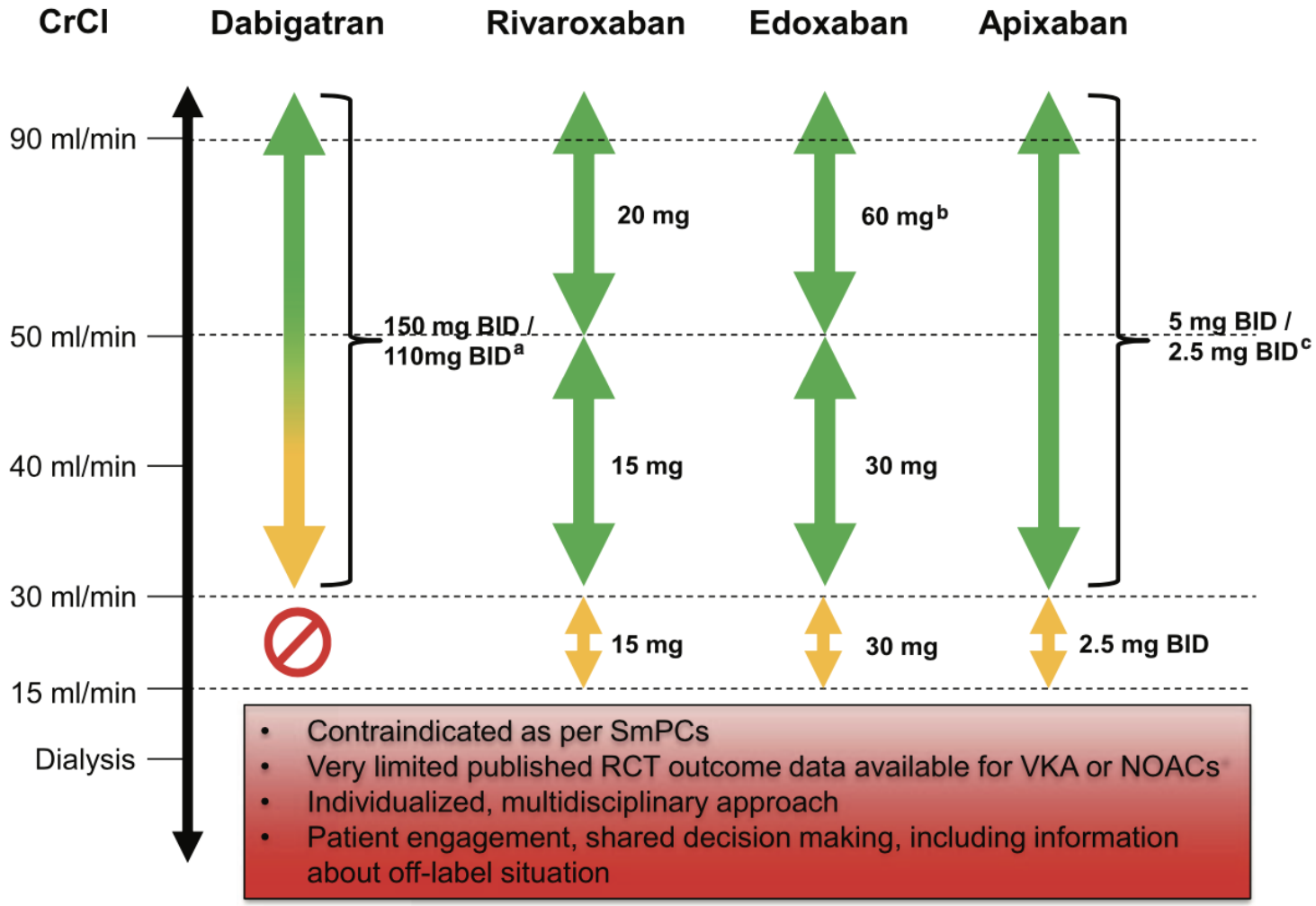
VTE prevention post-major orthopaedic surgery

	Standard dose	Comments/dose reduction
Apixaban[507]	2.5 mg BID	
Dabigatran[508,509]	220 mg QD/150 mg QD	[a]
Edoxaban[510,511]	30 mg QD	Not approved in Europe (only studied in Asia)
Rivaroxaban[512–515]	10 mg QD	

BID, twice daily; QD, once daily.

[a]SmPc: 1× 150 mg if CrCl 30–50 mL/min; concomitant verapamil, amiodarone, quinidine; age >75 years.




CrCl
Dabigatran
Rivaroxaban
Edoxaban
Apixaban
90 ml/min
50 ml/min
40 ml/min
30 ml/min
15 ml/min
Dialysis
150 mg BID / 110mg BID[a]
20 mg
60 mg[b]
5 mg BID / 2.5 mg BID[c]
15 mg
30 mg
15 mg
30 mg
2.5 mg BID
• Contraindicated as per SmPCs
• Very limited published RCT outcome data available for VKA or NOACs
• Individualized, multidisciplinary approach
• Patient engagement, shared decision making, including information about off-label situation

Reversal Agents or Methods

- Idarucizumab
- Dialysis
- PCC

Rivaroxaban

- **Xa inhibitors**

- **Dosage forms:**

Tablet 2.5, 10, 15, 20 mg

Rivaroxaban

Xarelto

Xalerban

Axabin

Clotover

Prexaban

Rivadax

Rixan

Xarivan

Xarexa

Rivix

Xeraltin

Clotox

Zabita

Unclot-IH

Rivalban

Rivaroxaban

- **Indications:**

VTE prophylaxis and treatment

AF

HIT

CAD (2.5 mg tablets)

Rivaroxaban

Administration

- **Once daily or Twice daily**
- **2.5 and 10 mg tablets: with or without food**
- **15 and 20 mg tablets: must use with food**
- **For patients who cannot swallow whole tablets the tablets may be crushed and mixed with applesauce immediately prior to use**

Rivaroxaban-Enteral feeding

1. Tablets may be crushed and mixed in 50 ml of water

2. Administer the suspension within 4 hours of preparation

3. Follow administration of the 15 mg and 20 mg tablets immediately with enteral feeding (2.5 mg and 10 mg tablets may be administered without regard to food)

4. Avoid administration distal to the stomach

Rivaroxaban	Stroke prevention in NVAF	Dosed with evening meal: CrCl >50 mL/minute: 20 mg daily CrCl 15–50 mL/minute: 15 mg daily CrCl <15 mL/minute: avoid
	Treatment of DVT and PE	CrCl ≥30 mL/minute: 15 mg bid × 21 days, then 20 mg daily CrCl <30 mL/minute: avoid
	Prevention of recurrent DVT and PE	10 mg daily
	Prevention of VTE after TKR and THR	10 mg daily for 12 days (TKR) or 35 days (THR)
	Prevention of VTE in hospitalized acutely ill medical patients	10 mg daily in hospital and after hospital discharge for total duration of 31–39 days
	Prevention of MACE in patients with chronic CAD or PAD	2.5 mg bid in combination with aspirin (75–100 mg) daily

Stroke prevention in atrial fibrillation (SPAF)

	Standard dose	Comments/dose reduction
Apixaban[47]	5 mg BID	2.5 mg BID if two out of three fulfilled: weight ≤60 kg, age ≥80 years, serum creatinine ≥133 µmol/L (1.5 mg/dL) (*or* single criterion: if CrCl 15–29 mL/min)
Dabigatran[48]	150 mg BID/110 mg BID	No pre-specified dose-reduction criteria in phase III trial[a]
Edoxaban[49]	60 mg QD	30 mg QD if: weight ≤60 kg *or* CrCl 15–49 mL/min *or* concomitant therapy with strong P-Gp inhibitor (see 'Pharmacokinetics and drug-drug interactions of NOACs' section)
Rivaroxaban[46]	20 mg QD	15 mg QD if CrCl ≤15–49 mL/min

'SmPc' refers to European SmPc.
BID, twice daily; CrCl, creatinine clearance; GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant; QD, once daily.
[a]SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding.

NOAC dosing in AF patients post-ACS/PCI (see 'Patients with atrial fibrillation and coronary artery disease' section)

	Standard dose	Comments/dose reduction
Apixaban[244]	5 mg BID	Dose reduction as for SPAF
Dabigatran[247]	150 mg BID or 110 mg BID	110mg as for SPAF[403]
Edoxaban[245]	60 mg QD	Dose reduction as for SPAF
Rivaroxaban[246]	15 mg QD	Dose reduction to 10 mg QD if CrCl 30–49 mL/min

In addition to single/dual antiplatelet therapy, where applicable. See 'Patients with atrial fibrillation and coronary artery disease' section for details.
BID, twice daily; CrCl, creatinine clearance; QD, once daily; SPAF, stroke prevention in atrial fibrillation.

Treatment of DVT/PE

	Initial therapy	Remainder of treatment phase
Apixaban[498]	10 mg BID, 7 days	5 mg BID, no dose reduction
Dabigatran[499]	Heparin/LMWH	150 mg BID, no dose reduction[a]
Edoxaban[500]	Heparin/LMWH	60 mg QD, same dose reduction as for SPAF (see above)
Rivaroxaban[501,502]	15 mg BID, 21 days	20 mg QD, no dose reduction[b]

BID, twice daily; GI, gastrointestinal; LMWH, low molecular weight heparin; QD, once daily; SPAF, stroke prevention in atrial fibrillation.
[a]Per SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding [based on pharmacokinetic/pharmacodynamic (PK/PD) analyses; not studied in this setting].
[b]Per SmPc: 15 mg if risk of bleeding outweighs risk for recurrent DVT and PE (based on PK/PD analyses; not studied in this setting).

Long-term prevention of recurrent DVT/PE

	Standard dose	Comments/dose adjustment
Apixaban[503]	2.5 mg BID	
Dabigatran[504]	150 mg BID	No pre-specified dose-reduction criteria in clinical trial[a]
Edoxaban[473,500,505]	60 mg QD[b]	
Rivaroxaban[506]	10 mg QD	[c]

BID, twice daily; QD, once daily.
[a]SmPC: 110 mg BID if age ≥80 years, concomitant verapamil (both based on pharmacokinetics/pharmacodynamics analyses; not studied in this setting).
[b]Not specifically studied, follow-up data available up to 12 months in phase III trial.
[c]SmPc: 20 mg QD in patients at high risk of recurrence.

VTE prevention post-major orthopaedic surgery

	Standard dose	Comments/dose reduction
Apixaban[507]	2.5 mg BID	
Dabigatran[508,509]	220 mg QD/150 mg QD	[a]
Edoxaban[510,511]	30 mg QD	Not approved in Europe (only studied in Asia)
Rivaroxaban[512–515]	10 mg QD	

BID, twice daily; QD, once daily.

[a]SmPc: 1× 150 mg if CrCl 30–50 mL/min; concomitant verapamil, amiodarone, quinidine; age >75 years.

Secondary prevention of atherothrombotic events post-ACS in patients without AF (i.e. no OAC indication)

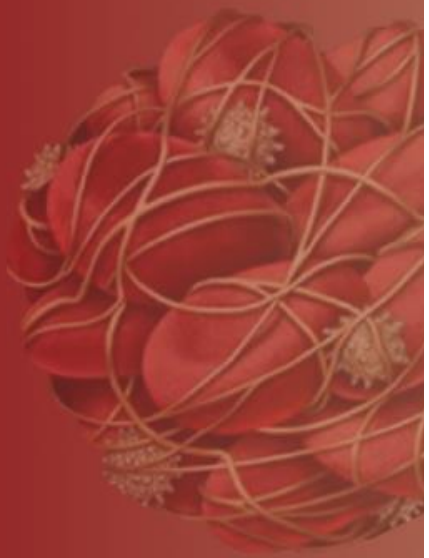
	Standard dose	Comments/dose reduction
Rivaroxaban[115]	2.5 mg BID	In addition to aspirin ± P2Y12 inhibitor

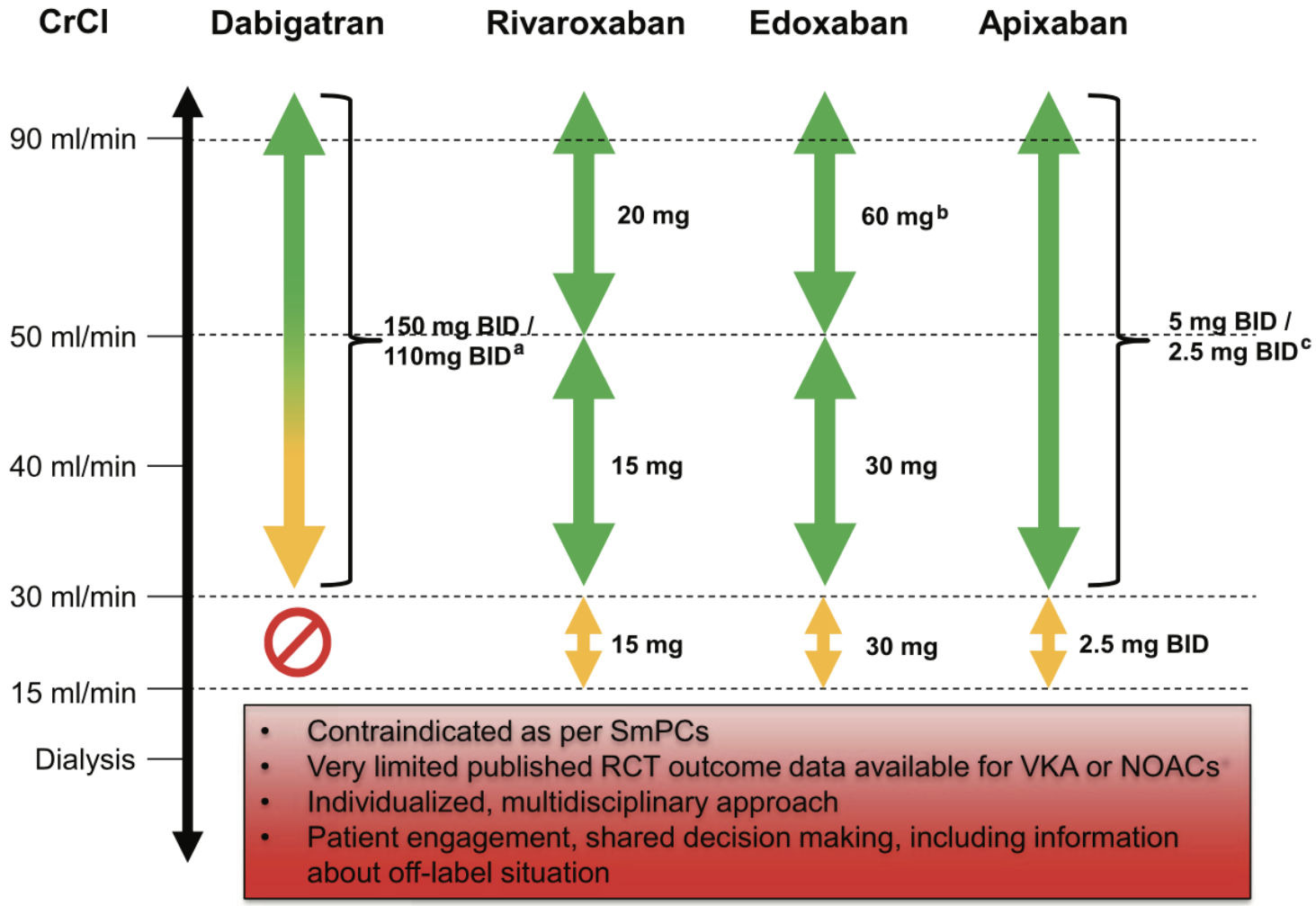
BID, twice daily.

Secondary prevention of atherothrombotic events in patients with chronic coronary syndrome and/or symptomatic peripheral artery disease patients without AF (i.e. no OAC indication)

	Standard dose	Comments/dose reduction
Rivaroxaban[516]	2.5 mg BID	In addition to aspirin

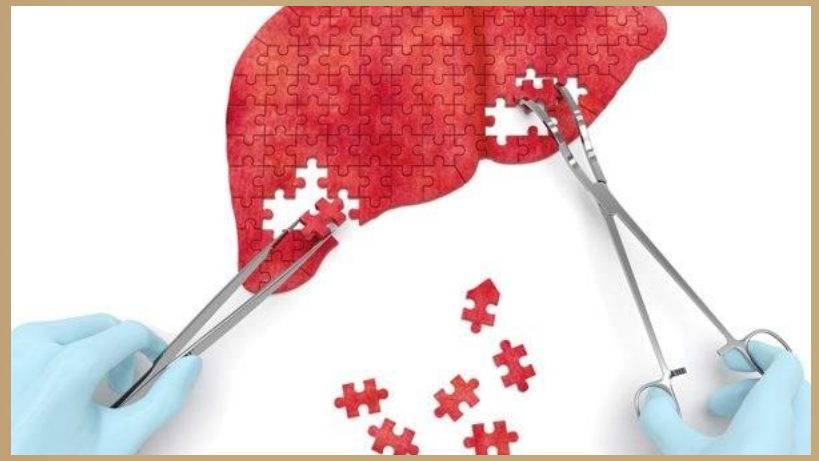
AF, atrial fibrillation; BID, twice daily; OAC, oral anticoagulation.




CrCl
Dabigatran
Rivaroxaban
Edoxaban
Apixaban
90 ml/min
50 ml/min
40 ml/min
30 ml/min
15 ml/min
Dialysis
150 mg BID / 110mg BID[a]
20 mg
60 mg[b]
5 mg BID / 2.5 mg BID[c]
15 mg
30 mg
15 mg
30 mg
2.5 mg BID
• Contraindicated as per SmPCs
• Very limited published RCT outcome data available for VKA or NOACs
• Individualized, multidisciplinary approach
• Patient engagement, shared decision making, including information about off-label situation

Hepatic impairment

- **Moderate to severe hepatic impairment**



Reversal Agents

- Andexanet alfa
- PCC

Apixaban

- **Xa inhibitors**

Tab. 2.5 mg

Tab. 5 mg

Apixaban

- **Brand names:**

Eliquis

Elaquit

Apirax

Xabano

Apiraban

Apixaban

- **Indications:**

VTE prophylaxis and treatment

AF

HIT

Apixaban

Administration

- **Twice daily**
- **With or without food**
- **If patient unable to swallow whole tablets, may crush 5 mg or 2.5 mg tablets and suspend in 60 mL of water, D5W, or apple juice or mix with applesauce; administer immediately**

Apixaban-Enteral feeding

1. For delivery through a nasogastric tube, crushed tablets may be suspended in 60 mL of water or D5W followed by immediate delivery.

2. Crushed tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours

3. Flush the feeding tube after this drug is given

Apixaban	Stroke prevention in NVAF	Most patients: 5 mg bid Any two of the following: 2.5 mg bid: SCr ≥1.5 mg/dL Age ≥80 years Weight ≤132.28 pounds (60 kg)
	Treatment of DVT and PE	10 mg bid × 7 days, then 5 mg bid No dose adjustment is recommended for renal function.[a] Strong dual inhibitors of CYP3A4 and P-gp: reduce dose by 50% or avoid coadministration. Dual P-gp inducers and strong CYP3A4 inducers: Avoid concomitant use.
	Prevention of recurrent DVT and PE	2.5 mg bid
	Prevention of VTE after TKR and THR	2.5 mg bid for 12 days (TKR) or 35 days (THR)

Stroke prevention in atrial fibrillation (SPAF)

	Standard dose	Comments/dose reduction
Apixaban[47]	5 mg BID	2.5 mg BID if two out of three fulfilled: weight ≤60 kg, age ≥80 years, serum creatinine ≥133 µmol/L (1.5 mg/dL) (*or* single criterion: if CrCl 15–29 mL/min)
Dabigatran[48]	150 mg BID/110 mg BID	No pre-specified dose-reduction criteria in phase III trial[a]
Edoxaban[49]	60 mg QD	30 mg QD if: weight ≤60 kg *or* CrCl 15–49 mL/min *or* concomitant therapy with strong P-Gp inhibitor (see 'Pharmacokinetics and drug-drug interactions of NOACs' section)
Rivaroxaban[46]	20 mg QD	15 mg QD if CrCl ≤15–49 mL/min

'SmPc' refers to European SmPc.
BID, twice daily; CrCl, creatinine clearance; GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant; QD, once daily.
[a]SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding.

NOAC dosing in AF patients post-ACS/PCI (see 'Patients with atrial fibrillation and coronary artery disease' section)

	Standard dose	Comments/dose reduction
Apixaban[244]	5 mg BID	Dose reduction as for SPAF
Dabigatran[247]	150 mg BID or 110 mg BID	110mg as for SPAF[403]
Edoxaban[245]	60 mg QD	Dose reduction as for SPAF
Rivaroxaban[246]	15 mg QD	Dose reduction to 10 mg QD if CrCl 30–49 mL/min

In addition to single/dual antiplatelet therapy, where applicable. See 'Patients with atrial fibrillation and coronary artery disease' section for details.
BID, twice daily; CrCl, creatinine clearance; QD, once daily; SPAF, stroke prevention in atrial fibrillation.

Treatment of DVT/PE

	Initial therapy	Remainder of treatment phase
Apixaban[498]	10 mg BID, 7 days	5 mg BID, no dose reduction
Dabigatran[499]	Heparin/LMWH	150 mg BID, no dose reduction[a]
Edoxaban[500]	Heparin/LMWH	60 mg QD, same dose reduction as for SPAF (see above)
Rivaroxaban[501,502]	15 mg BID, 21 days	20 mg QD, no dose reduction[b]

BID, twice daily; GI, gastrointestinal; LMWH, low molecular weight heparin; QD, once daily; SPAF, stroke prevention in atrial fibrillation.
[a]Per SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding [based on pharmacokinetic/pharmacodynamic (PK/PD) analyses; not studied in this setting].
[b]Per SmPc: 15 mg if risk of bleeding outweighs risk for recurrent DVT and PE (based on PK/PD analyses; not studied in this setting).

Long-term prevention of recurrent DVT/PE

	Standard dose	Comments/dose adjustment
Apixaban[503]	2.5 mg BID	
Dabigatran[504]	150 mg BID	No pre-specified dose-reduction criteria in clinical trial[a]
Edoxaban[473,500,505]	60 mg QD[b]	
Rivaroxaban[506]	10 mg QD	[c]

BID, twice daily; QD, once daily.
[a]SmPC: 110 mg BID if age ≥80 years, concomitant verapamil (both based on pharmacokinetics/pharmacodynamics analyses; not studied in this setting).
[b]Not specifically studied, follow-up data available up to 12 months in phase III trial.
[c]SmPc: 20 mg QD in patients at high risk of recurrence.

VTE prevention post-major orthopaedic surgery

	Standard dose	Comments/dose reduction
Apixaban[507]	2.5 mg BID	
Dabigatran[508,509]	220 mg QD/150 mg QD	[a]
Edoxaban[510,511]	30 mg QD	Not approved in Europe (only studied in Asia)
Rivaroxaban[512–515]	10 mg QD	

BID, twice daily; QD, once daily.

[a]SmPc: 1× 150 mg if CrCl 30–50 mL/min; concomitant verapamil, amiodarone, quinidine; age >75 years.

Apixaban can be used in patients under hemodialysis

Rivaroxaban may also be an alternative in patients under HD

Reversal Agents

- Andexanet alfa
- PCC

Class	VKA	Direct Thrombin Inhibitor	Factor Xa Inhibitor					
Name	**Warfarin**	**Dabigatran**	**Rivaroxaban**		**Apixaban**		**Edoxaban**	
Metabolism	S-isomer: CYP2C9 R-isomer: CYP1A2, CYP2C19, CYP3A4	Minimal	CYP3A4/5		CYP3A4		Minimal CYP3A4	
P-glycoprotein substrate	No	Yes	Yes		Yes		Yes	
Excretion	0% renal; very little warfarin excreted unchanged in urine	80% renal	66% renal, 28% feces		27% renal, 73% biliary and intestinal		50% renal, 50% liver and biliary/intestinal	
Half-life	20-60 h	12-17 h	5-9 h		12 h		10-14 h	
Renal dosing adjustment based on actual body weight	N/A	CrCl >30 mL/min	150 mg twice daily	CrCl >50 mL/min	20 mg daily with the biggest meal*	5 mg twice daily	CrCl >50-≤95 mL/ min	60 mg once daily
		CrCl 15-30 mL/ min	75 mg twice daily	CrCl 15-50 mL/min	15 mg daily with the biggest meal*	If any 2 of the following: age ≥80y, body weight ≤60 kg, SCr ≥1.5 mg/dL	2.5 mg twice daily	CrCl 15-50 mL/min	30 mg once daily

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

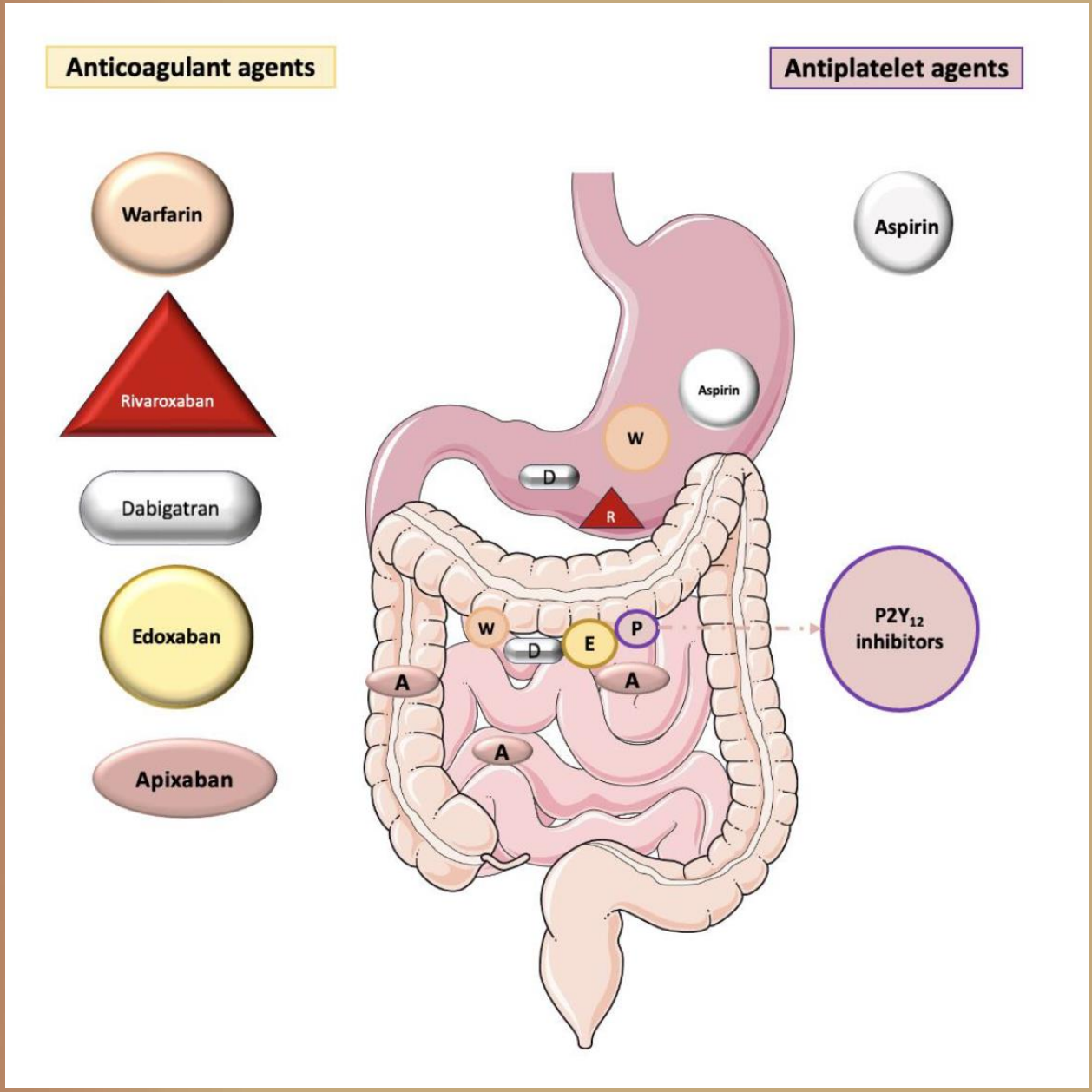
NOAC Use recommendations in liver disease

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

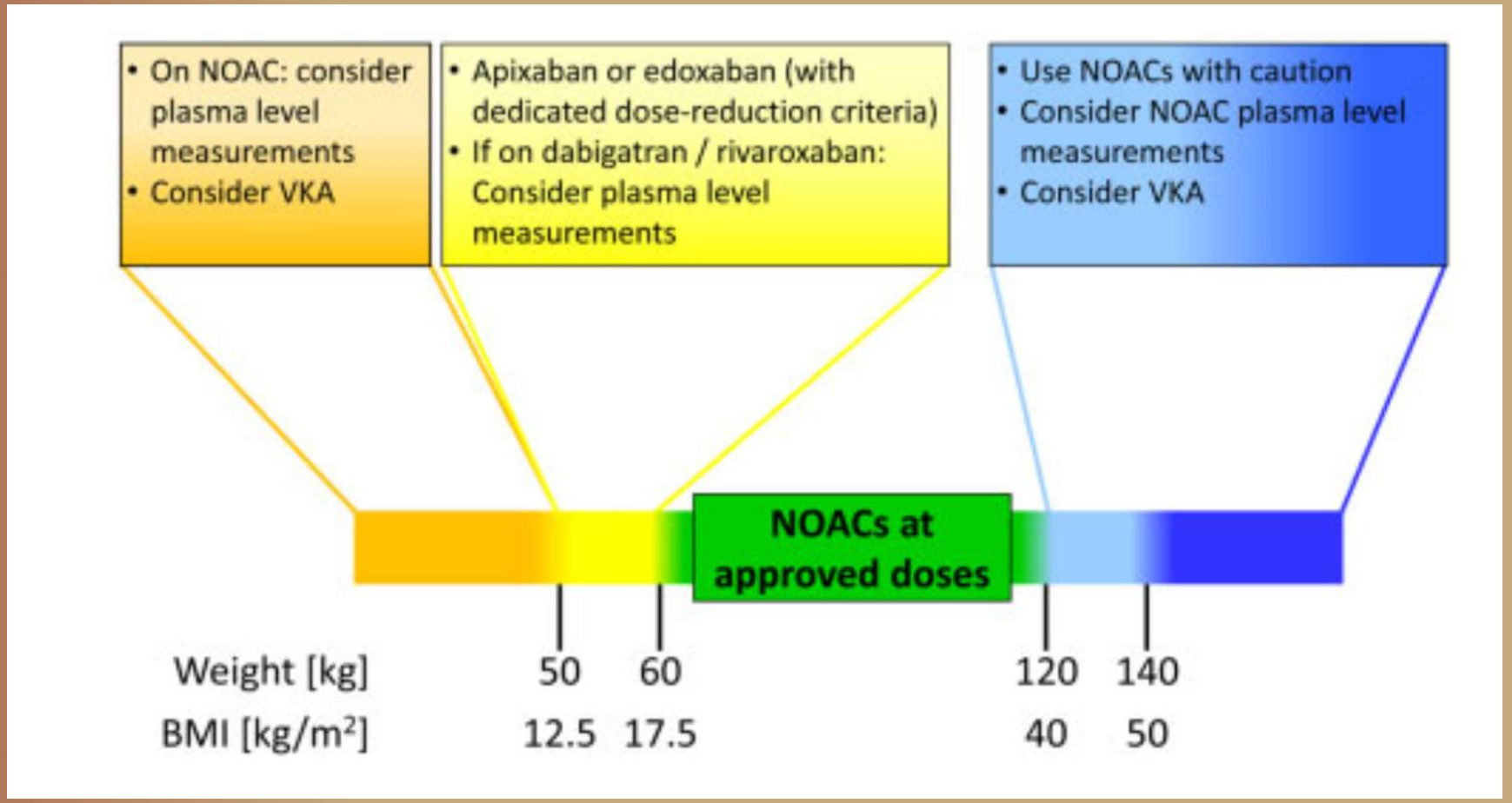
- ✓ Assess Child-Pugh score
- ✓ Check NOAC use recommendations in liver disease
- ✓ Check for drug-drug interactions
- ✓ Discuss in multidisciplinary team

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


Anticoagulant agents
Antiplatelet agents
Warfarin
Rivaroxaban
Dabigatran
Edoxaban
Apixaban
Aspirin
Aspirin
W
D
R
W
D
E
P
A
A
A
P2Y12 inhibitors

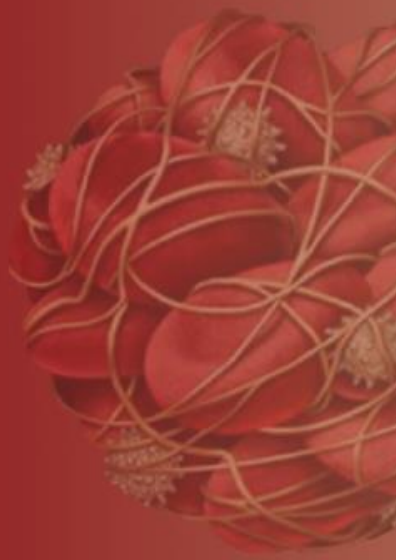
Obese patients with AF

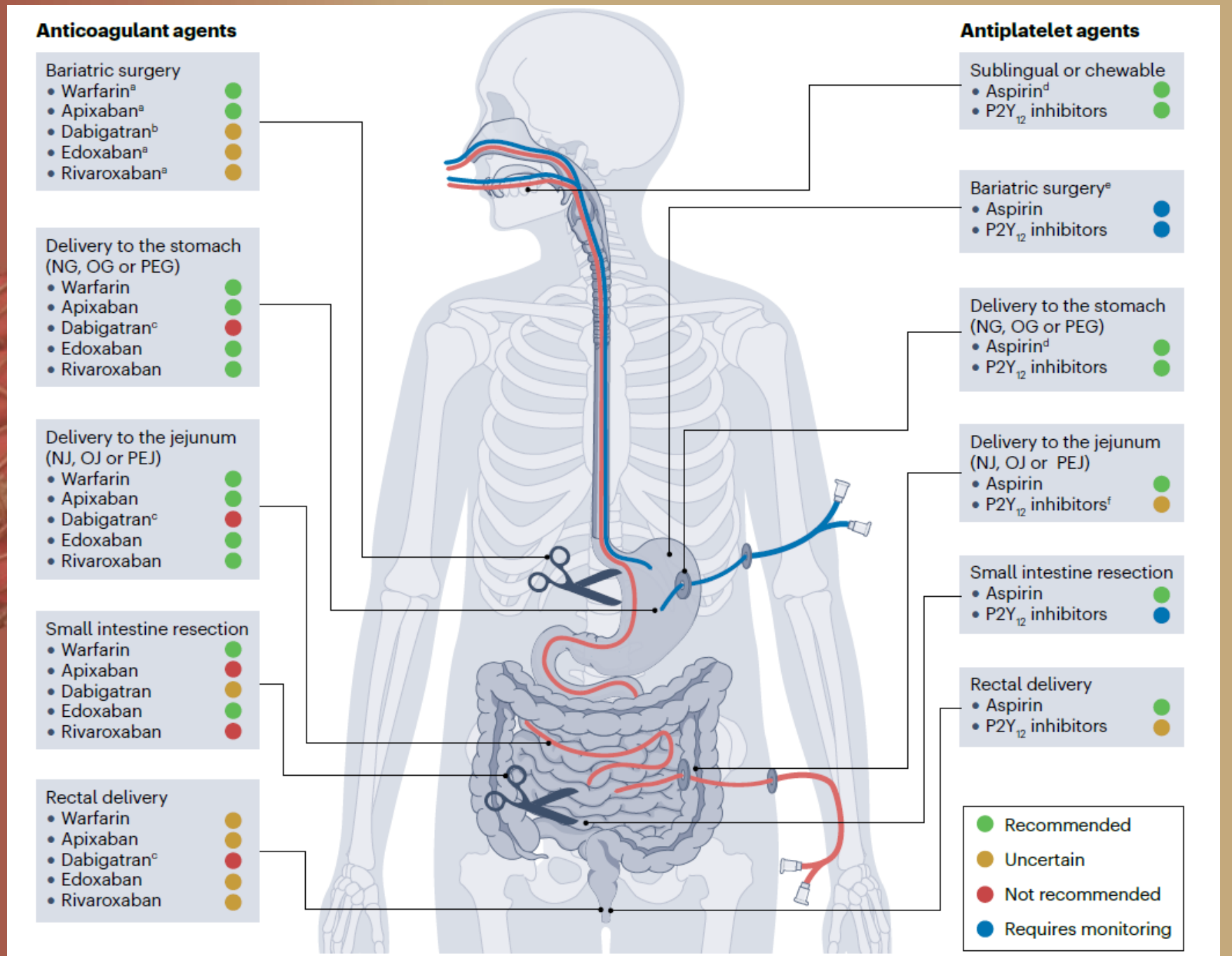


CLINICAL PRACTICE GUIDELINE

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

COR	LOE	RECOMMENDATIONS
2a	B-NR	1. In patients with AF and class III obesity (BMI ≥40 kg/m^2), DOACs are reasonable to choose over warfarin for stroke risk reduction.[1-5]




Anticoagulant agents
Bariatric surgery
• Warfarin[a]
• Apixaban[a]
• Dabigatran[b]
• Edoxaban[a]
• Rivaroxaban[a]
Delivery to the stomach (NG, OG or PEG)
• Warfarin
• Apixaban
• Dabigatran[c]
• Edoxaban
• Rivaroxaban
Delivery to the jejunum (NJ, OJ or PEJ)
• Warfarin
• Apixaban
• Dabigatran[c]
• Edoxaban
• Rivaroxaban
Small intestine resection
• Warfarin
• Apixaban
• Dabigatran
• Edoxaban
• Rivaroxaban
Rectal delivery
• Warfarin
• Apixaban
• Dabigatran[c]
• Edoxaban
• Rivaroxaban
Antiplatelet agents
Sublingual or chewable
• Aspirin[d]
• P2Y12 inhibitors
Bariatric surgery[e]
• Aspirin
• P2Y12 inhibitors
Delivery to the stomach (NG, OG or PEG)
• Aspirin[d]
• P2Y12 inhibitors
Delivery to the jejunum (NJ, OJ or PEJ)
• Aspirin
• P2Y12 inhibitors[f]
Small intestine resection
• Aspirin
• P2Y12 inhibitors
Rectal delivery
• Aspirin
• P2Y12 inhibitors
Recommended
Uncertain
Not recommended
Requires monitoring

Obese patients with VTE

ISTH Summary Guidance Statements: Use of DOACs in Patients With Obesity

BMI ≤ 40 kg/m² or Weight ≤ 120 kg:

VTE Treatment	VTE Prevention
✅✅✅✅✅ Use of **Any DOAC** is appropriate (Consistent with 2016 ISTH SSC recommendations)	

BMI >40 kg/m² or Weight >120 kg:

VTE Treatment	VTE Prevention
✅ **Rivaroxaban** ✅ **Apixaban** Fewer supportive data for apixaban	✅ **Rivaroxaban** ✅ **Apixaban** Note limited indications for use
❌ Dabigatran ❌ Edoxaban ❌ Betrixaban	❌ Dabigatran ❌ Edoxaban ❌ Betrixaban
🆗 VKA 🆗 Wt-based LMWH 🆗 Fondaparinux	
❌ Do not regularly follow peak/trough DOAC levels ❌	
	❌ Do not use in acute setting after bariatric surgery

Case 3

- 64-year-old lady with Hx of AF, CABG (2 years ago) to your pharmacy to fill her prescription:

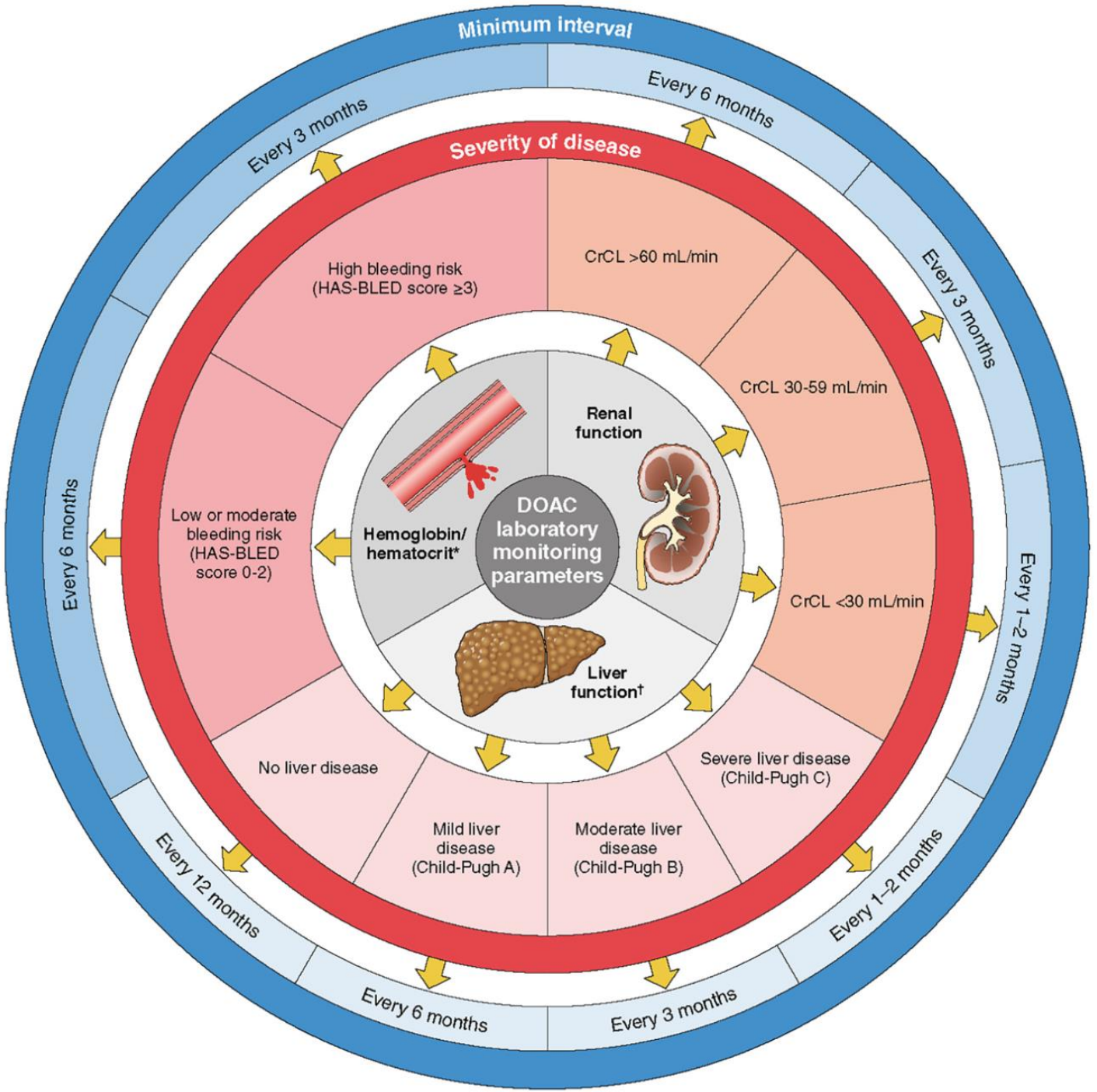
- Tab. Apixaban 5 mg BD
- Tab. Metoprolol succinate 23.75 mg daily
- Tab. ASA 80 mg daily
- Tab. pantoprazole 40 mg daily
- Tab. Atorvastatin 40 mg daily
- Tab. Valsartan/amlodipine 80/5 mg daily

- She asked about important laboratory tests for her medications.
- What's your recommendation?

Monitoring Parameters

- **Cr**
- **LFT**
- **CBC**
- **Weight**
- **Height**

. Blood sampling (including haemoglobin, renal, and liver function)	Yearly	• In all patients except those below
	4-monthly	• ≥75 years (especially if on dabigatran), or frail.
	Variable	• If renal function CrCl ≤60 mL/min: • CrCl/10 = minimum recheck interval (in months).
	If needed	• In case of intercurrent conditions, especially with potential impact on renal or hepatic function (e.g. infection, NSAID use, dehydration etc.).


Minimum interval
Every 3 months
Every 6 months
Every 3 months
Every 1–2 months
Every 6 months
Every 12 months
Every 6 months
Every 3 months
Every 1–2 months
Severity of disease
High bleeding risk (HAS-BLED score ≥3)
CrCL >60 mL/min
CrCL 30-59 mL/min
CrCL <30 mL/min
Severe liver disease (Child-Pugh C)
Moderate liver disease (Child-Pugh B)
Mild liver disease (Child-Pugh A)
No liver disease
Low or moderate bleeding risk (HAS-BLED score 0-2)
Renal function
Hemoglobin/ hematocrit*
DOAC laboratory monitoring parameters
Liver function†

Case 4

- A man maid a phone call to your pharmacy
- He asked about the missed dose of rivaroxaban

- What's your questions?
- What's your recommendation?

Missed dose for DOACs

- A forgotten dose may be taken until half of the dosing interval has passed. Hence, for **NOACs with a twice daily (BID) dosing regimen** (i.e., intake every 12 h), a forgotten full dose can be taken up until 6 h after the scheduled intake.
- **For NOACs with a once daily (QD) dosing regimen**, a forgotten dose can be taken up until 12 h after the sched- uled intake. After these time points, the dose should be skipped, and the next scheduled dose should be taken.

Double dose for DOACs

- **For NOACs with a BID dosing regimen**, the next planned dose (i.e. af- ter 12h) may be skipped, with the regular BID dosing regimen restarted 24 h after the double dose intake.

- **For NOACs with a QD dosing regimen**, the patient should continue the normal dosing regimen, i.e. without skipping the next daily dose.

Uncertainty about dose intake

- **For NOACs with a BID dosing regimen**, it is generally advisable to not take another tablet/capsule, but to continue with the regular dose regimen, i.e. starting with the next dose at the 12 h interval.

- **For NOACs with a QD dosing regimen**,
  - when thromboembolic risk is high (CHA2DS2-VASc >_3), it may generally be advisable to take another tablet 6–8 h after the original (uncertain) intake and then continue the planned dose regimen.
  - In case the thromboembolic risk is low (CHA2DS2-VASc <_2) we advise to wait until the next scheduled dose.

Case 5

58 y/o lady has come to your pharmacy to fill her prescription

Her prescription:

Tab. Rivaroxaban 20 mg daily, N=100
Tab. Pantoprazole 40 mg daily, N=56
Tab. Carvedilol 6.25 mg BD, N=60
Tab. Valsartan 80 mg BD, N=100
Tab. Valproate 500 mg BD, N=100

Table 7 **Anticipated effects of common antiepileptic drugs on non-vitamin K antagonist oral anticoagulants plasma levels**

	Via[426, 539-541]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Brivaracetam	–	No relevant interaction known/assumed			
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	-29% [542]	-50% (SmPC)	SmPC	SmPC
Ethosuximide	CYP3A4 competition	No relevant interaction known/assumed			
Gabapentin	–	No relevant interaction known/assumed			
Lacosamide	–	No relevant interaction known/assumed			
Lamotrigine	P-gp competition	No relevant interaction known/assumed			
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/possible P-gp induction		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC [543]	SmPC	SmPC	SmPC
Pregabalin	–	No relevant interaction known/assumed			
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction/inhibition				Ref 544
Zonisamide	CYP3A4 competition; weak P-gp inhibition	No relevant interaction known/assumed (SmPc)			

Colour coding is based on the respective NOAC SmPC, drug interaction databases, or expert opinion.[426] The hatched colour coding indicates no clinical or PK data available. Some of the colour codes will likely require adaptation as more data become available over time.
White: No relevant drug–drug interaction anticipated.
Blue (dark): Contraindicated due to reduced NOAC plasma levels.
Blue (light): Caution required, especially in case of polypharmacy or in the presence of ≥2 light blue interactions due to *reduced* NOAC plasma levels.

Table 5 Effect of drug-drug interactions and clinical factors on NOAC plasma levels and anticoagulant effects

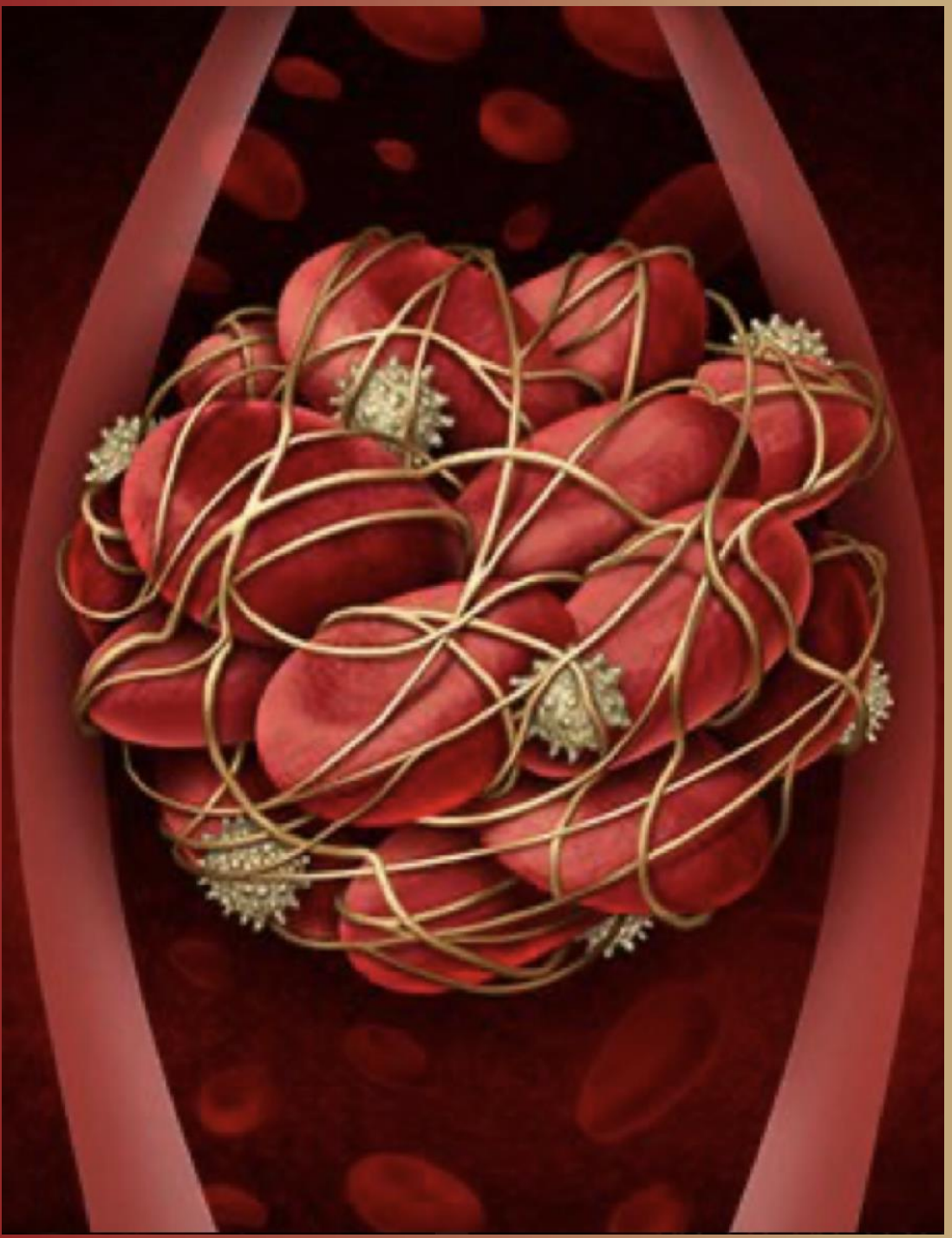
	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[519]
Antiarrhythmic drugs					
Amiodarone	Moderate P-gp inhibition	+12% to 60%[SmPC]	No PK data[a]	+40%[521-523]	Minor effect[a]
Digoxin	P-gp competition	No effect[SmPC]	No effect[524]	No effect[523]	No effect[525]
Diltiazem	Weak P-gp and CYP3A4 inhibition	No effect[SmPC]	+40%[526]	No data yet	No effect
Dronedarone	P-gp and CYP3A4 inhibition	+70% to 100%	With caution	+85%[b 523] (dose reduction to 30 mg once daily by label)	Moderate effect; should be avoided
Quinidine	P-gp inhibition	+53%[SmPC]	No data yet	+77%[523] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp inhibition and weak CYP3A4 inhibition	+12% to 180%[SmPC] (if taken simultaneously) (110 mg BID by label)	No PK data	+53% (SR)[523] (no dose reduction required by label)	+40%[527] (probably not relevant)[528]
Other cardiovascular drugs					
Atorvastatin	P-gp inhibition and CYP3A4 competition	No relevant interaction[529]	No data yet	No effect[523]	No effect[530]
Ticagrelor (see also 'Patients with atrial fibrillation and coronary artery disease' section)	P-gp inhibition	+24% to 65%[SmPC] (give loading dose 2h after dabigatran)[d]	No data – carefully monitor	No data – carefully monitor	No data – carefully monitor
Antibiotics					
Clarithromycin; Erythromycin	P-gp inhibition and strong CYP3A4 inhibition	Clarithromycin: +19% AUC; +15% C_{max} (SmPC)	Clarithromycin: +60% AUC; +30% C_{max} (SmPC)	Erythromycin: +85% AUC; +68% C_{max}[531] (dose reduction to 30 mg once daily by label)	Clarithromycin: +50% AUC; +40% C_{max} Erythromycin: +30% AUC; +30% C_{max} (SmPC)
Rifampicin	P-gp/ BCRP and CYP3A4 induction	– 66% AUC; – 67% Cmax (SmPC)	– 54% AUC; – 42% Cmax (SmPC)	– 35% AUC, (but with compensatory increase of active metabolites)[532]	– 50% AUC; – 22% Cmax (SmPC)

	via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Antiviral Drugs					
HIV protease inhibitors (e.g., ritonavir)	P-gp and BCRP inhibition or induction; CYP3A4 inhibition	Variable increase / decrease[533, 534]	Strong increase	No data yet	+153% AUC +55% C_{max} (Ritonavir 600 BID)[94]
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% AUC; +30% C_{max} (if given systemically)[94]
Itraconazole; Ketoconazole	Potent P-gp and BCRP competition; strong CYP3A4 inhibition	+140 to 150% (ketoconazole) (US: 2 × 75 mg if CrCl 30-50 mL/min)	+100% AUC; +64% C_{max} (ketoconazole)[526]	+87% AUC; +89% C_{max} (dose reduction to 30 mg once daily by label) (ketoconazole)[531]	+160% AUC; +72% C_{max} (ketoconazole, SmPc)
Voriconazole	Strong CYP3A4 inhibition	No data yet	SmPC	No data yet	SmPC
Posaconazole	Mild to moderate P-gp inhibition, strong CYP3A4 inhibition	SmPC	SmPC		SmPC
Other drugs					
Naproxen	P-gp competition; pharmacody-namically (increased bleeding time)	No data yet	+55% AUC; +61% C_{max}[535]	No difference in AUC[536]	No relevant increase of AUC[537]
H_2-blockers; PPI; Al-Mg-hydroxide	GI absorption	Minor effect, not clinically relevant[SmPC]	No effect	Minor effect, not clinically relevant[SmPC]	No effect[105, 538]
SSRIs; SNRIs	Pharmacodynamic effect on platelets	SmPC	SmPC	SmPC	SmPC
St. John's wort	P-gp/ BCRP and CYP3A4 induction				

Class	VKA	Direct Thrombin Inhibitor	Factor Xa Inhibitor		
Name	**Warfarin**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
				mg/dL	
Drug interaction management based on concomitant therapy of CYP3A4 inhibitors/ p-glycoprotein inhibitors	Adjust dose based on INR trends	CrCl 30-50 mL/min with concomitant use of dronedarone or systemic ketoconazole: 75 mg twice daily CrCl <30 mL/min: avoid dabigatran use concomitantly with dronedarone or systemic ketoconazole	Avoid rivaroxaban use with concomitant therapy of combined p-glycoprotein and strong CYP3A4 inhibitors (eg, systemic ketoconazole and ritonavir) No dose adjustment required with clarithromycin Avoid rivaroxaban use in patients with CrCl 15-<80 mL/min receiving combined p-glycoprotein and moderate CYP3A4 inhibitors (eg, erythromycin)	In patients receiving apixaban 5 mg twice daily, reduce dose to 2.5 mg twice daily when combined p-glycoprotein and strong CYP3A4 inhibitors (eg, itraconazole, systemic ketoconazole, ritonavir) are used concomitantly If patients already receiving apixaban 2.5 mg twice daily, avoid apixaban use if combined p-glycoprotein and strong CYP3A4 inhibitors are concomitantly used	No dose adjustment is required
Drug interaction management based on concomitant therapy of p-glycoprotein/ CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, St. John's wort)	Adjust dose based on INR trends	Avoid use	Avoid use	Avoid use	Avoid use with rifampin. No study evaluated the effect of other p-glycoprotein/ CYP3A4 inducers on edoxaban drug levels

Table 8 **Anticipated effects of common herbal medicines on non-vitamin K antagonist oral anticoagulants plasma levels**

	Via [545, 546; 547]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Curcumin	P-gp inhibition				
Echinacea purpurea	Mild CYP3A4 inhibition				
Garlic	Mild CYP3A4 inhibition; anticoagulation / antiplatelet effect				
Ginger	Anticoagulation / antiplatelet effect				
Ginkgo biloba	P-gp inhibition; anticoagulation / antiplatelet effect				
Ginseng	Anticoagulation / antiplatelet effect				
Green Tea	P-gp inhibition; anticoagulation / antiplatelet effect				
Horse chestnut	Anticoagulation / antiplatelet effect				
St. John's wort	P-gp/ BCRP and CYP3A4 induction	Should be avoided (per SmPc)	"With caution" (per SmPc)	"With caution" (per SmPc)	Should be avoided (per SmPc)
Valerian	Mild CYP3A4 inhibition				



Thank you