Practical considerations regarding anticoagulant regimens

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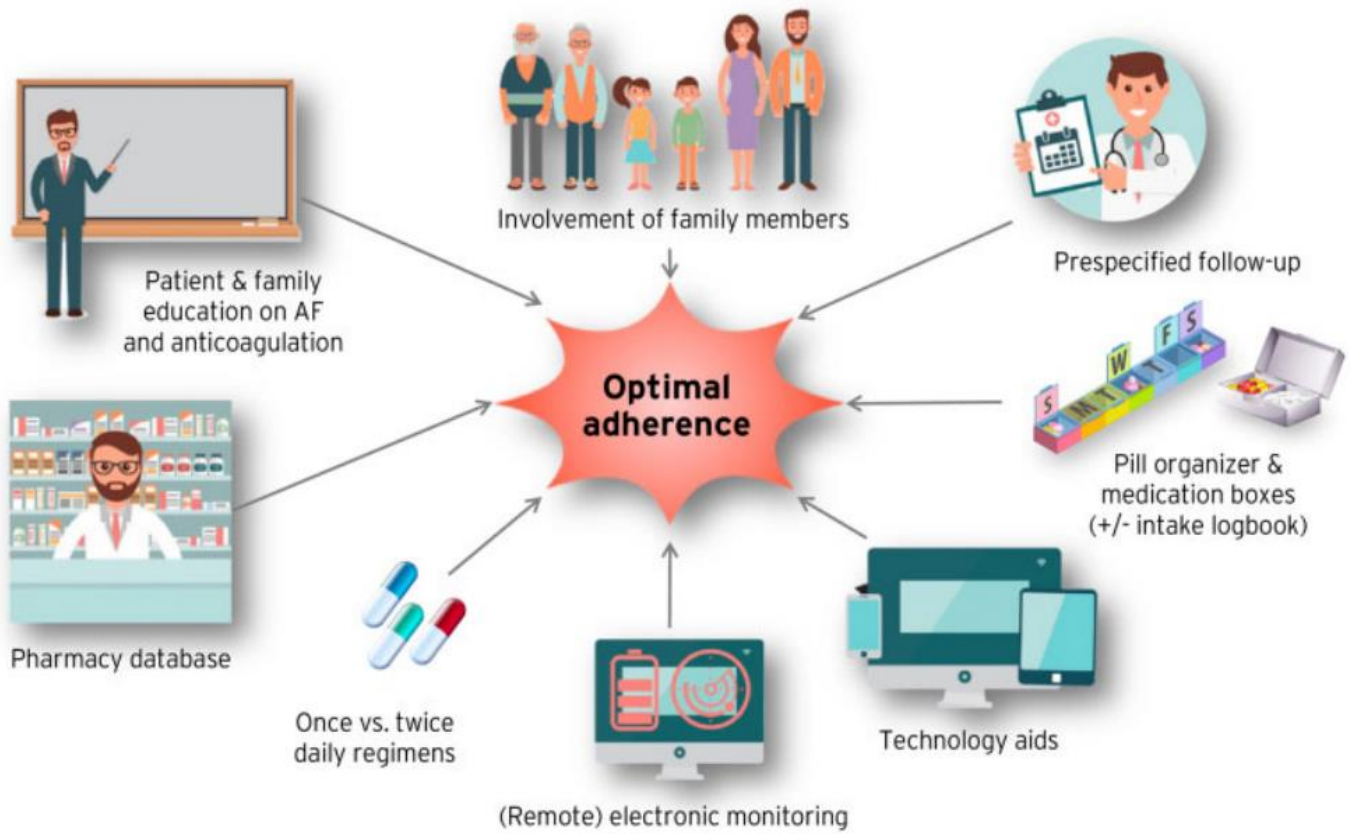


Figure 1 Selection of possibilities to increase adherence to NOACs. AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant.

Patient instructions

Important patient instructions

- A NOAC reduces the risk of dangerous blood clots which may cause a stroke.
- Not taking the drug means no protection
- Take your drug exactly as prescribed (once or twice daily).
- Do not skip a prescribed dose or stop your medication without consulting your physician.
- After a trauma or bleeding event, consult with your physician regarding further management
- If you experience any side effects consult your prescribing physician
- Do not add any additional medication without consulting your physician, not even short-term painkillers which are available without prescription.
- Alert your dentist, surgeon or other physician before an intervention.

What to do in certain situations

When should I contact a healthcare provider?
Bleeding is the most common side effect of an anticoagulant. Contact your healthcare provider if you have any signs or symptoms of bleeding such as:

- Unusual bruising, nosebleeds, bleeding of gums, bleeding from cuts that take a long time to stop
- Menstrual flow or vaginal bleeding that is heavier than normal
- Blood in urine, red or black stools
- Coughing up blood or vomiting blood
- Dizziness, paleness or weakness

What should I do if I missed a dose?

- Twice daily NOAC: Take missed dose if within 6 hours, otherwise leave out
- Once daily NOAC: Take missed dose if within 12 hours, otherwise leave out

What if I accidently took two doses at the same time?

- Twice daily NOAC: you can opt to leave out the next planned dose and restart after 24 h.
- Once daily NOAC: you can continue the normal regimen without skipping a dose.

Patients follow up

- **Routine monitoring of anticoagulation level is not required**
- **Yearly:** Hb, renal and liver function
- **If ≥ 75 years or frail:** 6-monthly renal function
- **If CrCl ≤ 60 ml/min:** recheck interval in months = "CrCl:10" (e.g., every 4 months if CrCl = 40)
- **If intercurrent condition that may have impact:** renal and/or liver function

Information for health care providers

- NOACs act as a direct thrombin inhibitor (dabigatran) or direct factor Xa inhibitors (apixaban, edoxaban, rivaroxaban).
- Check contraindications for NOACs according to the local SmPc (e.g., mechanical heart valve; rheumatic mitral stenosis).
- Standard tests (such as INR, PT or aPTT) do not adequately reflect level of anticoagulation.
- For certain procedures, NOAC should be stopped in advance but without bridging (for timing see EHRA NOAC Practical Guide).

Special considerations for NOAC use during the ‘coronavirus disease of 2019’ (COVID-19) pandemic

NOAC therapy comes with some potentially important practical advantages over VKAbased anticoagulation during the coronavirus disease of 2019 (COVID-19) pandemic, including the lack of necessity for frequent clinic/office visits for INR monitoring. Community teams for at home INR controls may equally be limited during these periods. As a result, both the individual’s risk for contracting the virus as well as the workload on the healthcare system would be reduced.

Covid-19 vaccination and NOAC

1.Leave out the morning dose of the NOAC prior to i.m. injection.

2. Use a fine-gauge needle for injection.

3. Apply firm pressure for 2–5 min after the injection.

4.In QD NOACs: take the left-out morning dose 3 h after the injection (esp. in case of high stroke risk and QD NOAC).

5. In BID NOACs: re-start NOAC with the next scheduled dose.

- If patients on NOACs are infected with COVID-19 and particularly in case of severe infection requiring hospitalization, increasing evidence indicates a benefit for continuing anticoagulation to stave off COVID-19 complications. However, clinical deterioration (particularly of renal function) as well as administration of concomitant medication should be considered.

- Assessment via a multidisciplinary expert team including cardiologist, intensive care specialists, haematologists, neurologist etc. and, if in doubt, conversion to low-molecular or unfractionated heparin (UFH) is advisable.

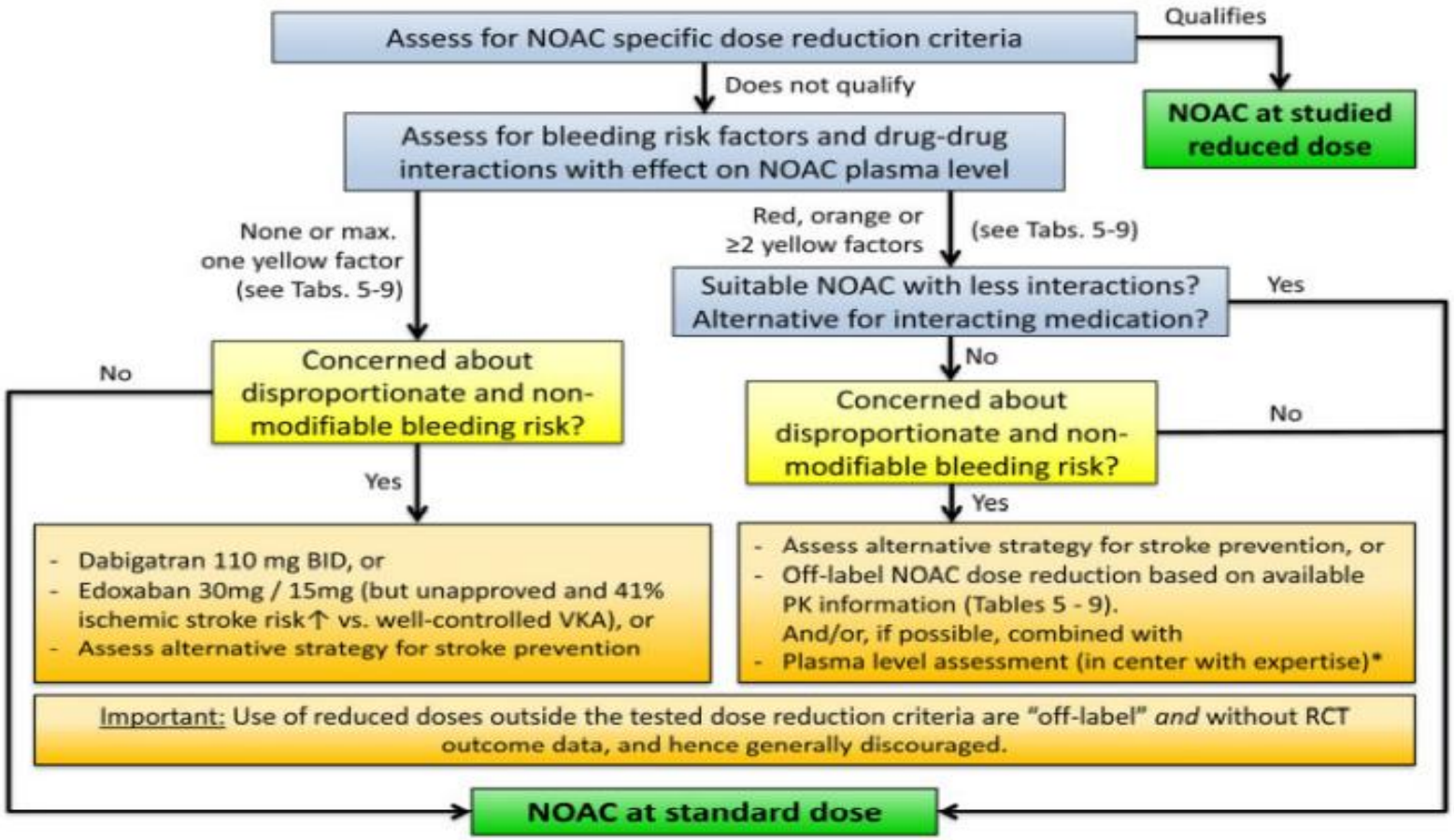

Assess for NOAC specific dose reduction criteria
Qualifies
NOAC at studied reduced dose
Does not qualify
Assess for bleeding risk factors and drug-drug interactions with effect on NOAC plasma level
None or max. one yellow factor (see Tabs. 5-9)
Red, orange or ≥2 yellow factors
(see Tabs. 5-9)
Suitable NOAC with less interactions? Alternative for interacting medication?
Yes
No
Concerned about disproportionate and non-modifiable bleeding risk?
No
Yes
Concerned about disproportionate and non-modifiable bleeding risk?
No
Yes
- Dabigatran 110 mg BID, or
- Edoxaban 30mg / 15mg (but unapproved and 41% ischemic stroke risk↑ vs. well-controlled VKA), or
- Assess alternative strategy for stroke prevention
- Assess alternative strategy for stroke prevention, or
- Off-label NOAC dose reduction based on available PK information (Tables 5 - 9). And/or, if possible, combined with
- Plasma level assessment (in center with expertise)*
Important: Use of reduced doses outside the tested dose reduction criteria are "off-label" and without RCT outcome data, and hence generally discouraged.
NOAC at standard dose

Table 3 **Checklist during follow-up contacts of AF patients on anticoagulation**

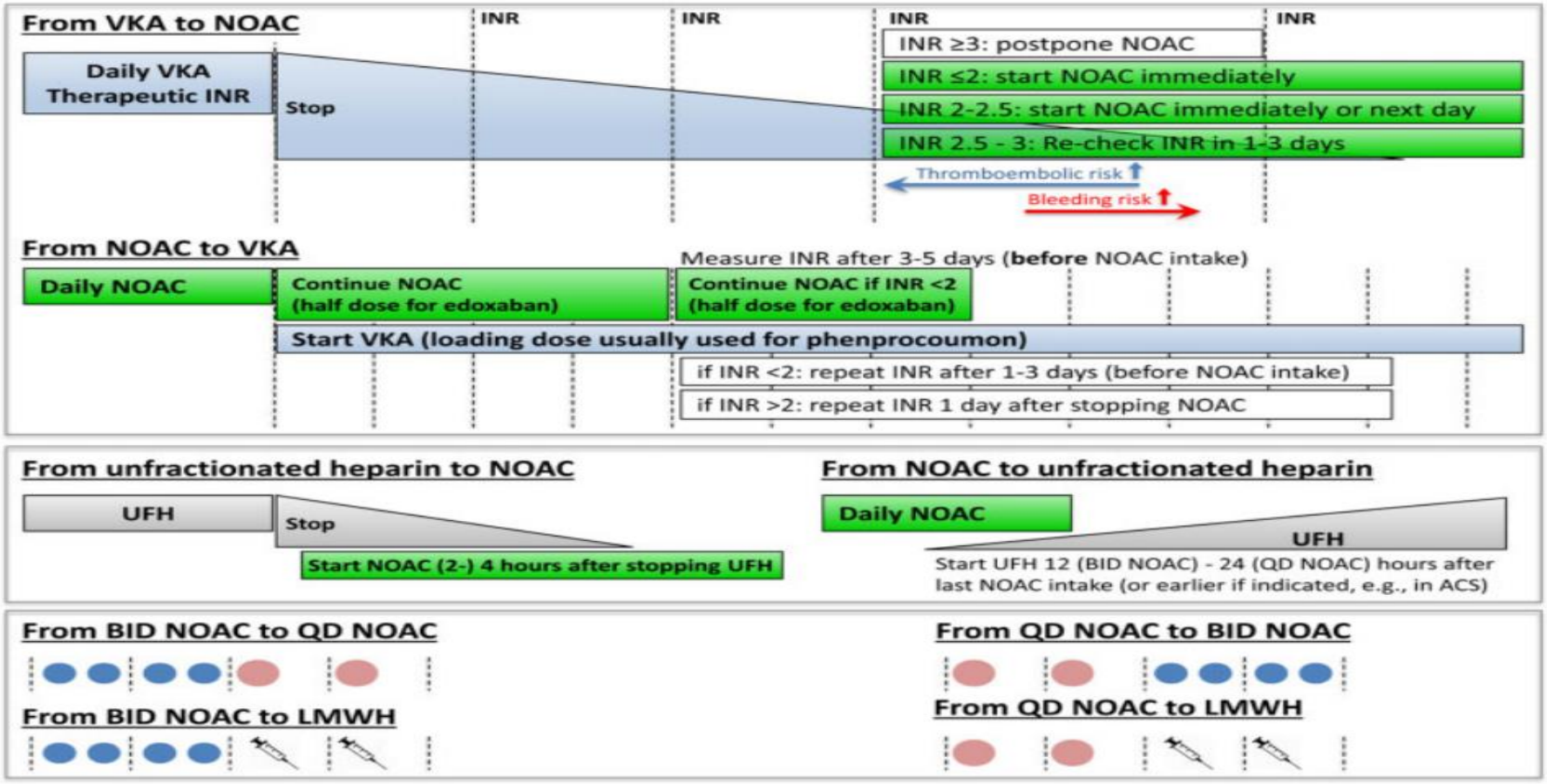
	Interval	Comments
1. Adherence	Each visit	• Instruct patient to bring NOAC card and complete list of medication: make note and assess adherence. • Re-educate on importance of strict intake schedule. • Inform about adherence aids (special boxes; smartphone applications; . . .). Consider specific adherence-measuring interventions (see 'Practical considerations for initiation and follow-up' section) • Inform about minor bleeding (gum, epistaxis, small ecchymosis) and instruct not to skip any dose without prior consultation • Assess cognitive function
2. Thromboembolism	Each visit	• Systemic circulation (TIA, stroke, peripheral). • Deep vein thrombosis, pulmonary embolism
3. Bleeding	Each visit	• For every bleeding: Look for reason. Cancer? Ulcer? Other causes, lesions etc.? Treatment or prevention possible? • 'Nuisance' bleeding: Reason? Treatment/prevention (see above)? • Assess impact on quality of life.
4. Other side effects	Each visit	• Carefully assess relation with NOAC: decide for continuation (and motivate) or change NOAC.
5. Co-medications	Each visit	• Prescription drugs; over-the-counter drugs. • Careful interval history (also temporary use, e.g. NSAIDs)

6. 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.).
7. Re-assess stroke risk	Each visit	• CHA_2DS_2-VASc score, as recommended by current guidelines[1]

8. Assessing and minimizing modifiable risk factors for bleeding	Each visit	• As recommended by current guidelines[1]
		• Particularly:
		  • Uncontrolled hypertension (systolic > 160 mmHg)
		  • Medication predisposing for bleeding (e.g. aspirin, NSAIDs)
		  • Labile INR (if on VKA)
		  • Excessive alcohol intake
		  • Falls

9. Assessing for optimal NOAC	Each visit	• Especially based on the above, re-assess whether

Switching between NOAC and other anticoagulants



Drugs interaction with NOACS

An important interaction mechanism for most NOACs consists of significant GI resecretion over a P-glycoprotein (P-gp) transporter after absorption in the gut. P-gp is also involved in active renal secretion of NOACs. Competitive inhibition of the P-gp pathway will result in increased plasma levels, which needs to be considered since many drugs used in AF patients are P-gp inhibitors (e.g. verapamil, dronedarone, amiodarone, ranolazine, and quinidine).

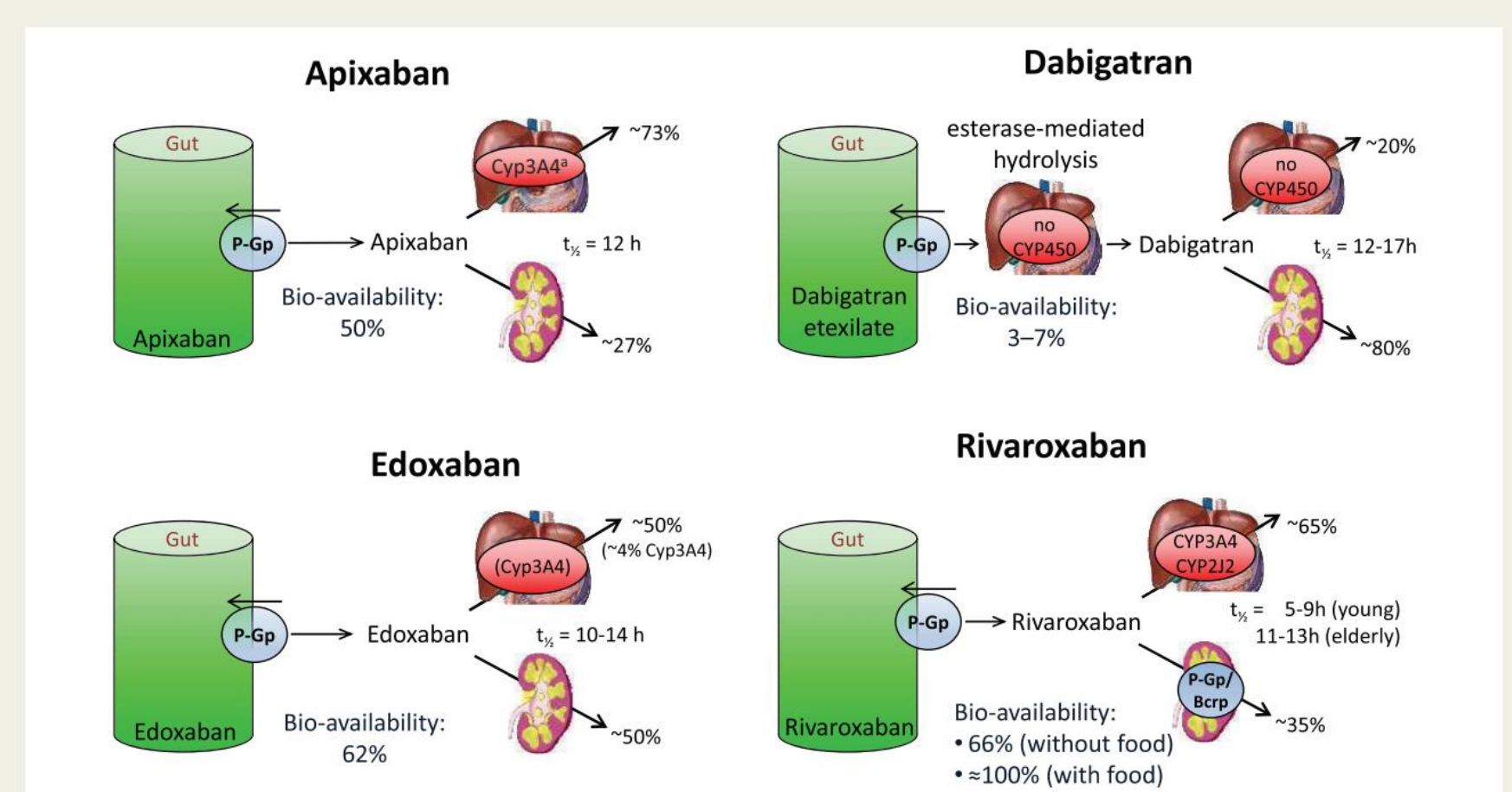
CYP3A4-type cytochrome P450- dependent elimination is relevantly involved in the hepatic clearance of rivaroxaban and apixaban. Strong cytochrome P (CYP) 3A4 inhibition or induction may affect plasma concentrations, and should be evaluated in context.

- In general, NOAC use is not advisable in combination with drugs that are strong inhibitors of both P-gp and/or CYP3A4. Conversely, strong inducers of Pgp and/or CYP3A4 (such as rifampicin, carbamazepine, etc.) will markedly reduce NOAC plasma levels; concomitant use with NOACs should be avoided or used with great caution .

Table 4 **Absorption and metabolism of the different NOACs**

	Dabigatran[106,376]	Apixaban[517]	Edoxaban[518]	Rivaroxaban[519,520]
Bioavailability	3–7%	50%	62%	15 mg/20 mg: 66% without food, 100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose	20%/80%	73%/27%	50%/50%	65%/35%
Plasma protein binding	35%	87%	55%	95%
Dialysability	50–60% (In part dialysable)	14% (Not dialysable)	NA (Not dialysable)	NA (Not dialysable)
Metabolism	Glucoronic acid conjugation	CYP3A4 (25%), CYP1A2, CYP2J2, CYP2C8, CYP2C9 CYP2C19	CYP3A4 (<4% of elimination)	CYP2A4 (18%)[519], CYP2J2
Absorption with food	No effect	No effect	6–22% more; minimal effect on exposure	+39% more (see above)
Absorption with H2B/PPI	−12% to 30% (not clinically relevant)	No effect	No effect	No effect
Time to peak levels (h)	3	3	2–4	2–4
Elimination half-life (h)	12–17	12	10–14	5–9 (young) 11–13 h (elderly)

Absorption and metabolism of different NOACS



	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]

Drugs interaction

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					

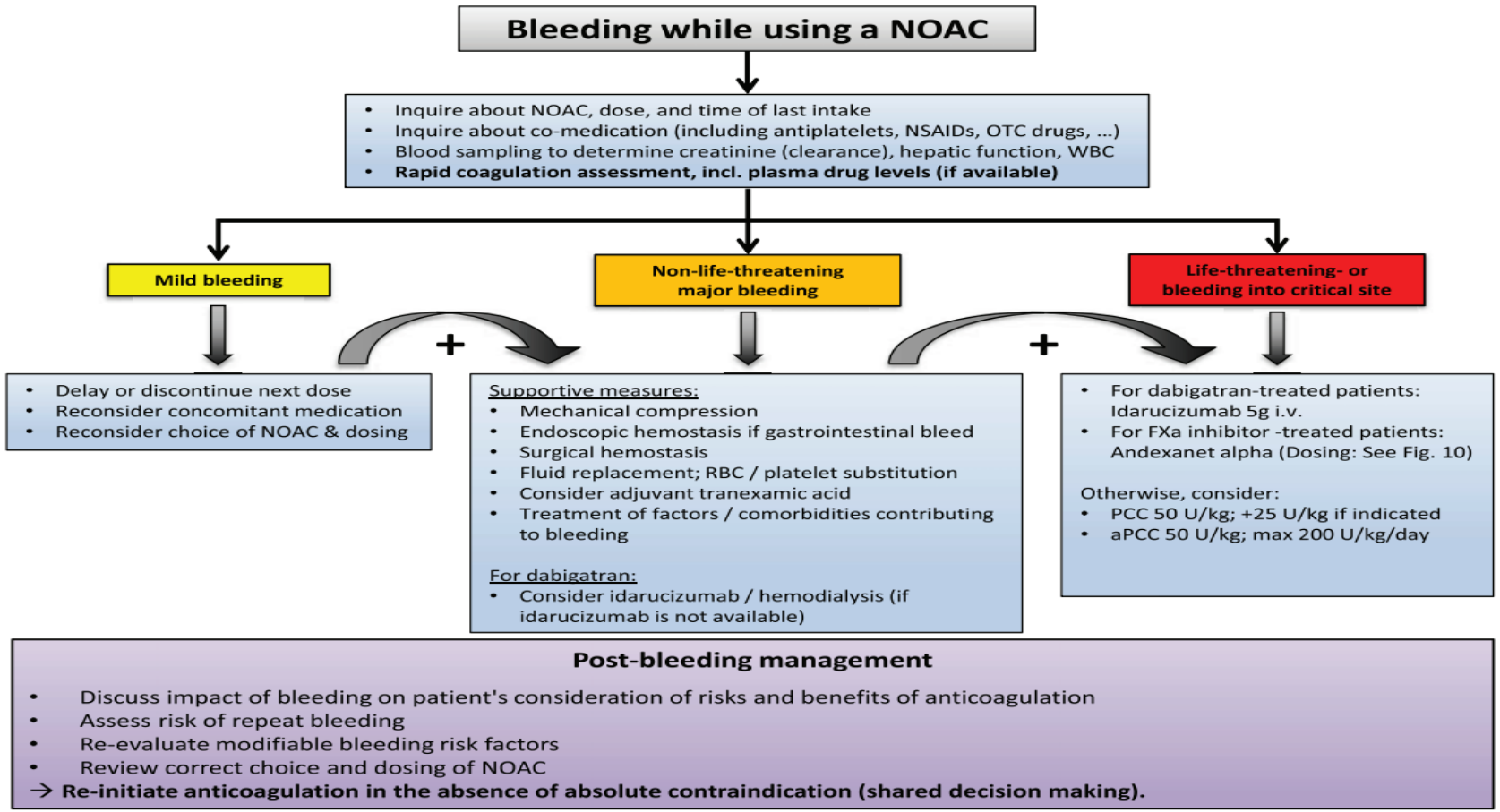
Imatinib, Crizotinib	Strong P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition				
Nilotinib, Lapatinib	Moderate-to-strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Vemurafenib	Moderate CYP3A4 induction; CYP3A4/P-gp competition				
Dasatinib	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Vandetanib, Sunitinib	Strong P-gp inhibition; CYP3A4 competition				
Erlotinib, Gefitinib	CYP3A4 competition; no relevant interaction anticipated				

	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)

- No studies have investigated if measurement of drug levels and dose adjustment based on laboratory coagulation parameters, e.g. by dose reduction in case of higher than expected levels or by dose increase in case of lower than expected levels, improve the overall benefit of NOACs during long-term treatment. As such, routine monitoring of plasma levels and subsequent dose adaptation is generally discouraged.

Bleeding while using NOACs

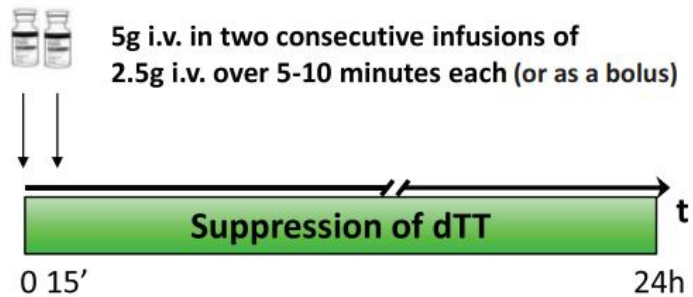
- NOACs cause less intracranial and less life-threatening bleeds than warfarin.
- Not only was there a similar or even a reduced bleeding incidence, but patients experiencing a major (particularly extracranial) bleed under NOACs were also shown to have a more favourable outcome than for bleeding under VKA treatment. This is underlined by the reduction in all-cause mortality as well as life-threatening/fatal bleeds which was observed with NOACs vs. warfarin.


Bleeding while using a NOAC
• Inquire about NOAC, dose, and time of last intake
• Inquire about co-medication (including antiplatelets, NSAIDs, OTC drugs, ...)
• Blood sampling to determine creatinine (clearance), hepatic function, WBC
• Rapid coagulation assessment, incl. plasma drug levels (if available)
Mild bleeding
Non-life-threatening major bleeding
Life-threatening- or bleeding into critical site
+
+
• Delay or discontinue next dose
• Reconsider concomitant medication
• Reconsider choice of NOAC & dosing
Supportive measures:
• Mechanical compression
• Endoscopic hemostasis if gastrointestinal bleed
• Surgical hemostasis
• Fluid replacement; RBC / platelet substitution
• Consider adjuvant tranexamic acid
• Treatment of factors / comorbidities contributing to bleeding
For dabigatran:
• Consider idarucizumab / hemodialysis (if idarucizumab is not available)
• For dabigatran-treated patients: Idarucizumab 5g i.v.
• For FXa inhibitor -treated patients: Andexanet alpha (Dosing: See Fig. 10)
Otherwise, consider:
• PCC 50 U/kg; +25 U/kg if indicated
• aPCC 50 U/kg; max 200 U/kg/day
Post-bleeding management
• Discuss impact of bleeding on patient's consideration of risks and benefits of anticoagulation
• Assess risk of repeat bleeding
• Re-evaluate modifiable bleeding risk factors
• Review correct choice and dosing of NOAC
→ Re-initiate anticoagulation in the absence of absolute contraindication (shared decision making).

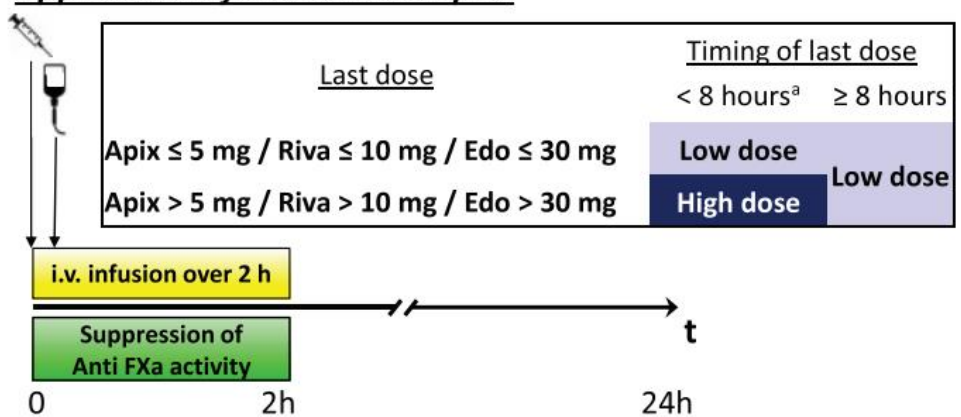
- Idarucizumab is a humanized antibody fragment that specifically binds dabigatran. In the ‘Reversal Effects of Idarucizumab in Patients on Active Dabigatran’ (RE-VERSE-AD) study the drug was successfully used in patients on dabigatran presenting with major or life-threatening bleeding, or with the necessity of emergency surgery. Idarucizumab completely reversed the anticoagulant activity of dabigatran within minutes in almost all patients.

- Andexanet alfa is a recombinant, inactive human FXa analogue that non-specifically binds FXa inhibitors thereby preventing all FXa inhibitors (including low-molecular weight- and UFHs) from inhibiting FXa. In the ‘Andexanet Alfa is successfully used in major or life-threatening bleeding; in contrast to RE-VERSE-AD the trial did not include patients undergoing emergency surgery.

Application of Idarucizumab

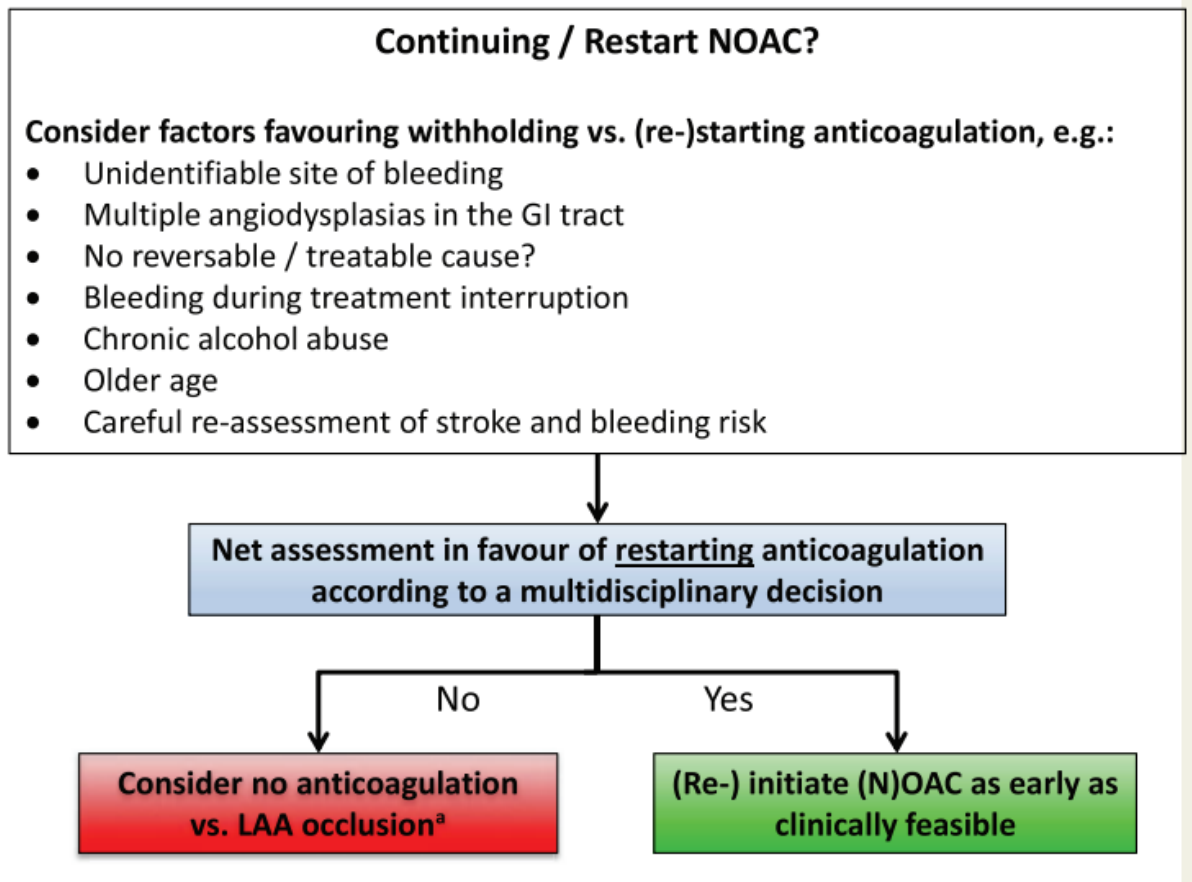


Application of Andexanet Alpha



Low dose:
- Bolus: 400mg (at 30 mg/min)
- Infusion: 4 mg/min (=480 mg)

High dose:
- Bolus: 800mg (at 30 mg/min)
- Infusion: 8 mg/min (=960 mg)


Continuing / Restart NOAC?
Consider factors favouring withholding vs. (re-)starting anticoagulation, e.g.:
• Unidentifiable site of bleeding
• Multiple angiodysplasias in the GI tract
• No reversable / treatable cause?
• Bleeding during treatment interruption
• Chronic alcohol abuse
• Older age
• Careful re-assessment of stroke and bleeding risk
Net assessment in favour of restarting anticoagulation according to a multidisciplinary decision
No
Yes
Consider no anticoagulation vs. LAA occlusion[a]
(Re-) initiate (N)OAC as early as clinically feasible

NOAC intake before elective 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

NOAC management in setting of unplanned surgery

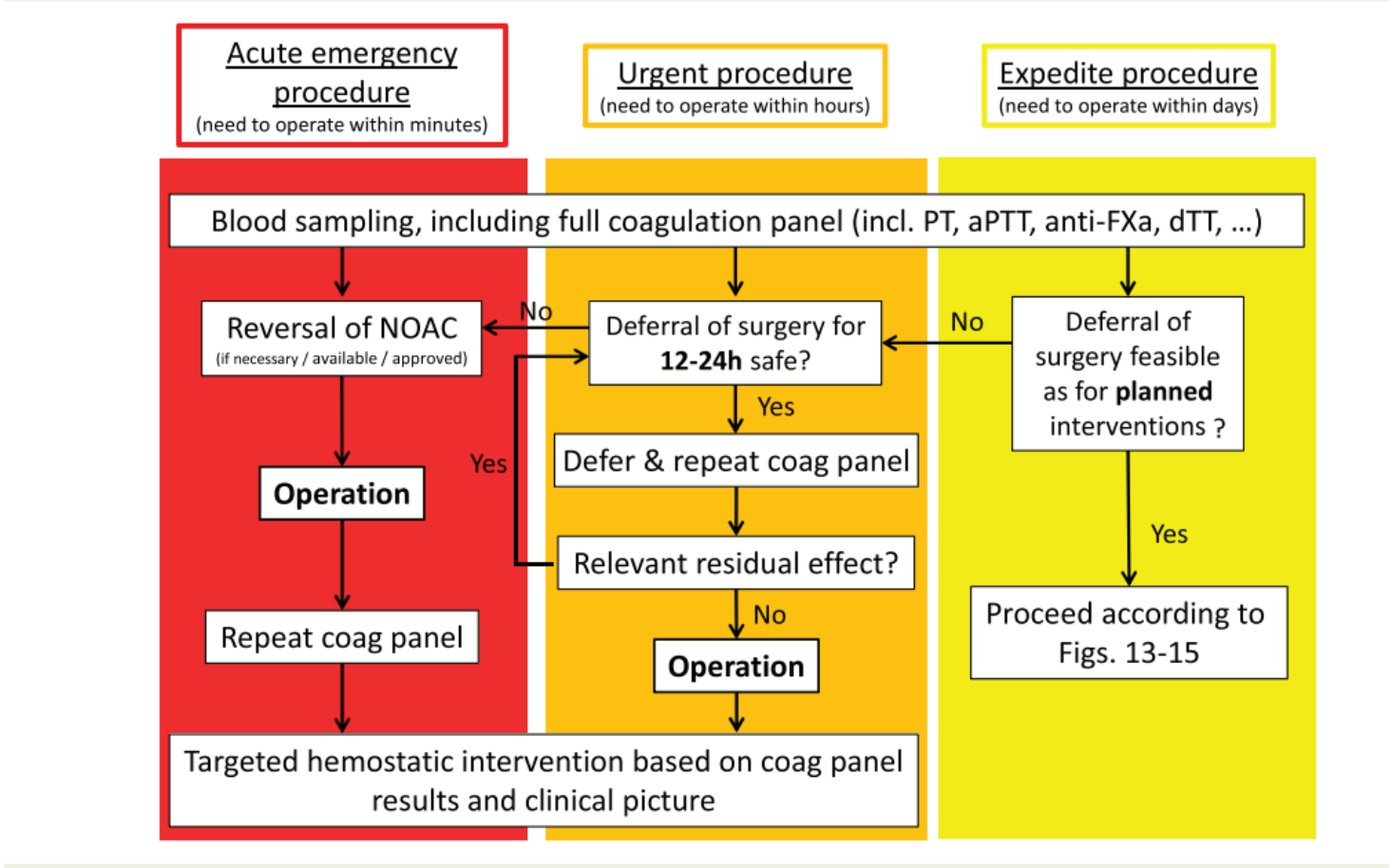


Table 12 Classification of elective surgical interventions according to bleeding risk

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