به‌نام خدای بخشاینده مهربان

In the name of Allah, the Beneficent, the Merciful.

NOACs

BENEFITS AND CHALLENGES

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ESC European Society of Cardiology

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2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

Table 1 **Selected indications and contraindications for NOAC therapy in AF patients**

Condition	Eligibility for NOAC	Comment
Mechanical prosthetic valve	Contraindicated	Excluded from pivotal RCTs Data indicating worse outcome[15,16]
Moderate to severe mitral stenosis (usually rheumatic)	Contraindicated	Excluded from pivotal RCTs Little rationale for less efficacy and safety vs. VKA
Other mild to moderate valvular disease (e.g. degenerative aortic stenosis, mitral regurgitation etc.) Bioprosthetic valve/valve repair (after >3 months postoperative)	Included in NOAC trials Acceptable	Data regarding efficacy and safety overall consistent with patients without valvular heart disease[12,17–22] Some data from NOAC RCTs Single RCT indicating non-inferiority to VKA[24] Patients without AF usually on ASA after 3–6 months post-surgery, hence NOAC therapy acceptable for stroke prevention if diagnosed with AF
Severe aortic stenosis	Limited data (excluded in RE-LY)	No pathophysiological rationale for less efficacy and safety Most will undergo intervention
Transcatheter aortic valve implantation	Acceptable	Single RCT + observational data May require combination with APT[25,26]
Percutaneous transluminal aortic valvuloplasty	With caution	No prospective data May require combination with APT
Hypertrophic cardiomyopathy	Acceptable	No rational for less efficacy and safety vs. VKA Observational data positive for NOACs[33–36]

Hatched, limited data; See text for details.

AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized clinical trial; VKA, vitamin K antagonist.

Table 2 OACs and approved/studied doses across indications

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.

Missed dose

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 scheduled intake. After these time points, the dose should be skipped, and the next scheduled dose should be taken.

Double dose

For NOACs with a *BID dosing regimen*, the next planned dose (i.e. after 12 h) 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) no added dose is needed

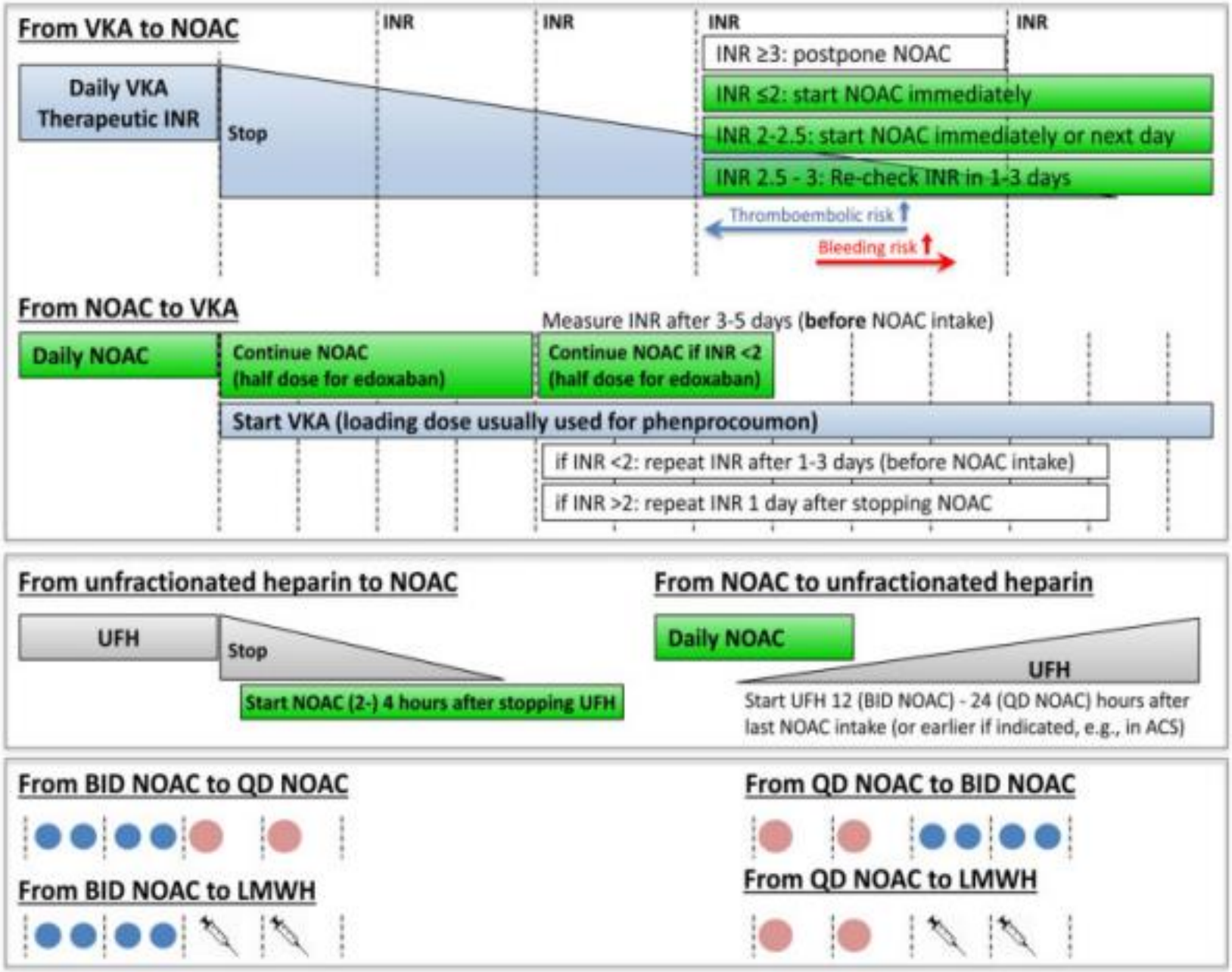

From VKA to NOAC
INR
INR
INR
INR
INR ≥3: postpone NOAC
Daily VKA Therapeutic INR
Stop
INR ≤2: start NOAC immediately
INR 2-2.5: start NOAC immediately or next day
INR 2.5 - 3: Re-check INR in 1-3 days
Thromboembolic risk
Bleeding risk
From NOAC to VKA
Measure INR after 3-5 days (before NOAC intake)
Daily NOAC
Continue NOAC (half dose for edoxaban)
Continue NOAC if INR <2 (half dose for edoxaban)
Start VKA (loading dose usually used for phenprocoumon)
if INR <2: repeat INR after 1-3 days (before NOAC intake)
if INR >2: repeat INR 1 day after stopping NOAC
From unfractionated heparin to NOAC
UFH
Stop
Start NOAC (2-) 4 hours after stopping UFH
From NOAC to unfractionated heparin
Daily NOAC
UFH
Start UFH 12 (BID NOAC) - 24 (QD NOAC) hours after last NOAC intake (or earlier if indicated, e.g., in ACS)
From BID NOAC to QD NOAC
From BID NOAC to LMWH
From QD NOAC to BID NOAC
From QD NOAC to LMWH

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	– 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 [522, 524]	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 [526]	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				
Other factors					
Age ≥ 80 years	Potential for *increased* plasma levels	110mg BID (SmPC)	b	c	
Age ≥75 years	Potential for *increased* plasma levels			c	
Weight ≤ 60 kg (see 'NOACs in high- and low body weights' section)	Potential for *increased* plasma levels		b	(dose reduction to 30mg according to label) b	
Weight ≥ 120 kg (see 'NOACs in high- and low body weights' section)	Potential for *decreased* plasma levels				
Chronic kidney disease	Potential for *increased* plasma levels				

Ciclosporine	Strong-to-moderate P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC	SmPC	+73% AUC (dose reduction to 30 mg once daily by label)	
Dexamethasone	Moderate CYP3A4 induction; CYP3A4 competition				
Tacrolimus	Strong-to-moderate P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC	Consider avoiding	Consider avoiding	Consider avoiding
Prednisone	Moderate CYP3A4 induction; CYP3A4 competition				
Temsirolimus, Sirolimus	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Everolimus	CYP3A4 competition; no relevant interaction anticipated				

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)			

	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				

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

Table 11 Plasma levels and coagulation assays in patients treated with NOACs for stroke prevention in AF

	Dabigatran[97,548,549]	Apixaban[550]	Edoxaban[98,100]	Rivaroxaban[519,520,551]
Expected plasma levels of NOACs in patients treated for AF*				
Peak levels	52–383	69–321	101–288	178–343
Trough levels	28–215	34–230	12–43	12–137
Expected impact of NOACs on routine coagulation tests[148,150,158,549,552–554]				
PT	(↑) peak (↑) if supratherapeutic[149]	(↑) at peak	↑ at therapeutic levels (if sensitive assay is used) Normal values do not exclude trough levels	↑ at therapeutic levels (if sensitive assay is used) Normal values do not exclude trough levels
aPTT	↑↑(↑) Normal values exclude supratherapeutic- but not therapeutic levels	(↑) at peak	(↑) at peak	(↑) at peak
ACT	↑(↑) Consistent with effect on aPTT	(↑)	(↑)	(↑)
TT	↑↑↑↑ Normal values exclude presence of Dabigatran	–	–	–

ACT, activated clotting time; AF, atrial fibrillation; aPTT, activated prothrombin time; NOAC, non-vitamin K antagonist oral anticoagulant; PT, prothrombin time.
*[ng/ml] 5–95% percentiles for FXa inhibitors and 10–90% percentiles (ng/ml) for Dabigatran).

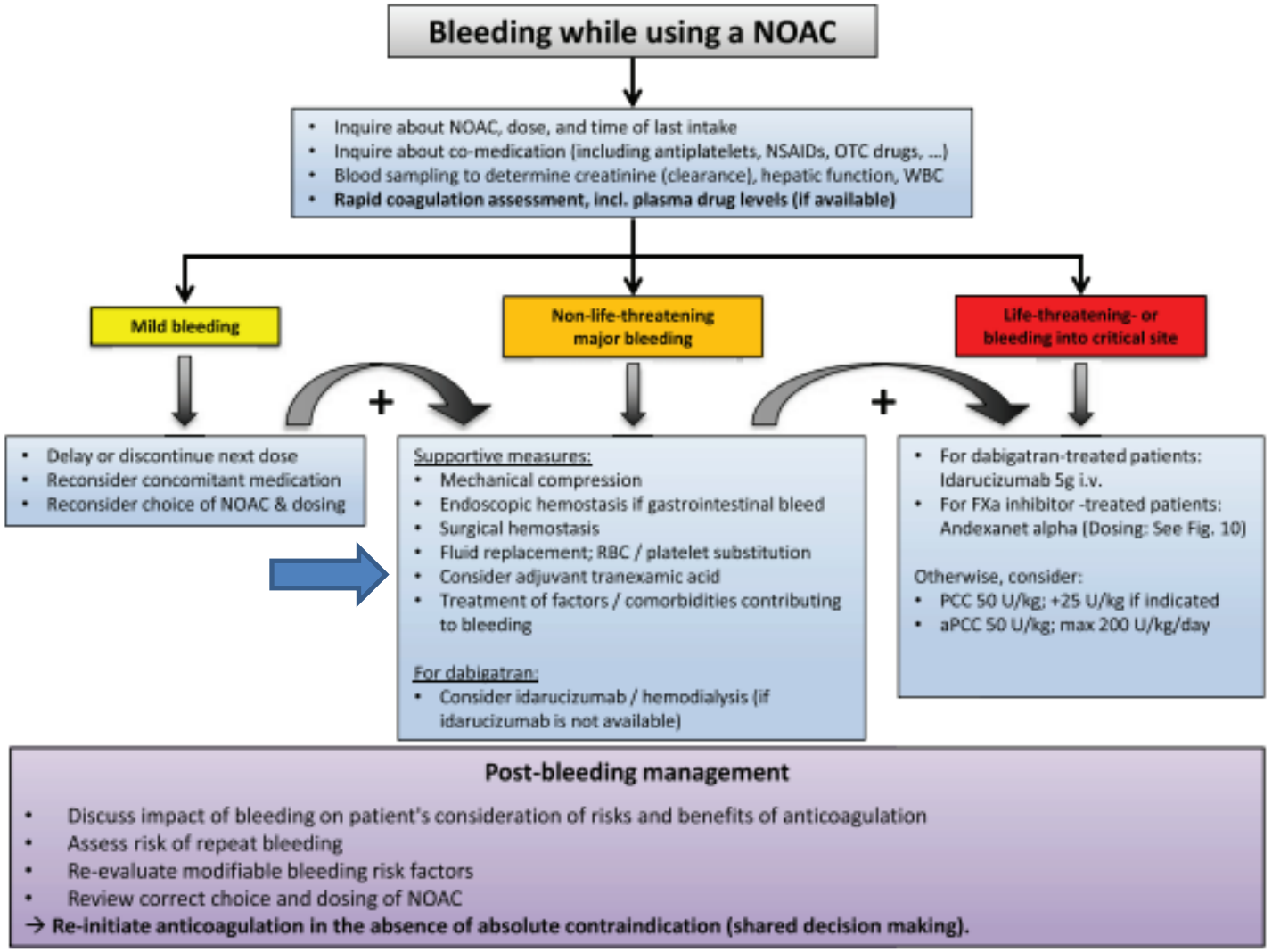


Figure 9 Management of bleeding in patients taking NOACs. aPCC, activated prothrombin complex concentrates; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; OTC, over-the-counter; PCC, prothrombin complex concentrates; RBC, red blood cell; WBC, white blood cell.

Table 12 Classification of elective surgical interventions according to bleeding risk

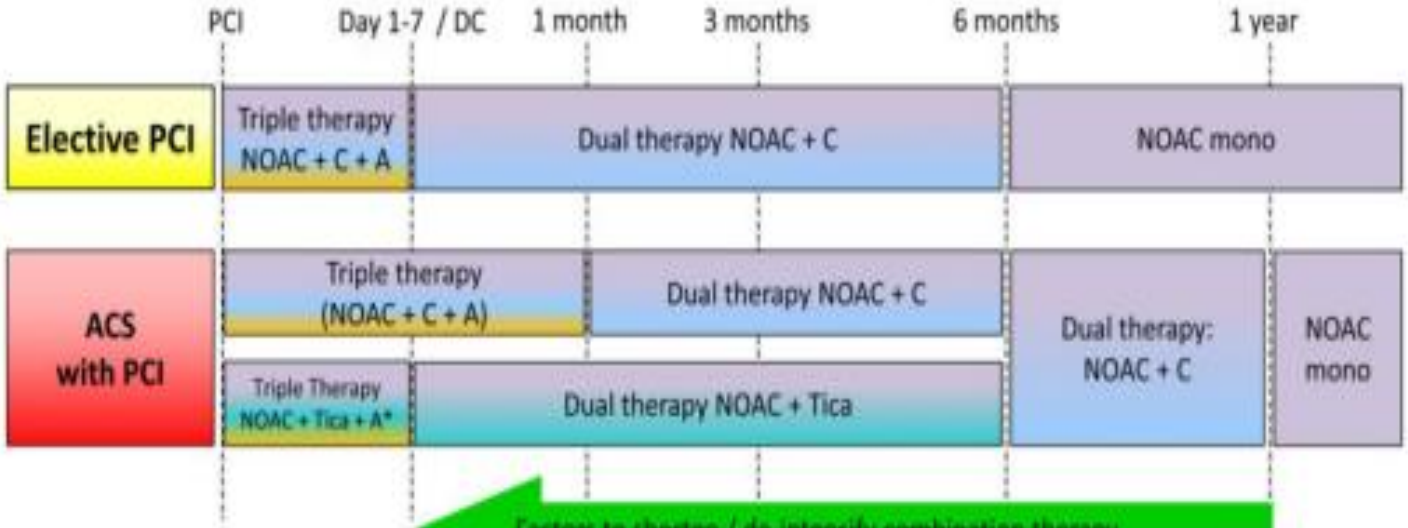
Minor risk interventions (i.e. infrequent bleeding and with low clinical impact)
Dental extractions (1–3 teeth), paradontal surgery, implant positioning, subgingival scalling/cleaning
Cataract or glaucoma intervention
Endoscopy without biopsy or resection
Superficial surgery (e.g. abscess incision; small 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

For each patient, individual factors relating to bleeding and thromboembolic risk need to be taken into account and be discussed with the operating physician and the patient (see *Figure 13*).

	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



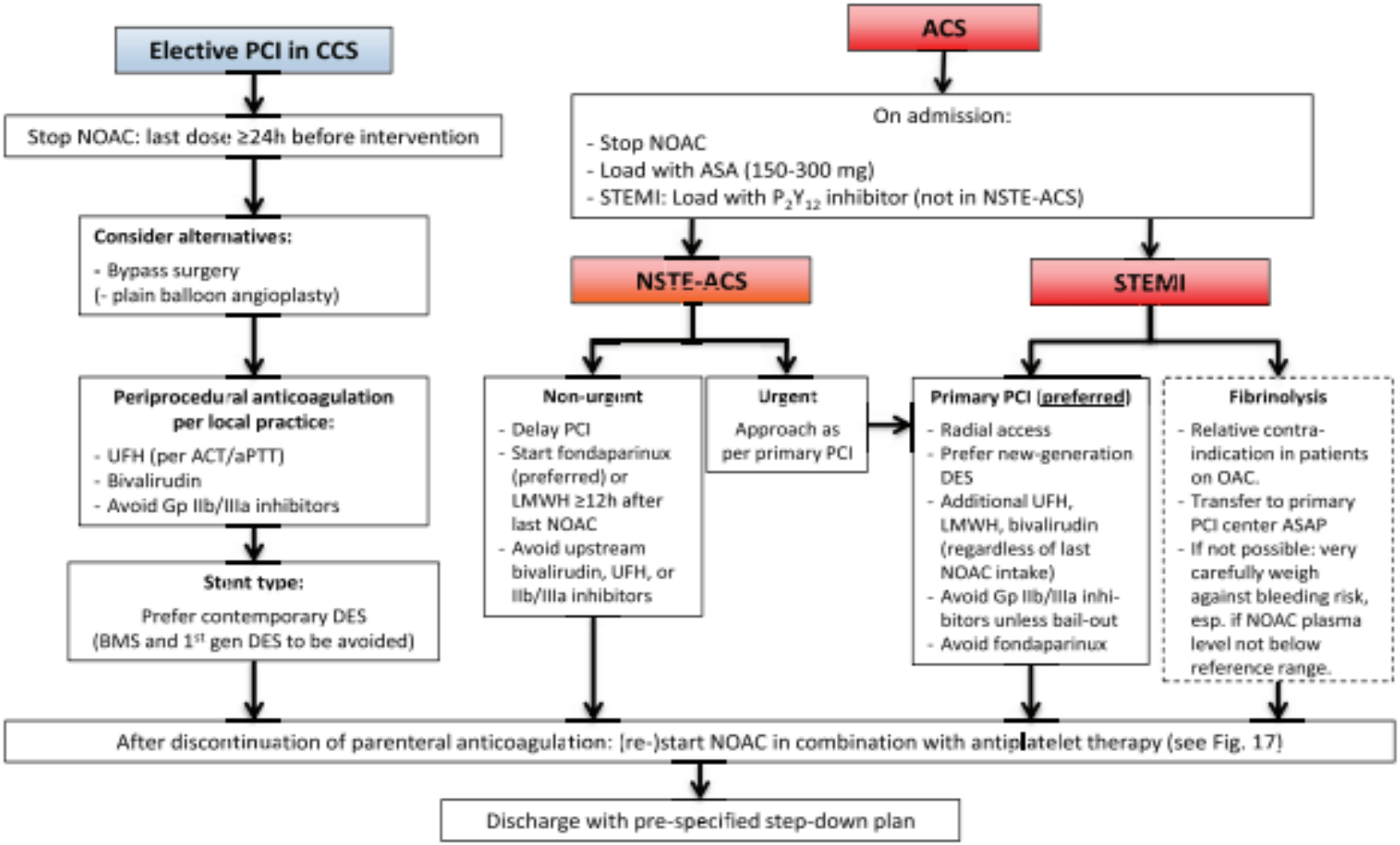
- (Uncorrectable) high bleeding risk
- Low atherothrombotic risk (by REACH or SYNTAX score if elective; GRACE < 140 if ACS)

Factors to lengthen / intensify combination therapy

- High atherothrombotic risk (scores as above; stenting of left main, proximal LAD, proximal bifurcation; recurrent MIs; stent thrombosis etc.) and low bleeding risk

In all patients:

- Avoid use of BMS / first generation DES
- Use PPI if on triple / dual therapy
- Minimize bleeding risk by assessing and treating modifiable bleeding risk factors (e.g., hypertension, etc.)
- Close follow-up; check for signs of (occult) bleeding



igure 18 Acute management of elective PCI or ACS in AF patients treated with NOAC. ACS, acute coronary syndrome; ACT, activated clotting me; AF, atrial fibrillation; aPTT, activated prothrombin time; BMS, bare metal stent; CCS, chronic coronary syndrome; DES, drug-eluting stent; MWH, low molecular weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UFH, unfractionated heparin.