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KEY MESSAGES

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European Heart
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Afib series

The 2018 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

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The 2018 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

Table of Contents

1. Eligibility for NOACs

Selected indications and contra-indications for NOAC therapy in AF

Condition	Eligibility for NOAC therapy
Mechanical prosthetic valve	Contraindicated
Moderate to severe mitral stenosis (usually of rheumatic origin)	Contraindicated
Mild to moderate other native valvular disease (e.g., mild-moderate aortic stenosis or regurgitation, degenerative mitral regurgitation etc.)	Included in NOAC trials
Bioprosthetic valve (after >3 months post operatively)	Not advised if for rheumatic mitral stenosis
	Acceptable if for degenerative mitral regurgitation or in the aortic position
Mitral valve repair (after >3 months post operatively)	Acceptable if for degenerative mitral regurgitation or in the aortic position
PTAV (percutaneous transluminal aortic valvuloplasty) TAVI (transcatheter aortic valve implantation)	No prospective data yet May require combination with single or dual antiplatelet therapy
Hypertrophic cardiomyopathy	Few data, but patients may be eligible for NOACs

Hatched – Limited data

2. Practical start-up and follow-up scheme for patients on NOACs

The EHRA universal NOAC Card (extract)

Oral Anticoagulation Card for NOACs in AF

Name of patient:

Date of Birth:

Address:

Oral anticoagulant:

Dosing:

Timing:

With or without food:

Started on:

More info:
www.NOACforAF.eu
www.noacforaf.eu

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Physician or clinic coordinating NOAC treatment

Name of physician:

Address:

Tel.:

Emergency information

In case of an emergency, please contact the relative(s) of the patient or the following person:

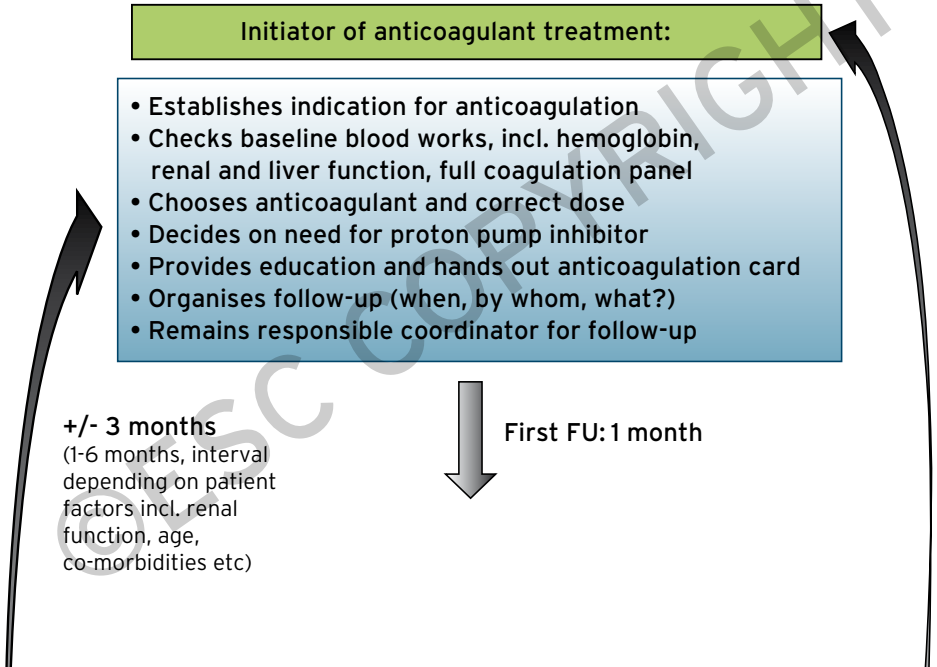
Name:

Tel.:

Name:

Tel.:

Structured follow-up



- Checks for thromboembolic and bleeding events
- Assesses adherence, re-enforces education
- Checks for side effects
- Assesses co-medications and over-the-counter drugs
- Assesses modifiable risk factors, takes every effort to minimise them
- Determines the need for blood sampling
- Assesses optimal NOAC and correct dosing

In case of problems: contacts initiator of treatment. Difficult decisions on anticoagulation should be taken by a multidisciplinary team.

Otherwise:

- Fills out anticoagulation card
- Reinforces key educational aspects
- Sets date/place for next follow-up

Checklist during follow-up contacts of AF patients on anticoagulation

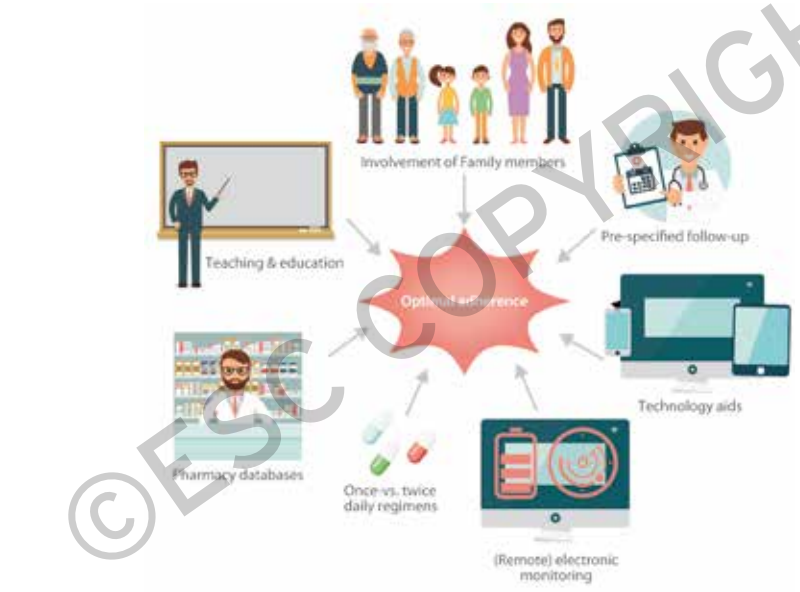
	Interval	Comments
1. Adherence	Each visit	- Instruct patient to bring NOAC card and complete list of medication: make note and assess average adherence. - Re-educate on importance of strict intake schedule. - Inform about adherence aids (special boxes; smartphone applications; ...). Consider specific adherence measuring interventions (review of pharmacy refill data; electronic monitoring; special education session; ...).
2.Thrombo-embolism	Each visit	- Systemic circulation (TIA, stroke, peripheral). - Pulmonary circulation.
3. Bleeding	Each visit	- "Nuisance" bleeding: preventive measures possible? Motivate to diligently continue anticoagulation. - Bleeding with impact on quality-of-life or with risk: prevention possible? Need for revision of anticoagulation indication, dose or timing?
4. Other side effects	Each visit	- Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation, or change of anticoagulant drug.
5. Co-medications	Each visit	- Prescription drugs; over-the-counter drugs. - Interval history: also temporary use can be risky
6. Blood sampling (incl. Hb, renal / liver function)	Yearly	In all patients except those below
	6-monthly	≥75yrs (especially if on dabigatran), or frail.
	x-monthly	If renal function CrCl ≤60ml/min: recheck interval = CrCl / 10 (e.g. every 4 months if CrCl = 40)
	If needed	If intercurrent condition that may impact renal or hepatic function.

Checklist during follow-up contacts of AF patients on anticoagulation (continued)

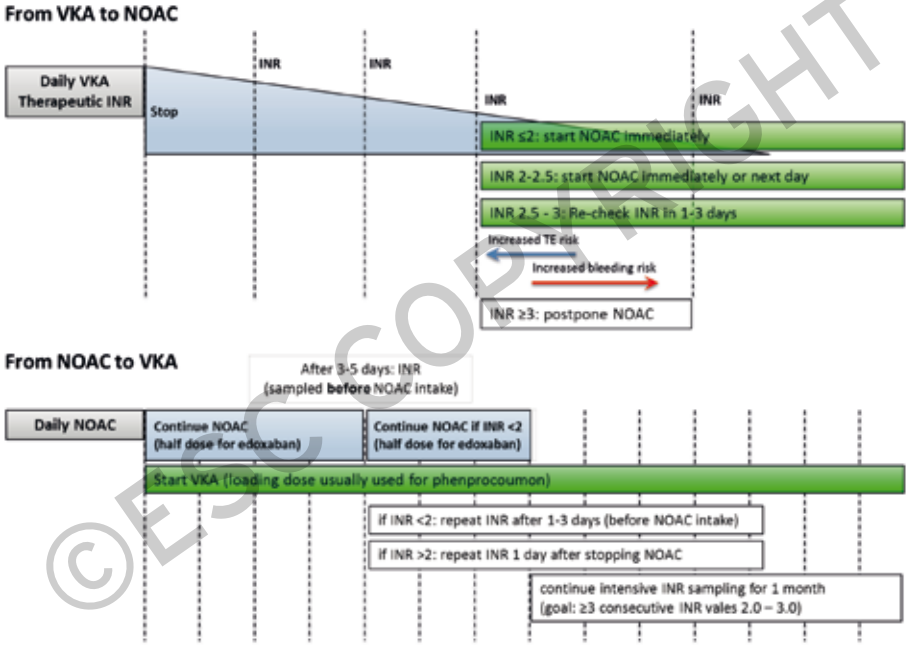
	Interval	Comments
7. Assessing and minimising modifiable risk factors for bleeding	Each visit	As recommended by current guidelines
		Particularly: Uncontrolled hypertension (systolic >160 mmHg, medication predisposing for bleeding (e.g., aspirin, NSAIDs), labile INR (if on VKA), excessive alcohol intake)
8. Assessing for optimal NOAC and correct dosing	Each visit	Especially based on the above, re-assess whether a) The chosen NOAC is the best for the patient b) The chosen dose is correct

3. Ensuring adherence to prescribed oral anticoagulant intake

Selection of possibilities to increase adherence to NOACs



4. Switching between anticoagulant regimens



5. Pharmacokinetics and drug-drug interactions of NOACs

Absorption and metabolism of the different NOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bio-availability	3–7%	50%	62%	15 mg / 20 mg: 66% without food, 80-100% 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)	not dialysable	not dialysable	not dialysable
Liver metabolism: CYP3A4 involved	No	Yes (elimination, moderate contribution [≈25%])	Minimal (<4% of elimination)	Yes (hepatic elimination ≈18%)
Absorption with food	No effect	No effect	6-22% more; minimal effect on exposure	+39% more (therefore needs to be taken with food)
Asian ethnicity	+25%	No effect	No effect	No effect
Elimination half-life	12–17 h	12 h	10–14 h	5–9 h (young) 11–13 h (elderly)

Effect of drug-drug interactions and clinical factors on NOAC plasma levels ('area under the curve, 'AUC')

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Antiarrhythmic drugs					
Amiodarone	moderate P-gp competition	+12–60%	No PK data	40%	Minor effect
Digoxin	P-gp competition	No effect	No effect	No effect	No effect
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect	+40%	No data yet	No effect
Dronedarone	P-gp competition and CYP3A4 inhibition	+70–100% (US: 2 x 75 mg if CrCl 30–50 mL/min)	No PK or PD data: caution	+85%	Moderate effect; should be avoided
Quinidine	P-gp competition	+53%	No data yet	+77% (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12–180% (if taken simultaneously)	No PK data	+53% (SR) (No dose reduction required by label)	No effect

Effect of drug-drug interactions and clinical factors on NOAC plasma levels ('area under the curve, 'AUC') (continued)

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	No relevant interaction	No data yet	No effect	No effect
Ticagrelor	P-gp competition	+ ~25% (give loading dose 2h after dabigatran)**	No data	No data	No data
Antibiotics					
Clarithromycin; Erythromycin	moderate P-gp competition and strong CYP3A4 inhibition	+15 to 20%	+60% AUC+ 30% Cmax	90%	+34% (erythromycin) / 54% (Clarithromycin)
Rifampicin	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	minus 66%	minus 54% 446	minus 35%, but with compensatory increase of active metabolites	Up to minus 50%

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase	No data yet	Up to +153%
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if given systemically
Itraconazole; Ketoconazole; Voriconazole	potent P-gp and BCRP competition; CYP3A4 inhibition	+140 to 150%(US: 2 x 75 mg if CrCl 30-50 ml/min)	+100%	+87 to 95% (reduce NOAC dose by 50%)	Up to +160%
Posaconasole	Mild to moderate P-gp inhibition				
Others					
Naproxen	P-gp competition	No data yet	+55%	No effect	No data yet
H2B; PPI; Al-mg-hydroxide	GI absorption	Minus 12% -30%	No effect	No effect	No effect
St. John's wort	P-gp/ BCRP and CYP3A4/CYP2J2 inducers				

Effect of drug-drug interactions and clinical factors on NOAC plasma levels ('area under the curve, 'AUC') (continued)

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Other factors:					
Age ≥80 ys	Potential for Increased plasma levels		Dose reduction based on published criteria	No significant effect of age after adjusting for weight and renal function	
Age ≥75 ys	Potential for Increased plasma levels				
Weight ≤60 kg	Potential for Increased plasma levels		Dose reduction based on published criteria	Dose reduction based on published criteria	
Renal function	Increased plasma level	See page 27			
Other increased bleeding risk		• Concomitant antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants • History of GI bleeding • Recent surgery on critical organ (brain; eye) • Frailty / falls risk • St.p bleeding or predisposition (anemia, thrombocyte-penia)			

Legend to table:

Hatched: no clinical or PK data available, recommendations based on NOAC SmPC (where available) or expert opinion.

White: No relevant drug-drug interaction anticipated

Yellow: Consider dose adjustment or different NOAC if ≥2 'yellow' factors are present (see Fig. 5)

Orange: Consider dose adjustment or different NOAC (see Fig. 5)

Red: contraindicated / not recommended.

Brown: Contraindicated due to reduced NOAC plasma levels

Blue: The label for edoxaban mentions that co-administration is possible in these cases, despite a decreased plasma level, which is deemed not clinically relevant. Since not tested prospectively, however, such concomitant use should be used with caution and avoided when possible.

$: Based on in vitro investigations, comparing the IC50 for P-gp inhibition to maximal plasma levels at therapeutic dose, and/or on interaction analysis of efficacy and safety endpoints in the phase-3 clinical trials. No direct PK interaction data available.

****:** Data from Phase I study. Evidence from Re-DUAL PCI indicate safety in the (small) subgroup on dabigatran and ticagrelor.

BCRP: breast cancer resistance protein; **NSAID:** non-steroidal anti-inflammatory drugs; **H2B:** H2-blockers; **PPI:** proton pump inhibitors; **P-gp:** P-glycoprotein; **GI:** gastro-intestinal.

Anticipated effects of common anticancer drugs on NOACs plasma levels

	Via	Dabi	Apix	Edo	Riva
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 Substrate		No	≈25%	<4%	≈18%
Antiarrhythmic drugs					
Paclitaxel	Moderate CYP3A4 induction; CYP3A4/P-gp competition				
Vinblastine	Strong P-gp induction; CYP3A4/P-gp competition				
Docetaxel, Vincristine	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Vinorelbine	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Antimetabolites					
Metotrexate	P-gp competition; no relevant interaction anticipated				
Pemetrexed, Purine analogs, Pyrimidine analogs	No relevant interaction anticipated				
Topoisomerase inhibitors					
Topotecan	No relevant interaction anticipated				
Irinotecan	CYP3A4/P-gp competition; No relevant interaction anticipated				
Etoposide	Mild CYP3A4 inhibition; CYP3A4/ P-gp competition				

	Via	Dabi	Apix	Edo	Riva
Anthracyclines / Anthracenediones					
Doxorubicin	Strong P-gp induction, mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Idarubicin	Mild CYP3A4 inhibition; P-gp competition				
Daunorubicin	P-gp competition; No relevant interaction anticipated				
Mitoxantrone	No relevant interaction anticipated				
Alkylating agents					
Ifosfamide	Mild CYP3A4 inhibition; CYP3A4 competition				
iclophosphamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Lomustine	Mild CYP3A4 inhibition				
Busulfan	CYP3A4 competition; No relevant interaction anticipated				
Bendamustine	P-gp competition; No relevant interaction anticipated				
Chlorambucil, Melphalan, Carmustine, Procarbazine, Dacarbazine, Temozolomide	No relevant interaction anticipated				

Anticipated effects of common anticancer drugs on NOACs plasma levels (continued)

	Via	Dabi	Apix	Edo	Riva
Platinum-based agents					
Cisplatin, Carboplatin, Oxaliplatin	No relevant interaction anticipated				
Intercalating agents					
Bleomycin, Dactinomycin	No relevant interaction anticipated				
Mitomycin C	No relevant interaction anticipated				
Tyrosine kinase inhibitors					
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 induction; CYP3A4 competition				
Erlotinib, Gefitinib	CYP3A4 competition; No relevant interaction anticipated				

	Via	Dabi	Apix	Edo	Riva
Monoclonal antibodies					
Brentuximab	CYP3A4 competition; No relevant interaction anticipated				
Rituximab, Alemtuzumab, Cetuximab, Trastuzumab, Bevacizumab	No relevant interaction anticipated				
Hormonal agents					
Abiraterone	Moderate CYP3A4 inhibition, strong P-gp inhibition; CYP3A4/P-gp competition				
Enzalutamide	Strong CYP3A4 induction, strong P-gp inhibition; CYP3A4/P-gp competition				
Bicalutamide	Moderate CYP3A4 inhibition				
Tamoxifen	Strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4 competition				
Anastrozole	Mild CYP3A4 inhibition				
Flutamide	CYP3A4 competition; No relevant interaction anticipated				
Letrozole, Fulvestrant	CYP3A4 competition; No relevant interaction anticipated				

Anticipated effects of common anticancer drugs on NOACs plasma levels (continued)

	Via	Dabi	Apix	Edo	Riva
Hormonal agents					
Raloxifene, Leuprolide, Mitotane	No relevant interaction anticipated				
Immune-modulating agents					
Cyclosporine	Strong-to-moderate P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC	SmPC	+73%	
Dexamethasone	Strong CYP3A4/P-gp induction; CYP3A4/P-gp competition				
Tacrolimus	Moderate CYP3A4 induction; CYP3A4 competition	SmPC			
Prednisone	Moderate CYP3A4 induction; CYP3A4 competition				
Temsirolimus, Sirolimus	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Everolimus	CYP3A4 competition; No relevant interaction anticipated				

Anticipated effects of antiepileptic drugs on NOACs plasma levels

	Via	Dabi	Apix	Edo	Riva
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 Substrate		No	≈25%	<4%	≈18%
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	SmPC	-50% (SmPC	-35% (SmPC	SmPC
Ethosuximide	CYP3A4 competition; No relevant interaction known/assumed				
Gabapentin	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/P-gp induction; P-gp competition		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC	SmPC	SmPC	SmPC
Pregabalin	No relevant interaction known/assumed				
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction				
Zonisamide	CYP3A4 competition; No relevant interaction known/assumed				

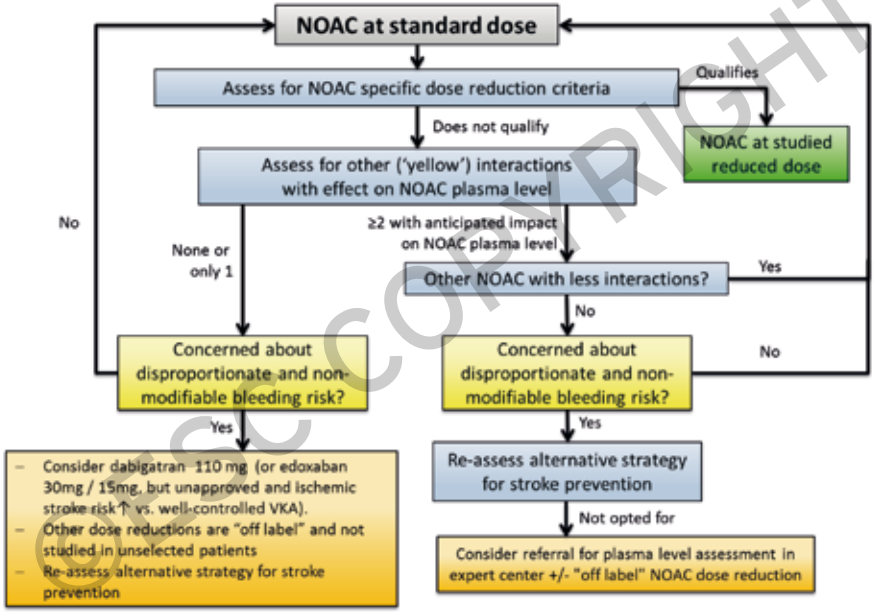
Legend to table:

Hatched colour coding indicates no clinical or PK data available, and recommendations based on the respective NOAC SmPC (where available) or expert opinion. Some of the colour codes will likely require adaptation as more data become available over time.

White: No relevant drug-drug interaction anticipated.
Yellow (light): Caution is needed in case of polypharmacy or in the presence of ≥2 bleeding risk factors.
Yellow: Consider dose adjustment or different NOAC if 2 or more 'yellow' factors are present
Orange: Consider dose adjustment or different NOAC.
Red: contra-indicated/not recommended.
Brown (dark): Contraindicated due to reduced NOAC plasma levels.
Brown (light): Use with caution or avoid. Either expert opinion or the NOAC label mentions that co-administration is possible despite a decreased plasma level, which is deemed not clinically relevant (nevertheless, since not tested prospectively, such concomitant use should be used with caution, and avoided when possible).

Where no data or SmPC instructions were available, expert opinion was based on the following principles:
Strong CYP3A4 and/or P-gp inducer – should not be used (dark brown)
Moderate CYP3A4 or P-gp inducer – use with caution or avoid (light brown)
Strong CYP3A4 and/or inhibitor – should not be used (red)
Moderate CYP3A4 or P-gp inhibitor – use with caution, consider dose reduction or different NOAC (orange)
Mild CYP3A4 and/or P-gp inducers or inhibitors – caution is needed with polypharmacy or in the presence of ≥2 bleeding risk factors (yellow)

NOAC selection based on drug-drug interactions and / or risk of bleeding



Important pointers:

- Identify best NOAC and correct dose to individualize treatment.
- **Dose reduction primarily recommended according to the published dose reduction criteria.**
- **Whenever possible, the tested standard dose of NOACs should be used.**
- Consider patient age, weight, renal function, co-medications and other comorbidities
- Consider interactions
- The use of **plasma level monitoring for NOAC dose-adjustment is discouraged** for the vast majority of patients due to the lack of outcome data. Only to be used in very rare cases (see page 28) and in centres with extensive experience.
- An elevated HAS-BLED score in itself should not automatically result in decision not to anticoagulate.
- Minimize modifiable risk factors for bleeding

6. NOACs in patients with chronic kidney or advanced liver disease

Calculation of the Child-Pugh score and use of NOACs in hepatic insufficiency

Parameter	1 point	2 points	3 points
Encephalopathy	No	Grade 1-2 (suppressed with medication)	Grade 3-4 (refractory / chronic)
Ascites	No	Mild (diuretic-responsive)	Moderate-severe (diuretic-refractory)
Bilirubin	<2 mg/dL	2-3 mg/dL	>3 mg/dL
	<34 μmol/L	34-50 μmol/L	>50 μmol/L
Albumin	>3.5 g/dL	2.8-3.5 g/dL	<2.8 g/dL
	>35 g/L	28-35 g/L	<28 g/dL
INR	<1.7	1.71-2.30	>2.30

Child-Pugh category	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
A (5-6 points)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B (7-9 points)	Use with caution	Use with caution	Use with caution	DO NOT USE
C (10-15 points)	DO NOT USE	DO NOT USE	DO NOT USE	DO NOT USE

Diagnosing CKD; estimation of renal function; categories of renal dysfunction

Decreased GFR*	- GFR <60 mL/min/1.73m^2
Markers of kidney damage (≥1)	- Excessive albuminuria (Albumin Excretion Rate ≥30 mg/24h; Albumin-to-Creatinine Ratio ≥30 mg/g or ≥3 mg/mmol) - Urine sediment abnormalities - Electrolyte or other abnormality caused by tubular disorders - Abnormal histology - Structural abnormalities detected by kidney imaging - History of kidney transplantation

GFR category	CKD stage	GFR *	Description
G1	1	≥90	Normal or high
G2	2	60–89	Mildly decreased
G3a	3	45–59	Mildly to moderately decreased
G3b		30–44	Moderately to severely decreased
G4	4	15–29	Severely decreased
G5	5	<15	Kidney failure (requires renal replacement therapy)

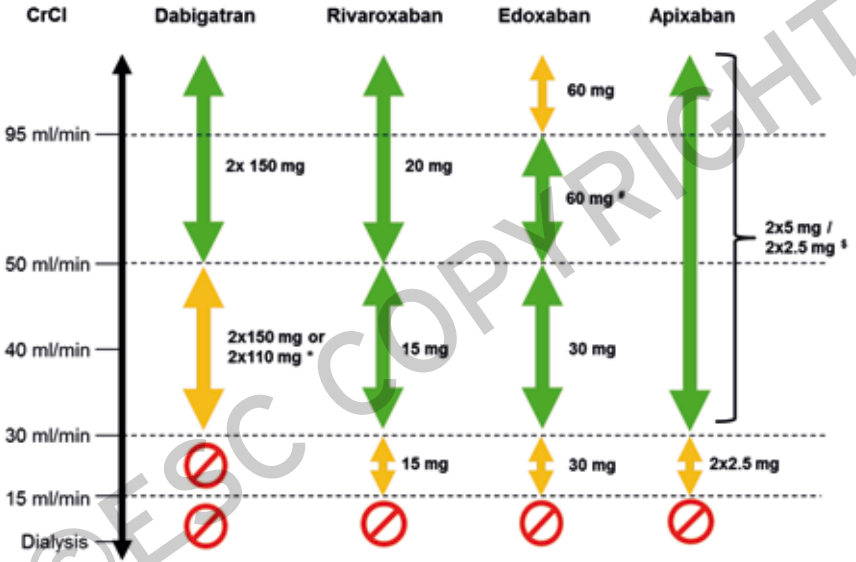
* Glomerular filtration rate [ml/min/1.73m^2]

Estimation of renal function in NOAC patients by Creatinine Clearance (Cockroft-Gault):

$$\text{CrCl [mg/dl]} = \frac{(140 - \text{age}) \times \text{weight (in kg)} \times [0.85 \text{ if female}]}{72 \times \text{serum creatinine (in mg/dL)}}$$

Rule of thumb: Minimum frequency of renal function testing in months = CrCl / 10

Use of NOACs according to renal function



*: 2x 110 mg in patients at high risk of bleeding (post-hoc; per SmPc) - #: Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy)- $: 2x2.5 mg only if at least 2 out of 3: Age ≥80 years, Body weight ≤60 kg, Creatinine ≥1.5 mg/dl (133 μmol/l).
Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function).

7. How to measure the anticoagulant effect of NOACs

Peak / trough levels of NOACs and effect on routine coagulation assays

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Expected plasma levels of NOACs in patients treated for AF				
Expected range of plasma levels **at peak** for standard dose (ng/ ml)	64 - 443	69 - 321	91 - 321	184 - 343
Expected range of plasma levels **at trough** for standard dose (ng/ ml)	31 - 225	34 - 230	31 - 230	12 - 137
Effect of NOACs on routine coagulation assays				
PT	↑	(↑)	↑(↑)	↑↑(↑)
aPTT	↑↑(↑)	(↑)	↑	↑
ACC	↑(↑)	↑	↑	↑
TT	↑↑↑↑	-	-	-

Ranges indicate the P5/95 percentiles for dabigatran, rivaroxaban and apixaban, and the interquartile ranges for edoxaban.

Consider plasma level measurements in case of:

- Severe or life-threatening bleeding
- Emergency operation (or elective operation with high bleeding risk)
- Ischemic stroke on NOAC
- Special situations (e.g., multiple drug-drug interactions; very obese / underweight)

8. Plasma NOAC level measurement: rare indications, precautions and potential pitfalls

- **NOACs do not require monitoring of coagulation.**
- However, laboratory assessment of drug exposure and anticoagulant effect may help clinicians in certain situations (see previous page)
- This, however, should only be done under the guidance of a coagulation expert and in the knowledge that hard clinical outcome data do not exist for such a strategy.
- The anticoagulant effects of NOACs can be measured via specific coagulation assays developed for the quantification of NOAC plasma levels. The use of appropriate calibrators allows for the determination of plasma concentrations of all NOACs.
- **Routine coagulation tests (PT and aPTT) generally do not provide an accurate assessment** of NOAC plasma levels.

9. How to deal with dosing errors

Missed dose

- A forgotten dose may be taken until 50% of the dosing interval has passed.
- **BID dosing regimen (i.e. intake every 12 h):** forgotten dose can be taken up until 6 h after the scheduled intake.
- **OD dosing regimen:** forgotten dose can be taken up until 12 h after the scheduled intake. After this time point, the dose should be skipped and the next scheduled dose should be taken.
- These intervals may be extended in patients with a high stroke risk.

Double dose

- **BID dosing regimen:** The next planned dose (i.e. after 12 h) may be left out, and BID intake restarted 24 h after the double dose intake.
- **OD dosing regimen:** Continue normal dosing regimen, i.e. without skipping the next daily dose.

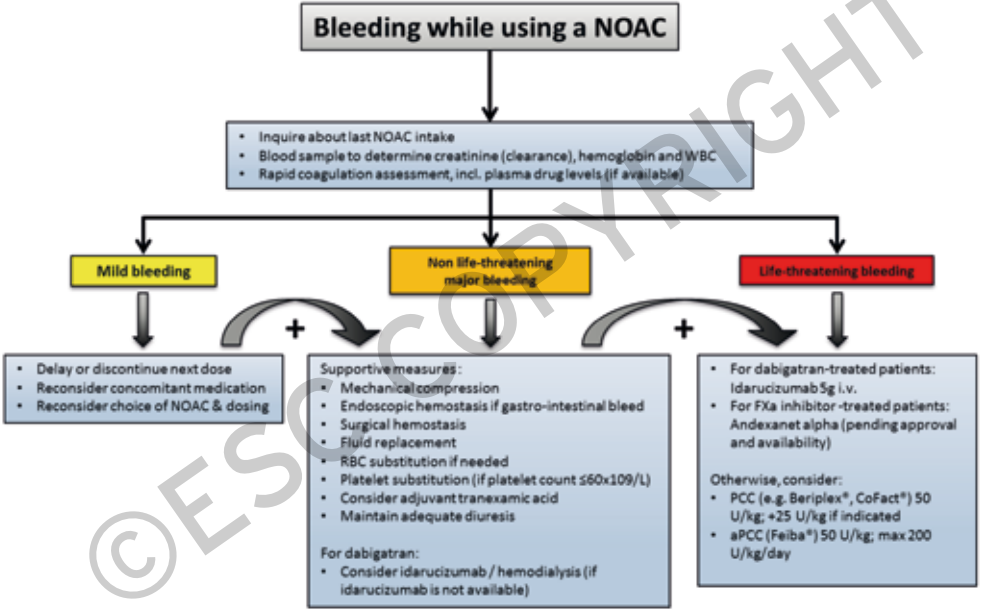
Uncertainty about dose intake

- **BID dosing regimen:** Generally do not take another tablet / capsule, but continue with the regular dose regimen, i.e. starting with the next dose at the 12 h interval.
- **OD dosing regimen:**
  - High thromboembolic risk (e.g., CHA_2DS_2-VASc ≥3): take another tablet and then continue the planned dose regimen.
  - Low thromboembolic risk (e.g., CHA_2DS_2-VASc ≤2): wait until the next scheduled dose.

10. Suspected overdose without bleeding / Clotting test indicating a potential risk of bleeding

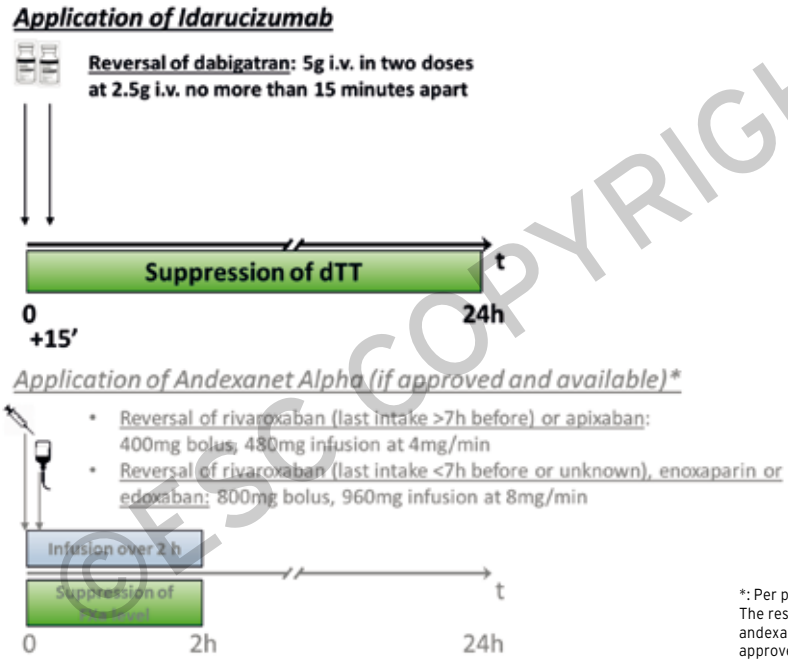
- A normal aPTT excludes high levels of dabigatran
- A normal PT excludes very high levels of rivaroxaban and edoxaban (but not apixaban).
- Important: Routine coagulation tests are not appropriate for a quantitative assessment of high levels of NOACs.
- 'Wait-and-see' strategy can be used in most cases without active bleeding (short half-lives of NOACs)
- Recent acute ingestion of an overdose (especially when ≤2h ago): Consider activated charcoal (standard dosing scheme for adults: 30–50 g).
- If more aggressive normalization of plasma levels is deemed necessary: See chapter 11 (next pages).
- Non-specific support of haemostasis: Only in exceptional cases (balance against pro-thrombotic risk!)

11. Management of bleeding under NOAC therapy



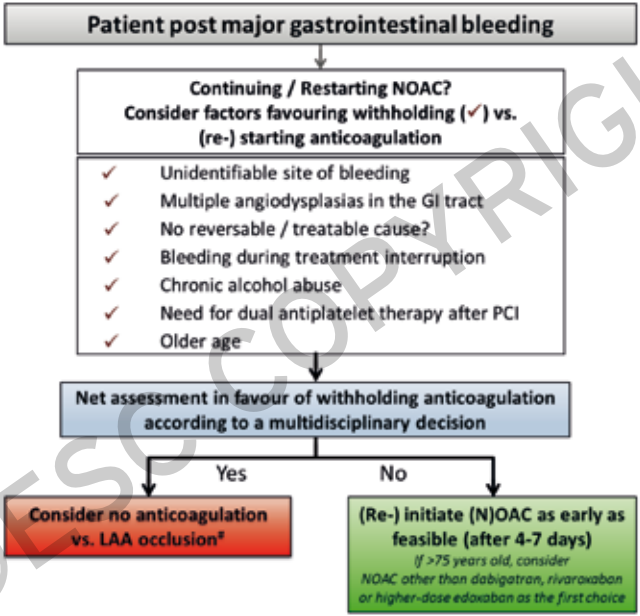
Andexanet alpha: Final results of the outcome study (ANNEXA-4) are still pending, the drug is not yet approved and not yet available.

Application and effect of idarucizumab and andexanet alpha



*: Per protocol of ANNEXA-4. The results are still pending; andexanet alpha is not yet approved and not yet available.

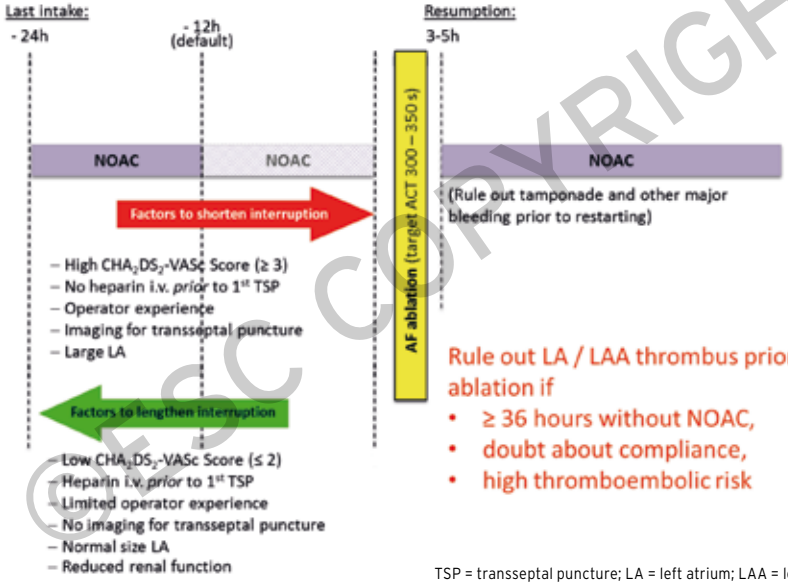
(Re-) initiation of anticoagulation post gastrointestinal bleeding



#: without RCT evidence; ideally include patient in ongoing trial.

12. Patients undergoing a planned invasive procedure, surgery or ablation

NOAC management before and after atrial fibrillation ablation



TSP = transseptal puncture; LA = left atrium; LAA = left atrial appendage.

Classification of elective surgical interventions acc. to bleeding risk

Interventions with minor bleeding risk
Dental interventions
Extraction of 1 to 3 teeth
Paradontal surgery
Incision of abscess
Implant positioning
Cataract or glaucoma intervention
Endoscopy without biopsy or resection
Superficial surgery (e.g. abscess incision; small dermatologic excisions; ...)
Interventions with low bleeding risk (i.e. infrequent or with low clinical impact)
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or catheter ablation (except complex procedures, see below)
Non-coronary angiography (for coronary angiography and ACS: see Section 14, page 42)
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)

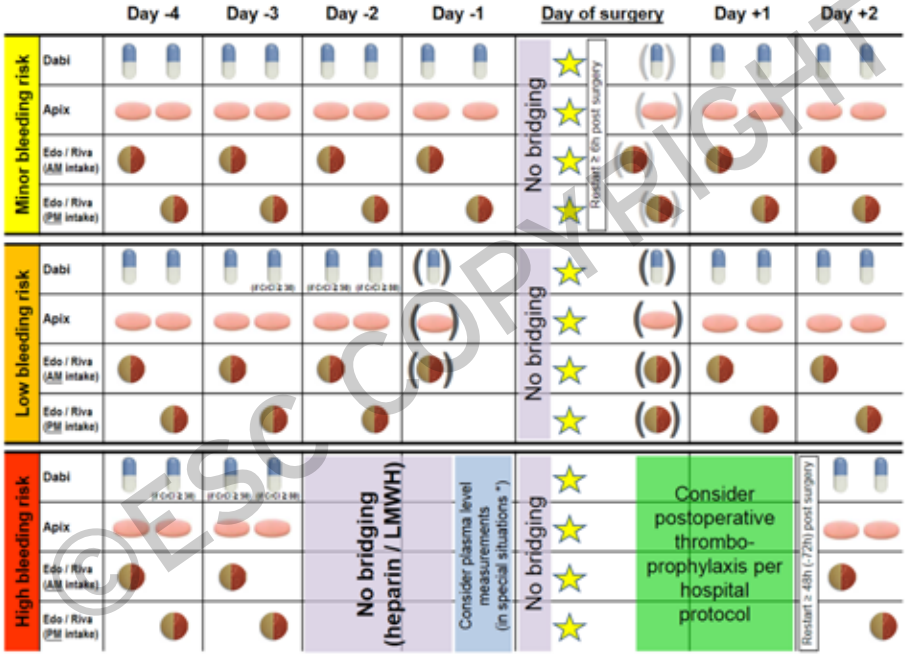
Classification of elective surgical interventions acc. to bleeding risk

Interventions with high bleeding risk (i.e. frequent and/or with high impact)
Complex endoscopy (e.g. polypectomy, ERCP with sphincterotomy etc.)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopaedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy
Extracorporeal shockwave lithotripsy (ESWL)
Complex left-sided ablation (pulmonary vein isolation; some VT ablations)

Timing of last NOAC intake before start of an elective intervention

<table>
<tr><th></th><th colspan="2">Dabigatran</th><th colspan="2">Apixaban - Edoxaban
Rivaroxaban</th></tr>
<tr><td></td><td colspan="4">No important bleeding risk and/or adequate local haemostasis possible:
perform at trough level (i.e. 12 h or 24 h after last intake)</td></tr>
<tr><td></td><td>Low risk</td><td>High risk</td><td>Low risk</td><td>High risk</td></tr>
<tr><td>CrCl ≥80 ml/min</td><td>≥24 h</td><td>≥48 h</td><td rowspan="3">≥24 h</td><td rowspan="4">≥48 h</td></tr>
<tr><td>CrCl 50–79 ml/min</td><td>≥36 h</td><td>≥72 h</td></tr>
<tr><td>CrCl 30–49 ml/min</td><td>≥48 h</td><td>≥96 h</td></tr>
<tr><td>CrCl 15–29 ml/min</td><td>Not indicated</td><td>Not indicated</td><td>≥36 h</td></tr>
<tr><td>CrCl <15 ml/min</td><td colspan="4">No official indication for use</td></tr>
<tr><td colspan="5">No bridging with LMWH/UFH</td></tr>
<tr><td colspan="5">Resume full dose of NOAC ≥24h post low bleeding risk interventions and 48 (-72) h
post high-bleeding risk interventions (see also Figure 10)</td></tr>
<tr><td colspan="5">Patients undergoing a planned intervention should receive a written note indicating the anticipated date
and time of their intervention, and the date and time of the last intake of their NOAC
(and any other medication)</td></tr>
</table>

Stopping and re-initiation of NOAC therapy in elective surgery



See legend following page.

Stopping and re-initiation of NOAC therapy in elective surgery (legend)

Yellow star = Time point of the intervention / operation

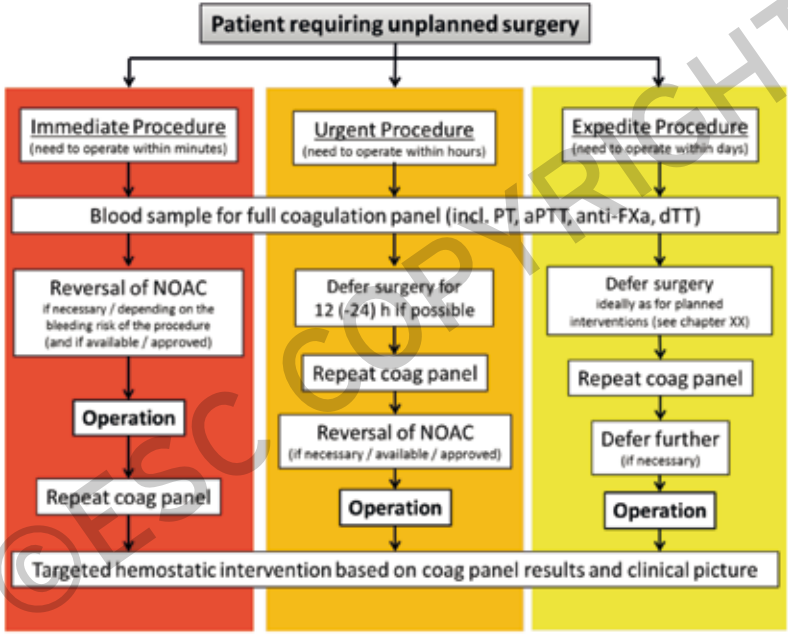
Consider +24 hours of interruption in situations likely resulting in increased plasma levels (e.g., patients taking verapamil, body weight <50kg, significant interactions (see chapter 5)

***:** Consider measurement of plasma levels in very special situations, e.g. highest risk neurosurgery / cardiac surgery, severe renal insufficiency, combination of factors predisposing to higher NOAC levels.

Rivaroxaban needs to be taken with food for stroke prevention in AF, which needs to be looked after consideration (also) in the post-operative setting

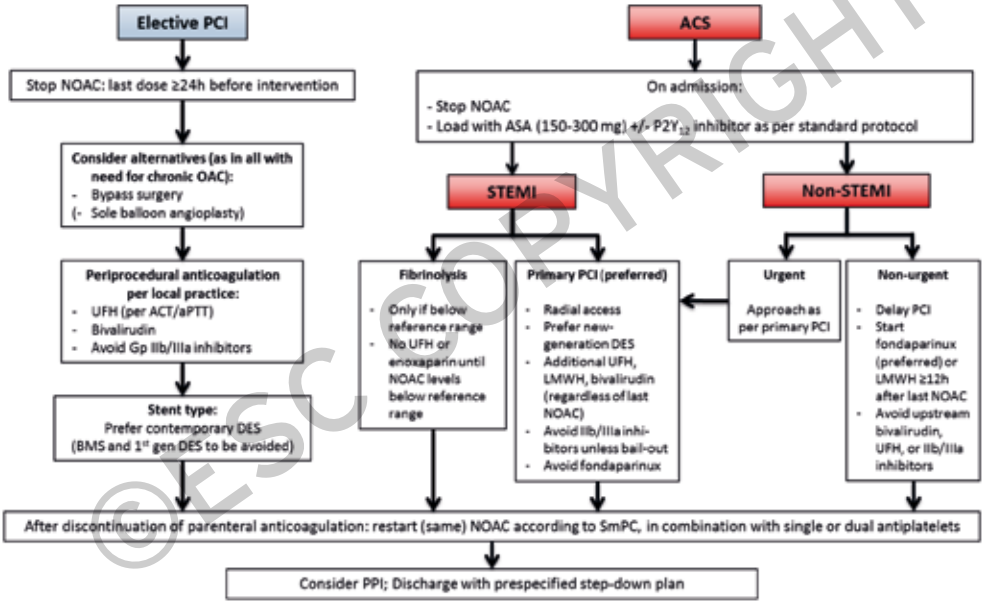
LMWH = Low molecular weight heparin; **Apix** = Apixaban; **Dabi** = Dabigatran; **Edo** = Edoxaban; **Riva** = Rivaroxaban; **CrCl** = Creatinine Clearance.

13. Patients requiring an urgent surgical intervention

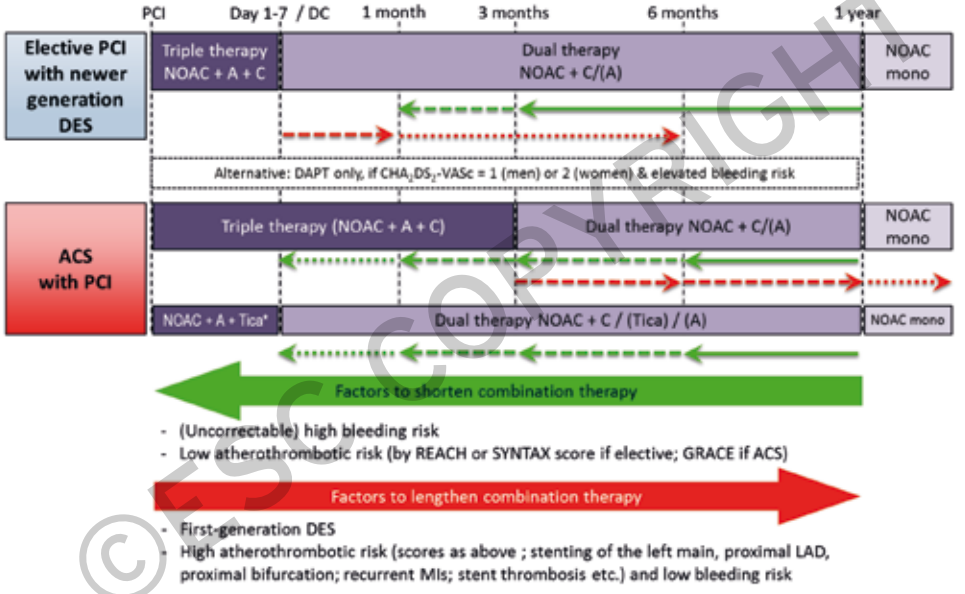


14. Patients with AF and coronary artery disease

Acute management of elective PCI or ACS in AF patients treated with NOAC



Long-term treatment of pts on NOAC therapy after elective PCI or ACS



A = aspirin 75–100 mg OD; C = clopidogrel 75 mg OD; Tica = Ticagrelor 90 mg BID.
*: If triple therapy needs to be continued after discharge clopidogrel is preferred over ticagrelor (due to lack of data).

Important pointers:

- There are innumerable possible variations of (N)OAC + antiplatelet therapy. Patient characteristics and institutional practices should be taken into account to **individualise the approach** to each and every single patient based on a careful assessment of ischaemic versus bleeding risk.

- In general the bleeding risk seems to be lower with a NOAC plus antiplatelet than with a VKA plus antiplatelet.

- The length of DAPT does not depend (anymore) on the type of stent (i.e., DES or BMS) but on the clinical presentation of the patient (i.e., ACS vs. elective stenting)

- In the setting of dual therapy (platelet inhibitor + oral anticoagulant) it may be feasible to use one of the newer P2Y12 inhibitors with a (N)OAC under certain circumstances such as perceived high thrombotic risk, ACS, or prior stent thrombosis.

- The 2017 ESC DAPT and 2016 AF guidelines recommend discontinuing any antiplatelet agent at 12 months after a PCI or ACS episode and to only consider keeping one antiplatelet plus a (N)OAC beyond 12 months in patients at very high risk of coronary events.

15. Avoiding confusion with NOAC dosing across indications

Stroke prevention in Atrial Fibrillation (SPAF)		
	Standard dose	**Comments / dose reduction**
Apixaban	2x 5 mg	2x 2x.5 mg if 2 out of 3: Weight ≤60 kg, Age ≥80 ys, serum Creatinine ≥133 umol/ (1.5 mg/dl) [or if CrCl 15-29 ml/min]
Dabigatran	2x 150 mg or 2x 110 mg	No pre-specified dose-reduction criteria*
Edoxaban	1x 60 mg	1x 30 mg if: Weight ≤60 kg, CrCl ≤50 ml/min, Concomitant therapy with strong P-gp inhibitor
Rivaroxaban	1x 20 mg	1x 15 mg if CrCl ≤50 ml/min

*: SmPC: 2x 110 mg if age ≥80 ys, concomitant verapamil, increased risk of GI bleeding.

Treatment of DVT / PE		
	Initial Therapy	**Remainder of treatment phase**
Apixaban	2x 10 mg, 7 days	2x 5 mg, no dose reduction
Dabigatran	Heparin / LMWH	No pre-specified dose-reduction criteria#
Edoxaban	Heparin / LMWH	1x 60 mg, **same dose reduction as for SPAF! (see above)**
Rivaroxaban	2x 15 mg, 21 days	1x 20 mg, no dose reduction**

#: SmPC: 2x 110 mg if age ≥80 ys, concomitant verapamil, increased risk of GI bleeding (based on PK/PD analyses; not studied in this setting).
**: 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 (i.e. after 6 months)		
	Standard dose	**Comments / dose reduction**
Apixaban	2x 2.5 mg	
Dabigatran	2x 150 mg	No pre-specified dose-reduction criteria#
Edoxaban	not specifically studied	
Rivaroxaban	1x 10 mg	**

#: SmPC: 2x 110 mg if age ≥80 ys, concomitant verapamil (both based on PK/PD analyses; not studied in this setting).
**: SmPc: 1x 20 mg in patients at high risk of recurrence.

VTE prevention post major orthopaedic surgery		
	Standard dose	**Comments / dose reduction**
Apixaban	2x 2.5	
Dabigatran	1x 220 mg	**
Edoxaban	1x 30 mg	Not approved in Europe (only studied in Asia)
Rivaroxaban	1x 10 mg	

**: SmPc: 1x 150 mg if CrCl 30-50 ml/min; concomitant verapamil, amiodarone, quinidine; age >75 ys.

Stroke prevention post PCI (WITH concomitant atrial fibrillation)*		
	Standard dose	**Comments / dose reduction**
Apixaban	To be determined (pending results of AUGUSTUS trial)	
Dabigatran	150 mg BID or 110 mg BID	+ Clopidogrel or Ticagrelor; no dose red.
Edoxaban	To be determined (pending results of ENTRUST-AF PCI trial)	
Rivaroxaban	15 mg OD (+ Clopidogrel)	Dose red. to 10 mg OD if CrCl 30-49 ml/min

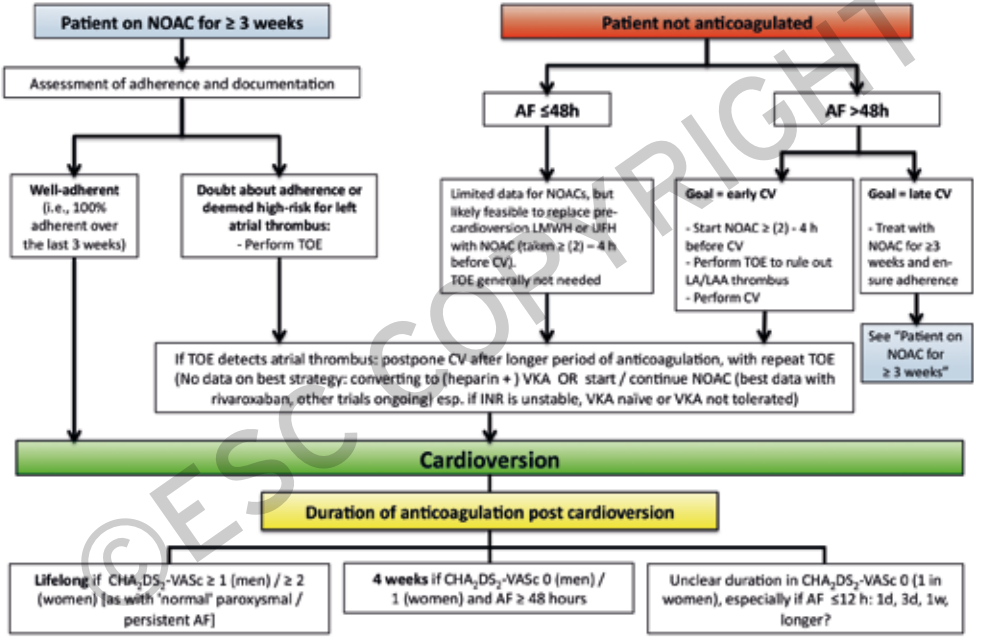
*: Both PIONEER AF-PCI as well as RE-DUAL PCI were powered for safety and were underpowered to determine non-inferiority for individual efficacy endpoints.

Secondary prevention of atherothrombotic events post ACS (without AF)		
	Standard dose	**Comments / dose reduction**
Rivaroxaban	2.5 mg BID	In addition to Aspirin +/- P2Y12 inhibitor

Secondary prevention of atherothrombotic events in stable CAD (without AF)		
	Standard dose	**Comments / dose reduction**
Rivaroxaban	2.5 mg BID	In addition to Aspirin*

*: as studied in COMPASS; approval of this indication and regimen is pending.

16. Cardioversion in a NOAC-treated patient



17. AF patients presenting with acute stroke / intracranial bleed while on NOAC

Acute management of acute ischaemic stroke in a patient on NOAC

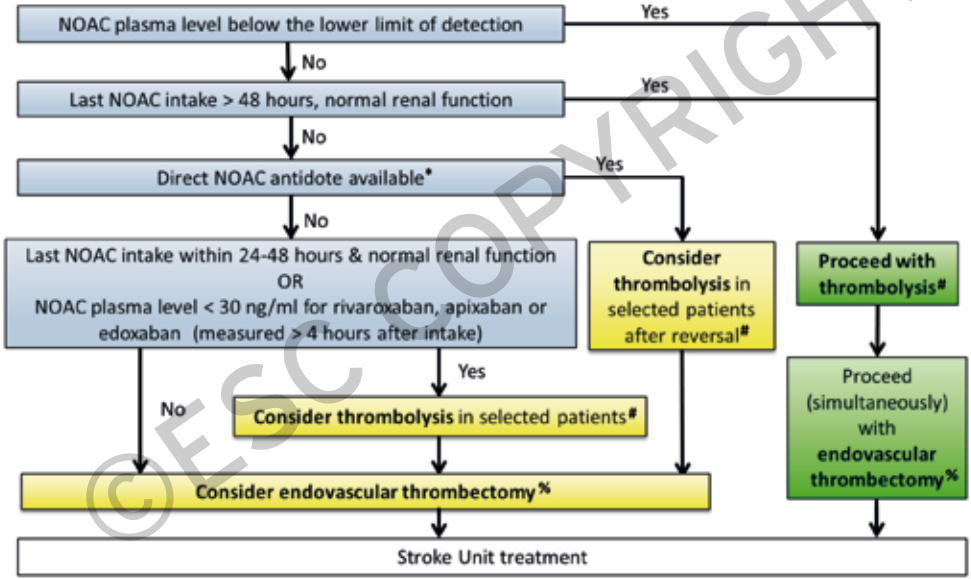


Figure legend (previous page):

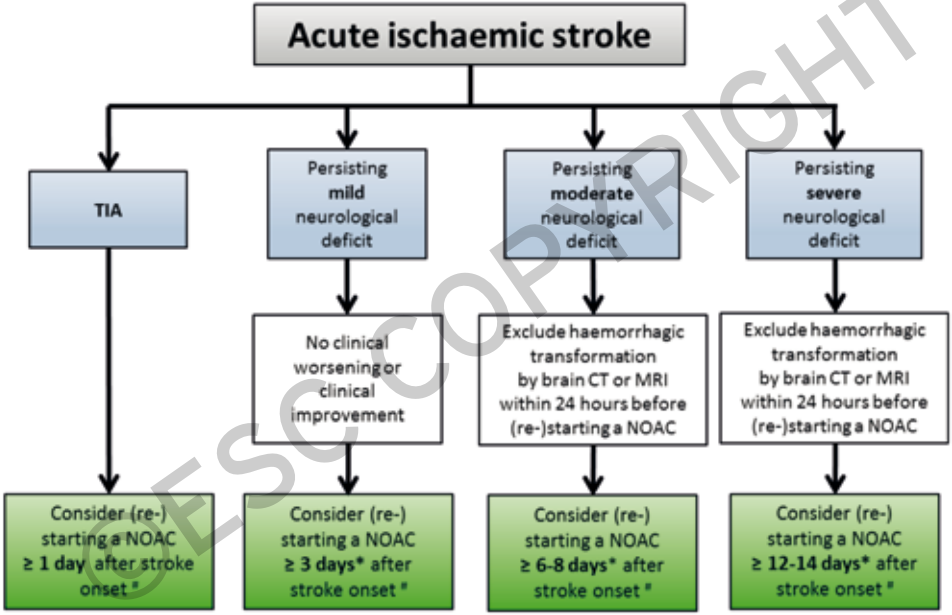
***:** Currently only available for dabigatran (idarucizumab).
#: Perform systemic thrombolysis only if there are no (other) contra-indications for intravenous application of rt-PA according to its label.
%: Perform endovascular thrombectomy only if there is a target vessel occlusion and procedure is indicated and feasible according to present evidence.

Figure legend (facing page)

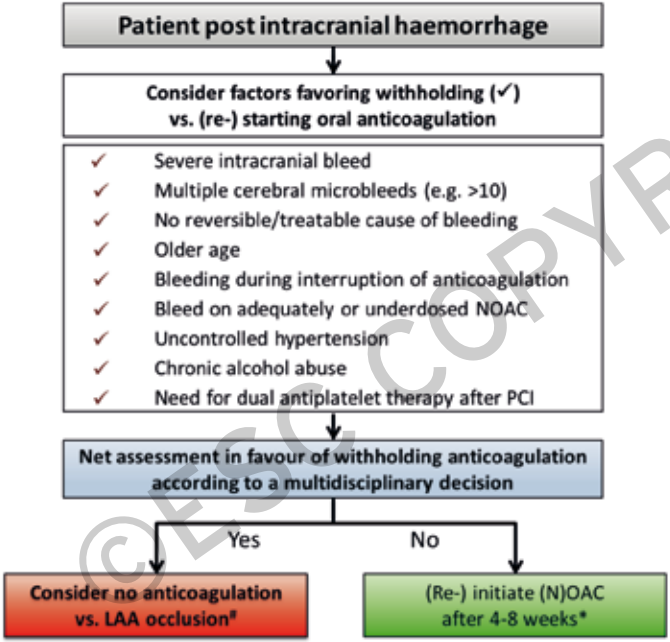
(Re-) start only in the absence of contraindications and if stroke size is not expected to substantially increase the risk of secondary haemorrhagic transformation

***:** Consider shorter delays to (re-) start a NOAC if there is a very high risk of stroke recurrence (e.g. LA(A) thrombus) and no haemorrhagic transformation on follow-up brain imaging (using CT or MRI). Consider longer delays to (re-)start a NOAC according to the recommendations made in the ESC AF Guidelines 2016.
#: Without proven evidence; consider inclusion of patient in an ongoing trial.

(Re-) initiation of anticoagulation after TIA/stroke



(Re-) initiation of anticoagulation post intracranial bleeding



#: without RCT evidence; ideally include patient in ongoing trial.

*: Brain imaging should be considered before (re-)initiation of (N)OAC.

18. NOACs in special situations

The 'Canadian Study of Health and Aging' (CHSA) Clinical Frailty Scale

- Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.
- Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.
- Managing Well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.
- Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.
- Mildly Frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.
- Moderately Frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.
- Severely Frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).
- Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.
- Terminally Ill - Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Modified from http://www.csha.ca and Rockwood et al., Lancet 1999

Examples tools for assessing falls risk

A) High risk of falls

(from ENGAGE-AF TIMI 48)

Presence of one or more of

- prior history of falls
- lower extremity weakness
- poor balance
- cognitive impairment
- orthostatic hypotension
- use of psychotropic drugs
- severe arthritis
- Dizziness

B) Probability falls assessment

1 point for each 'yes'

• Previous falls	Yes / No
• Medications	
>4	Yes / No
Psychotropics	Yes / No
• Low visual acuity	Yes / No
• Diminished sensation	Yes / No
• Near tandem stand 10s	Yes / No
• Alternate step test 10s	Yes / No
• Sit to stand 12s	Yes / No

Score:	0-1	2-3	4-5	6+
Probability of fall per year	7%	13%	27%	49%

- A "perceived" increased risk of falls should be objectively validated (see above)
- Increased risk of falls should not automatically result in lack of anticoagulation
- Efficacy and safety of NOACs (tested for edoxaban and apixaban) consistent in patients at increased risk of falls

Modified from (A) Steffel et al., J Am Coll Cardiol 2016 / (B) Tiedemann et al., J Gerontol A Biol Sci Med Sci 2010

19. Anticoagulation in AF patients with a malignancy

1) Estimate individual patient risk profile

- AF-related risk factors (CHA_2DS_2-VASc, bleeding risk)
- Cancer-related risk factors (type, liver metastases, coagulopathy, renal / hepatic function etc.
- Treatment-related risk factors (thrombocytopenia, surgery, radiation, central lines etc.)

2) Choose anticoagulant

- Current standard of care: VKA / (LMWH)
- NOACs: Available data scarce, but encouraging
- Consider patient preference (VKA vs. NOAC)

3) Protect the patient

- Gastric protection (PPI / H_2 blockers)
- Beware of drug-drug interactions
- Dose reduction / treatment interruption (if platelets < 50k, renal dysfunction, bleeding, ...)

Beware:

- Risk of thromboembolism ↑
- Risk of bleeding ↑

Interdisciplinary Teamwork!

20. Optimising dose adjustments of VKA

Maintenance Warfarin dosing for out-of-therapeutic-range INR

INR	Dose adjustment per week
≤1.5	↑ by 15% / week
1.6–1.9	↑ by 10% / week
2–2.9	Unchanged
3–3.9	↓ by 10% / week
4–4.9	Hold 1 dose, then restart with dose ↓ by 10% / week
≥5	Hold until INR is 2–3, then restart with dose ↓ by 15% / week

Importantly, dosing is optimised not using daily dose adjustments but adjustments based on the weekly intake in warfarin

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List of topics AFib Syncope Inherited / SCD / VT Devices

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Notes

Notes

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