EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

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EUROPEAN Heart Rhythm ASSOCIATION
A Registered Branch of the ESC

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Update to 2013 Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

- ESC Guidelines describe indications for NOACs but do not discuss *use* of NOACs in specific clinical situations[1,2]
- First Practical Guide was published in 2013 to supplement the Guidelines[3]

1. Camm et al, Europace 2010;12:1360-420
2. Camm et al, Eur Heart J 2012; 33:2719-47
3. Heidbuchel et al Europace 2013;15:625-51

AF patients deemed eligible for stroke prevention with NOACs

	Eligible	Contraindicated
Mechanical prosthetic valve		✓
Moderate to severe mitral stenosis (usually of rheumatic origin)		✓
Mild to moderate other valvular disease	✓	
Severe aortic stenosis	✓ Limited data Most will undergo intervention	
Bioprosthetic valve*	✓ (except for first 3 months post-operatively)	
Mitral valve repair*	✓ (except for first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets; consider bleeding risk)	
Hypertropic cardiomyopathy	✓ (but no prospective data)	

PTAV = percutaneous transluminal aortic valvuloplasty; TAVI = transcatheter aortic valve implantation.
*US guidelines do not recommend NOACs in patients with biological heart valves or after valve repair

NOACs approved for prevention of systemic embolism or stroke in patients with non-valvular AF

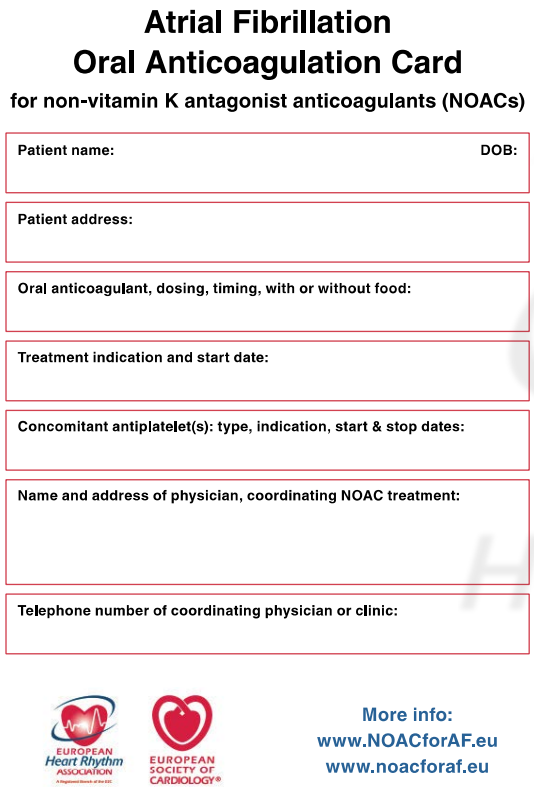
	Dabigatran	Apixaban	Edoxaban***	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa (FXa) inhibitor	Activated factor Xa (FXa) inhibitor	Activated factor Xa (FXa) inhibitor
Dose	150 mg BID 110 mg BID* (75 mg BID)**	5 mg BID 2.5 mg BID	60 mg OD 30 mg OD	20 mg OD 15 mg OD
Phase III clinical trial	RE-LY	ARISTOTLE AVERROES	ENGAGE-AF	ROCKET-AF

* 110 mg BID not approved by FDA. ** 75 mg BID approved in US only. *** FDA provided boxed warning that 'edoxaban should not be used in patients with CrCL >95 ml/min. EMA advised 'edoxaban should only be used in patients with high creatinine clearance after a careful evaluation of the individual thrombo-embolic and bleeding risk'.

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

- Risk/benefit analysis: is a NOAC indicated?
- When choosing a NOAC, consider co-medications taken by patient (see pages 13–15).
- Provide patient with information card: a generic card such as the card proposed by EHRA (see page 4) could serve for all NOACs and could facilitate structured follow-up.
- Nurse co-ordinated AF clinics may be helpful.

EHRA proposal for a universal NOAC anticoagulation card



Atrial Fibrillation
Oral Anticoagulation Card

for non-vitamin K antagonist anticoagulants (NOACs)

Patient name: **DOB:**
Patient address:
Oral anticoagulant, dosing, timing, with or without food:
Treatment indication and start date:
Concomitant antiplatelet(s): type, indication, start & stop dates:
Name and address of physician, coordinating NOAC treatment:
Telephone number of coordinating physician or clinic:

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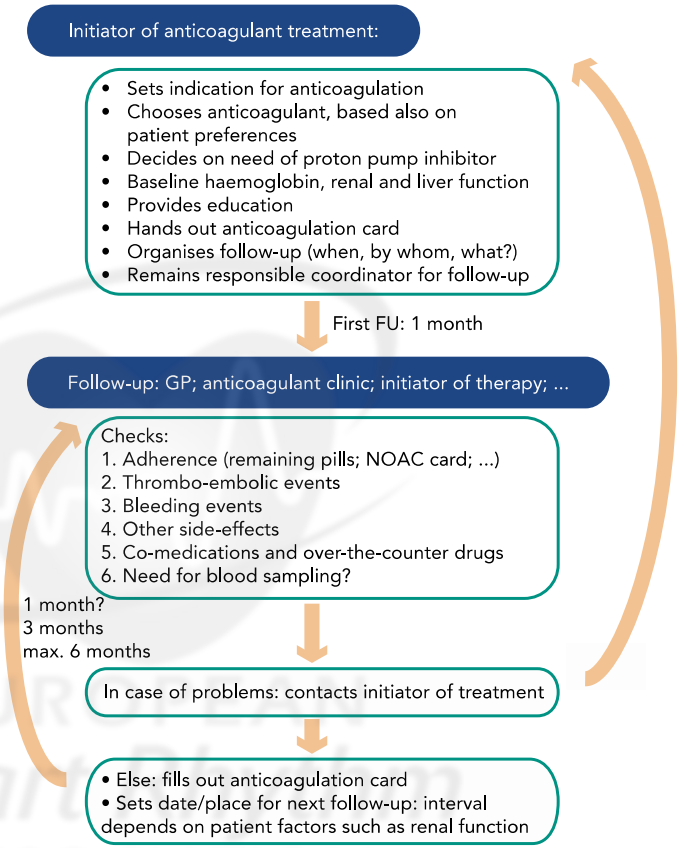
More info:
www.NOACforAF.eu
www.noacforaf.eu

Card can be downloaded in a printer-ready form from www.NOACforAF.eu

Suggested structured initiation and follow-up



Checklist during follow-up of AF patients on NOACs

	Interval	Comments
Adherence	Each visit	Inspect remaining medication Re-educate on importance of adherence Inform about compliance aids (boxes, smartphone apps, etc)
Thrombo-embolism	Each visit	Systemic circulation (transient ischaemic attack [TIA], stroke, peripheral) Pulmonary circulation
Bleeding	Each visit	'Nuisance' bleeding: prevention possible? (proton pump inhibitor [PPI], haemorrhoidectomy, etc.) Motivate patient to diligently continue anticoagulation Bleeding with risk or impact on QoL – prevention possible? Need to revise dose?
Other side-effects	Each visit	Continuation? Temporary cessation with bridging? Change of anticoagulant drug?
Co-medications	Each visit	Prescription or over-the-counter drugs (especially aspirin/NSAIDs)? Even temporary use can be risky
Blood sampling	Yearly 6-monthly x-monthly on indication	Haemoglobin, renal, liver function Age 75–80 years (especially dabigatran or edoxaban) or frail If renal function ≤60 ml/min: recheck interval = CrCL/10 (in months) If intercurrent condition may impact renal or hepatic function

2. How to measure the anticoagulant effect of NOACs

- Important to know exactly when NOAC was administered relative to time of blood sampling. Maximum effect at ~3 h after intake with elimination half-life of 12 or 24 h.
- Activated partial thromboplastin time (aPTT): qualitative assessment of dabigatran.
- Prothrombin time (PT) is somewhat sensitive to the effect of factor Xa inhibitors but sensitivity of reagents varies: therefore, PT cannot be used as a tool to monitor FXa inhibitor effects.
- Quantitative assays for direct thrombin inhibitors and factor Xa inhibitors are now commercially available. However, there are no data on a cut-off level below which surgery is safe and therefore their use in this respect is not recommended at present.

Measuring the anticoagulant effect of NOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Plasma peak	2 h after ingestion	1–4 h after ingestion	1–2 h after ingestion	2-4 h after ingestion
Plasma trough	12–24 h after ingestion	12 h after ingestion	24 h after ingestion	24 h after ingestion
Prothrombin time (PT)	cannot be used	can be prolonged but no known relation with bleeding risk	prolonged but variable and no known relation with bleeding risk	prolonged but no known relation with bleeding risk. Range at trough:12–26 s with Neoplastin Plusas reagent; local calibration required
INR	cannot be used	cannot be used	cannot be used	cannot be used
Activated partial thromboplastin time (aPTT)	range (P10–P90) at trough D150: 40.3–76.4 s range (P10-P90) at tough D110: 37.5–69.9 s at trough: >2x ULN may be associated with excess bleeding risk	cannot be used	prolonged but no known relation with bleeding risk	cannot be used

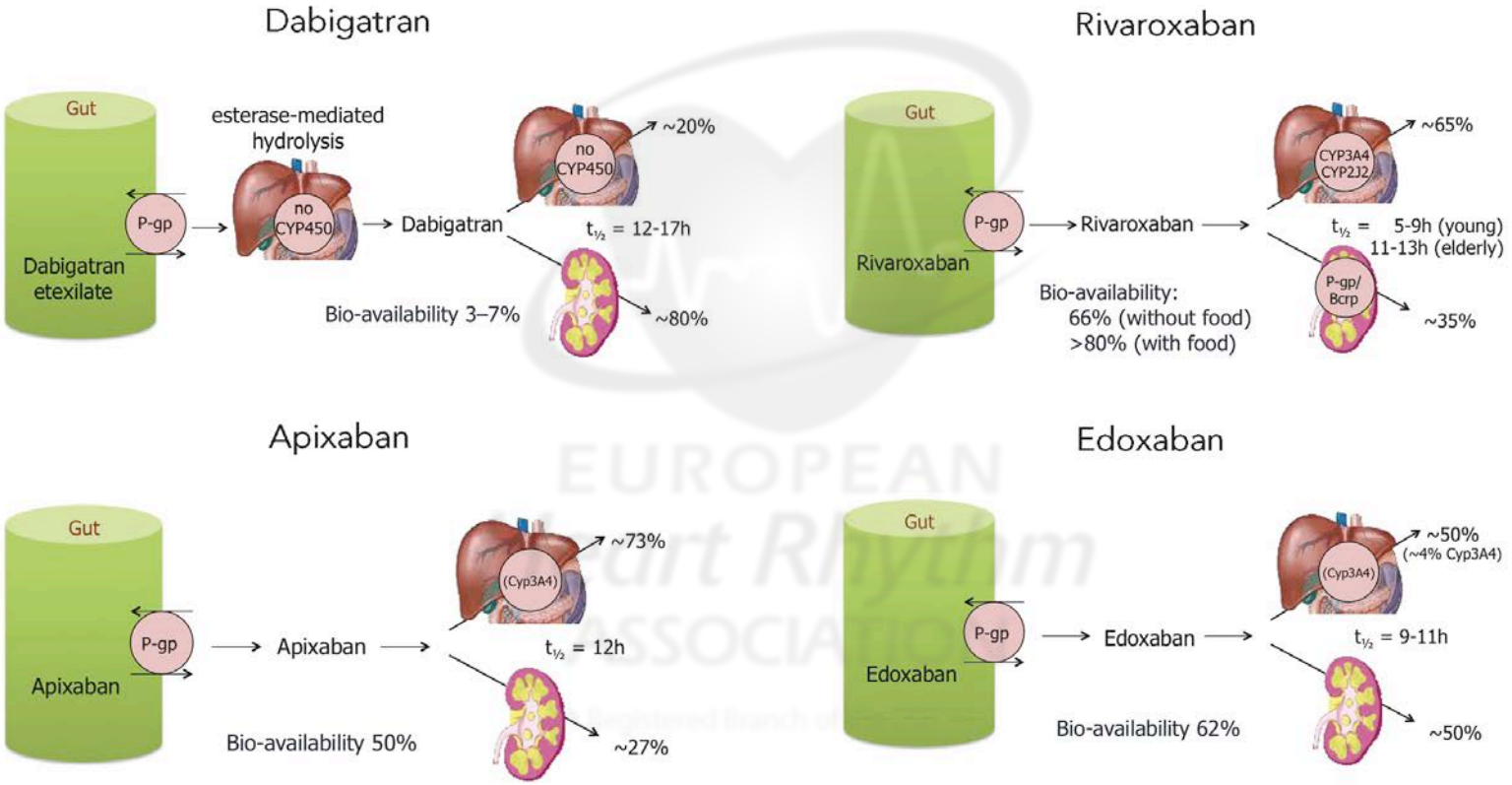
INR = international normalised ratio; ULN = upper limit of normal

Measuring the anticoagulant effect of NOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Diluted thrombin time (dTT)	No data from RE-LY trial on range of values. At trough >200 ng/ml or ≥65 s: excess bleeding risk	cannot be used	cannot be used	cannot be used
Anti-FXa chromogenic assays	not applicable	quantitative; no data on threshold values for bleeding or thrombosis range at trough: 1.4–4.8 IU/mL	quantitative; no data on threshold values for bleeding or thrombosis range at trough: 0.05–3.57 IU/mL	quantitative; no data on threshold values for bleeding or thrombosis range at trough: 6–239 µg/ml
Ecarin clotting time	range (P10–P90) at trough D150: 44.3-103 range (P10–P90) at tough D110: 40.4–84.6s at trough: ≥3x ULN: excess bleeding risk	not affected	not affected	not affected
Activated clotting time (ACT)	Rather flat dose response. No investigation on its use.	No data: cannot be used	No data: cannot be used	Minor effect: cannot be used

3. Drug–drug interactions and pharmacokinetics

Absorption and metabolism of NOACs



Absorption and metabolism of NOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	3–7 %	50 %	62 %	66 % (without food) ~100 % with food
Prodrug	yes	no	no	no
Clearance: non-renal/renal of absorbed dose if normal renal function	20 %/80 %	73 %/27 %	50 %/50 %	65 %/35 %
Liver metabolism: CYP3A4 involved	no	yes (elimination, moderate contribution)	minimal (< 4% of elimination)	yes (elimination, moderate contribution)
Absorption with food	no effect	no effect	6–22 % more; minimal effect on exposure	+39 %
Intake with food?	no	no	no	mandatory
Absorption with H_2-blocker/PPI	-12 to -30 % (not clinically relevant)	no effect	no effect	no effect
Asian ethnicity	+25 %	no effect	no effect	no effect
GI tolerability	dyspepsia 5–10 %	no problem	no problem	no problem
Elimination half-life	12–17 h	12 h	10–14 h	5–9 h (young) 11–13 h (elderly)

Possible drug–drug interactions: effect on NOAC plasma levels (part 1)

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
			Antiarrhythmic drugs		
Amiodarone	moderate P-gp competition	+12–60 %	No PK data[$]	+40 %	Minor effect[$] (use with caution if CrCl <50 mL/min)
Digoxin	P-gp competition	No effect	No data yet	No effect	No effect
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect	+40 %	No data yet	Minor effect[#] (use with caution if CrCl 15–50 mL/min)
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 % (Reduce NOAC dose by 50 %)	Moderate effect[#] but no PK or PD data: caution and try to avoid
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 % (reduce NOAC dose and take simultaneously)	No PK data	+53 % (SR) (No dose reduction required by label)	Minor effect[***] (use with caution if CrCl 15–50 mL/min)

Red – contraindicated/not recommended; orange – reduce dose; yellow – consider dose reduction if another yellow factor present; hatching – no PK data available. $Based on in vitro investigations and/or efficacy/safety trial endpoints; #SmPC specifies dose reduction from 5 to 2.5 mg twice daily if 2 of 3 criteria fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL; ***Some interactions lead to reduced NOAC plasma levels.

Possible drug–drug interactions: effect on NOAC plasma levels (part 2)

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
			Other cardiovascular drugs		
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%	No data yet	No effect	No effect
			Antibiotics		
Clarithromycin; Erythromycin	moderate P-gp competition and CYP3A4 inhibition	+15–20 %	No data yet	+90 % (reduce NOAC dose)	+30–54 %
Rifampicin***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66 %	minus 54 %	avoid if possible: minus 35 %, but with compensatory increase of active metabolites	Up to minus 50 %
			Antiviral drugs		
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCR 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 systemically administered)
Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140–150% (US: 2 x 75 mg if CrCl 30–50 mL/min)	+100 %	+87–95 % (reduce NOAC dose by 50 %)	Up to +160 %

Red – contraindicated/not recommended; orange – reduce dose; yellow – consider dose reduction if another yellow factor present; hatching – no PK data available. $Based on in vitro investigations and/or efficacy/safety trial endpoints; #SmPC specifies dose reduction from 5 to 2.5 mg twice daily if 2 of 3 criteria fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL; ***Some interactions lead to reduced NOAC plasma levels.

Possible drug–drug interactions: effect on NOAC plasma levels (part 3)

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
			Immunosuppressive		
Cyclosporin; Tacrolimus	P-gp competition	Not recommended	No data yet	+73 %	Extent of increase unknown
			Antiphlogistics		
Naproxen	P-gp competition	No data yet	+55 %	No effect (but pharmacodynamically increased bleeding time)	No data yet
			Antacids		
H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12–30 %	No effect	No effect	No effect
			Others		
Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66 %	minus 54 %	minus 35 %	Up to minus 50 %
			Other factors		
Age ≥80 years	Increased plasma level		#	%	
Age ≥75 years	Increased plasma level			%	

Red – contraindicated/not recommended; orange – reduce dose; yellow – consider dose reduction if another yellow factor present; hatching – no PK data available. $Based on in vitro investigations and/or efficacy/safety trial endpoints; #SmPC specifies dose reduction from 5 to 2.5 mg twice daily if 2 of 3 criteria fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL; ***Some interactions lead to reduced NOAC plasma levels.

Factors associated with raised plasma levels of NOACs (part 4)

		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
		Other factors			
Weight ≤60 kg	Increased plasma level		#		
Renal function	Increased plasma level	See Table 8			

Other increased bleeding risk

Pharmacodynamic interactions – antiplatelet drugs, NSAIDs

Systemic steroid therapy

Other anticoagulants

History of GI bleeding

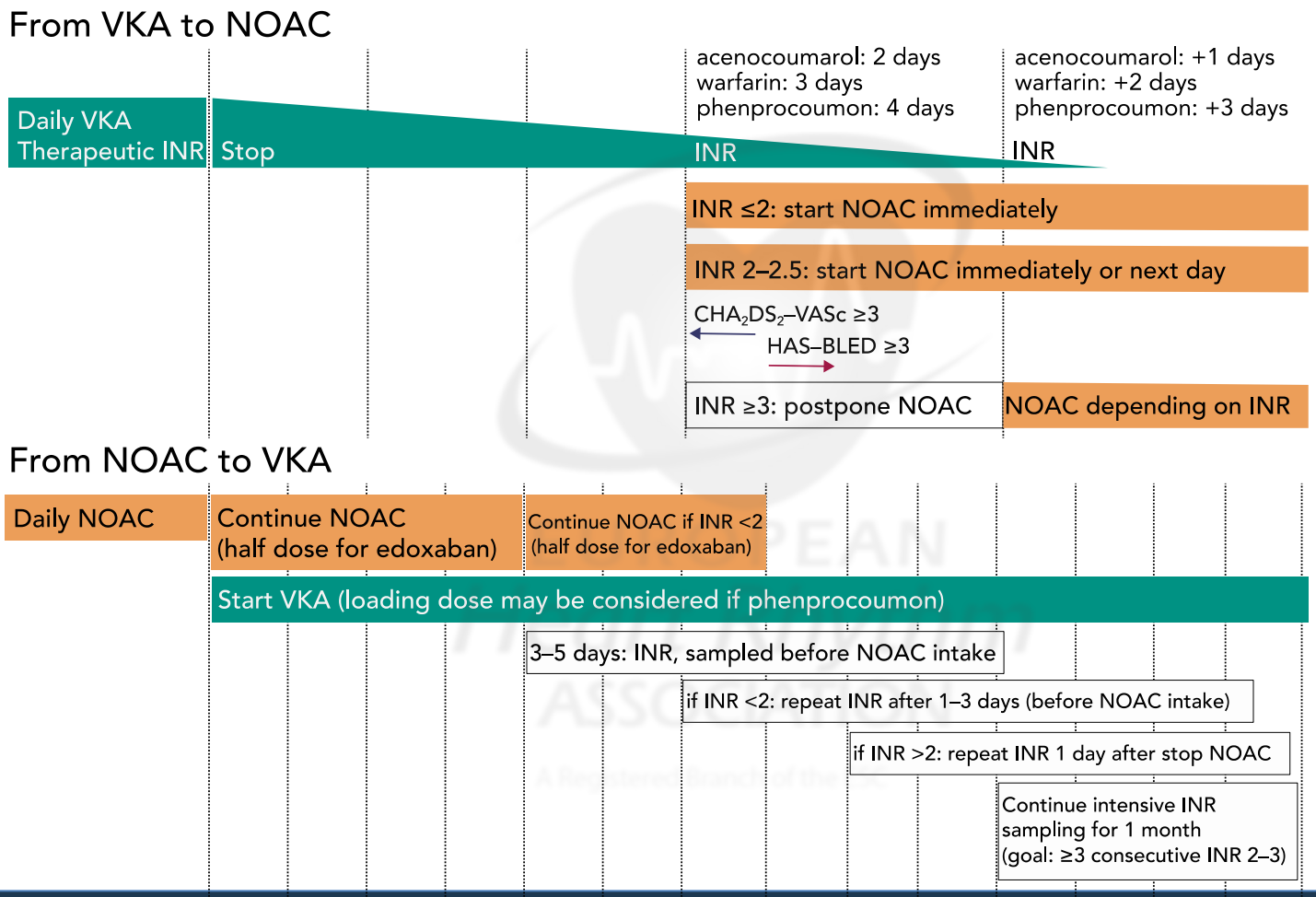
Recent surgery on critical organ (brain; eye)

Thrombocytopenia (e.g. chemotherapy)

HAS-BLED ≥3

Red = contraindicated/not recommended; Orange = reduce dose (from 150 mg twice daily to 110 mg twice daily for dabigatran; from 20 mg to 15 mg once daily for rivaroxaban; from 5 mg twice daily to 2.5 mg twice daily for apixaban); Yellow = consider dose reduction if another 'yellow' factor is present. Hatching = no pharmacokinetic data available. BCRP = breast cancer resistance protein; NSAID = non-steroidal anti-inflammatory drugs; H2B = H2-blockers; PPI = proton pump inhibitors; P-gp = P-glycoprotein; NSAID: non-steroidal anti-inflammatory agent; GI = gastrointestinal; ***Some interactions lead to reduced NOAC plasma levels in contrast to most interactions that lead to increased NOAC plasma levels. This may also constitute a contraindication for simultaneous use, and such cases are coloured brown. The label for edoxaban mentions that co-administration is possible in these cases, despite a decreased plasma level, which are deemed not clinically relevant (blue). 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 III clinical trials. No direct PK interaction data available. #The SmPC specifies dose reduction from 5 to 2.5 mg twice daily if two of three criteria are fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL..

4. Switching between anticoagulant regimens



5. Ensuring adherence with NOAC intake

- Important: anticoagulant effect drops rapidly after 12–24 h

- Once daily better adherence than twice daily for cardiovascular drugs in general, but no data on superior dosing scheme for NOAC in clinical practice.
- Patient education crucial: leaflets and instruction at initiation, patient safety card, group sessions.
- Involve family members.

Ensuring adherence with NOAC intake (continued)

- Clearly defined follow-up schedule (GP, cardiologist, electrophysiologist and/or nurse-coordinated AF centres).
- Technological aids – format of blisters, medication boxes, smartphone apps and/or SMS alerts.
- Some patients prefer INR monitoring. Patient preference needs to be taken into account.
- Network pharmacy database tracking prescriptions.
- If low compliance, consider vitamin K antagonists (VKAs).

6. How to deal with dosing errors

Missed dose	Twice daily: take missed dose up to 6 h after scheduled intake. If not possible skip dose and take next scheduled dose. Once daily: take missed dose up to 12 h after scheduled intake. If not possible skip dose and take next scheduled dose.
Double dose	Twice daily: skip next planned dose and restart twice daily after 24 h. Once daily: continue normal regimen.
Uncertainty about intake	Twice daily: continue normal regimen. Once daily: take another dose then continue normal regimen.
Overdose	Hospitalisation advised.

7. Patients with chronic kidney disease

Estimated $t_{½}$ and AUC NOAC plasma concentrations compared with healthy controls

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
CrCl ≥ 80 ml/min	12–17 h	12 h	10–14 h	5–9 h (young) 11–13 h (elderly)
CrCl 50 – 80 ml/min CKD Stage I and II	~ 17 h (+50 %)	~ 14.6 h (+16 %)	~ 8.6 h (+32 %)	~ 8.7 h (+44 %)
CrCl 30–50 ml/min CKD Stage III	~ 19 h (+320 %)	~ 17.6 h (+29 %)	~ 9.4 h (+74 %)	~ 9.0 h (+52 %)
CrCl 15–30 ml/min CKD Stage IV	~ 28 h (+530 %)	~ 17.3 h (+44 %)	~ 16.9 h (+72 %)	~ 9.5 h (+64 %)
CrCl ≤ 15 ml/min CKD Stage V; off-dialysis	No data	- (+36 %)	- (+93 %)	- (+70 %)

NOACs in renal dysfunction – Approved European labels and dosing recommendations

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
% of absorbed dose renally excreted	80 %	27 %	50 %	35 %
Bioavailability	3–7 %	50 %	62 %	66 % without food ~ 100 % with food
% of administered dose renally excreted	4 %	12-29 %	37 %	33 %
Approved for CrCl	≥30 ml/min	≥15 ml/min	≥15 ml/min	≥15 ml/min
Label dosing recommendation	CrCl ≥15 ml/min, no adjustment (i.e. 150 mg twice daily)	Serum creatinine ≥1.5 ml/dl, no adjustment (i.e. 5 mg twice daily)	CrCl ≥50 ml/min, no adjustment (i.e. 60 mg once daily)	CrCl ≥ 50 ml/min, no adjustment (i.e. 20 mg once daily)
Dosing if CKD	When CrCl 30–49 ml/min, 150 mg twice daily is possible (SmPC) but 110 mg twice daily should be considered as per ESC guidelines Note: 75 mg twice daily approved in US only ** - if CrCl 15–30 ml/min - if CrCl 30–49 ml/min - and other orange factor (e.g. verapamil)	CrCl 15–29 ml/min: 2.5 mg twice daily Serum creatinine ≥1.5 mg/dl in combination with age ≥80 years or weight ≤60 kg (SmPC) : 2.5 mg twice daily	30 mg once daily when CrCl 15–49 mL/min	15 mg once daily when CrCl 15–49 ml/min
Not recommended if:	CrCl <30 mL/min	CrCl <15 mL/min	CrCl <15 mL/min	CrCl <15 mL/min

** No EMA indication

8. What to do if there is a (suspected) overdose without bleeding, or a clotting test is indicating a risk of bleeding

- Acute recent ingestion of overdose: activated charcoal to reduce absorption (standard dosing scheme of 30 to 50 g for adults).
- Consider coagulation tests to assess possible bleeding risk.
- In absence of bleeding, wait-and-see approach.

9. Management of bleeding complications

Possible measures to take in case of bleeding (part 1)

Non life-threatening

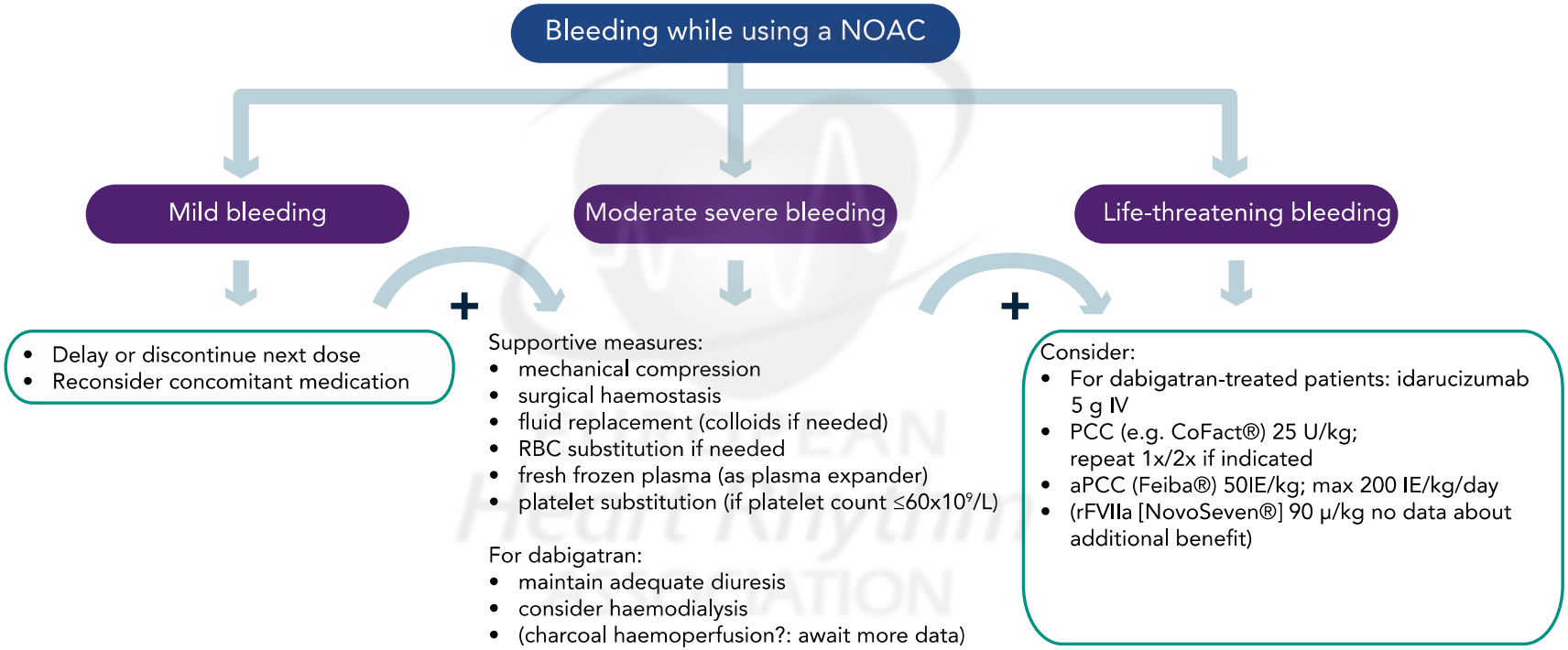
Dabigatran	FXa inhibitors
Inquire last intake + dosing regimen Estimate normalization of haemostasis Normal renal function: 12–24 h CrCl 50-80 ml/min:24–36 h CrCl 30-50 ml/min: 36–48 h CrCl <30 ml/min: ≥48 h Maintain diuresis Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 x 10^9 /L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (primary evidence: - 65 % after 4 h) Charcoal haemoperfusion can be considered (based on preclinical data)	Inquire last intake + dosing regimen Normalisation of haemostasis: 12–24 h Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 x 10^9 /L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy)

Possible measures to take in case of bleeding (part 2)

Life-threatening

Dabigatran	FXa inhibitors
All of the above Idarucizumab 5 g IV	All of the above
If not available: prothrombin complex concentrate (PCC) 25 U/g (but no clinical evidence)	Prothrombin complex concentrate 25 U/kg (may be repeated once or twice but no clinical evidence)
Activated PCC 50 IE/kg; max 200 IE/day: no strong data about additional benefit over PCC. Can be considered before PCC if available	Activated PCC 50IE/kg; max 200 IE/day: no strong data about additional benefit over PCC. Can be considered before PCC if available
Activated factor VII (rFVIIa; 90 µg/kg); no data about additional benefit + expensive (only animal evidence)	Activated factor VII (rFVIIa; 90 µg/kg); no data about additional benefit + expensive (only animal evidence)

Possible measures to take in case of bleeding



10. Patients undergoing a planned surgical intervention or ablation

- Some procedures can be done without interruption of anticoagulation. Other procedures should be performed after temporary cessation of the NOAC.
- Schedule intervention at a time which is at least the interval after last intake as specified in the following table.
- For procedures with immediate and complete haemostasis, the NOAC can be resumed 6–8 hours after the intervention.
- For complex procedures, one could administer a reduced venous thromboprophylactic or intermediate dose of LMWH 6 to 8 hours after surgery and restart NOACs 48–72 hours after the invasive procedure.
- Catheter ablation of AF is a special case. Continuous NOAC administration may be safe, although most centres will opt to drop the morning dose of NOAC or to give the last dose 12–24 hours before the planned ablation. Further controlled trial data are awaited.

When to stop NOACs before a planned surgical intervention

Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban, Edoxaban, Rivaroxaban	
	No important bleeding risk and/or local haemostasis possible: perform at trough level (i.e. ≥12 h or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 ml/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 ml/min §	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 ml/min §	not indicated	not indicated	**≥36 h**	**≥48 h**
CrCl <15 ml/min	no official indication for use			
	There is no need for bridging with LMWH/UFH			

Bold values deviate from common stopping rule of ≥24 h low risk and ≥48 h high risk.
Low risk: low frequency and/or minor impact of bleeding. High risk: high risk or impact of bleeding. § many of these patients may be on the lower dose of dabigatran (i.e. 2 x 110 mg/d) or apixaban (i.e. 2 x 2.5 mg/d), or have to be on the lower dose of rivaroxaban (15 mg/d) or edoxaban (30 mg/d).

Classification of surgical interventions according to bleeding risk (part 1)

Interventions not necessarily requiring discontinuation of anticoagulant
Dental interventions - Extraction of one to three teeth - Paradontal surgery - Incision of abscess - Implant positioning
Ophthalmology - Cataract or glaucoma intervention
Endoscopy without surgery
Superficial surgery (e.g. abscess incision, small dermatological excision)
Interventions with minor bleeding risk (i.e. infrequent or with low clinical impact)
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or radiofrequency catheter ablation for right-sided supraventricular tachycardia
Non-coronary angiography
Pacemaker or ICD implantation (unless complex anatomical setting e.g. congenital heart disease)

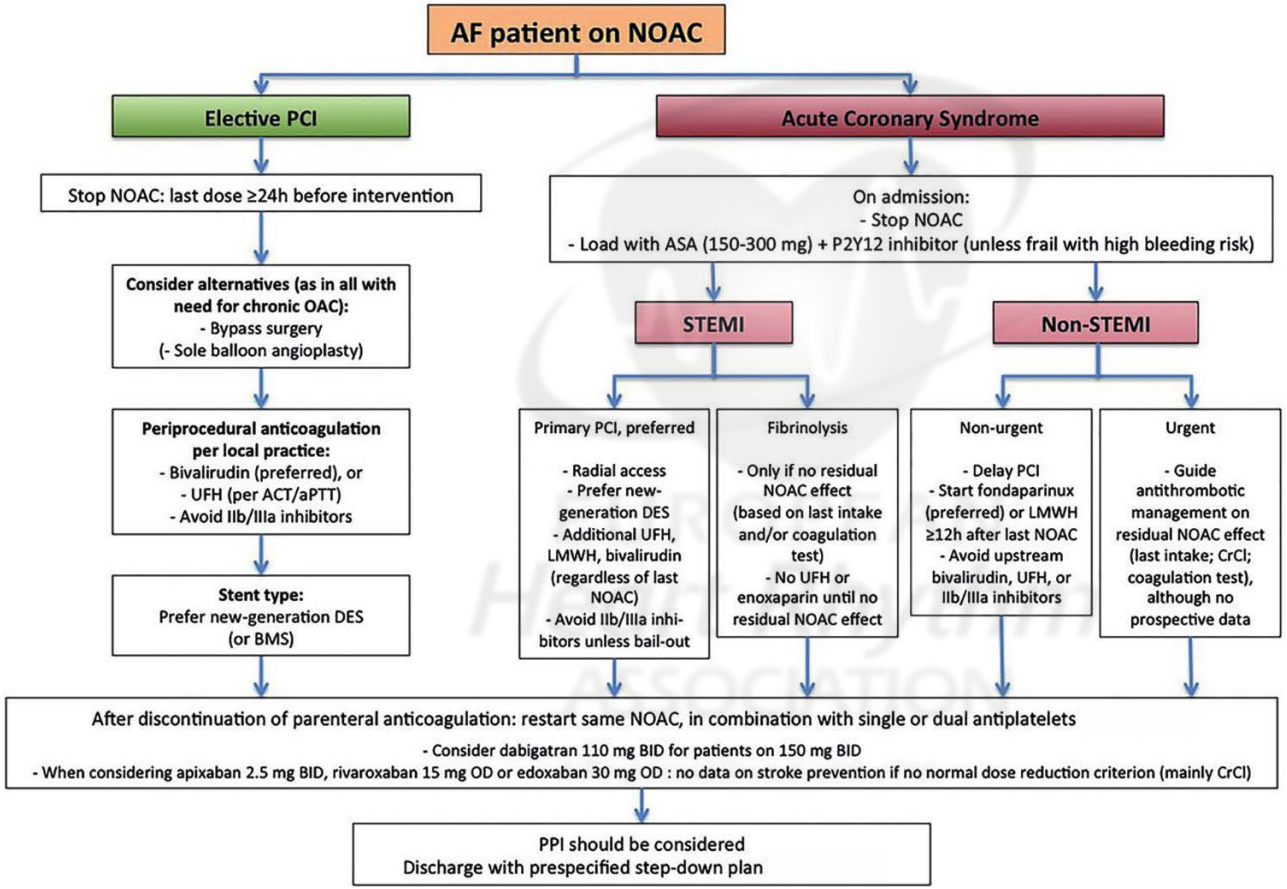
Classification of surgical interventions according to bleeding risk (part 2)

Interventions with major bleeding risk (i.e. frequent and/or high clinical impact)
Catheter ablation of simple left-sided supraventricular tachycardia (e.g. WPW)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopaedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy
Extracorporeal shockwave lithotripsy (EWSL)
Interventions with major bleeding risk AND increased thrombo-embolic risk
Complex left-sided ablation (AF ablation, some VT ablation)

11. Patients undergoing an urgent surgical intervention

- Discontinue NOAC.
- Try to defer surgery at least 12 h and ideally 24 h after last dose.
- For patients on dabigatran: idarucizumab 5g IV reverses anticoagulation without pro-thrombotic side-effects and may allow urgent intervention.
- For patients on FXa inhibitors: no specific reversal agents available yet, but under development. A strategy with PCC or aPCC pre-operatively has not been studied and cannot be recommended.
- Coagulation tests can be considered (classical test or specific tests) but strategy based on these results has never been evaluated. Therefore such strategy cannot be recommended and should not be used routinely.

Acute management of revascularisation or ACS in AF patients treated with NOACs



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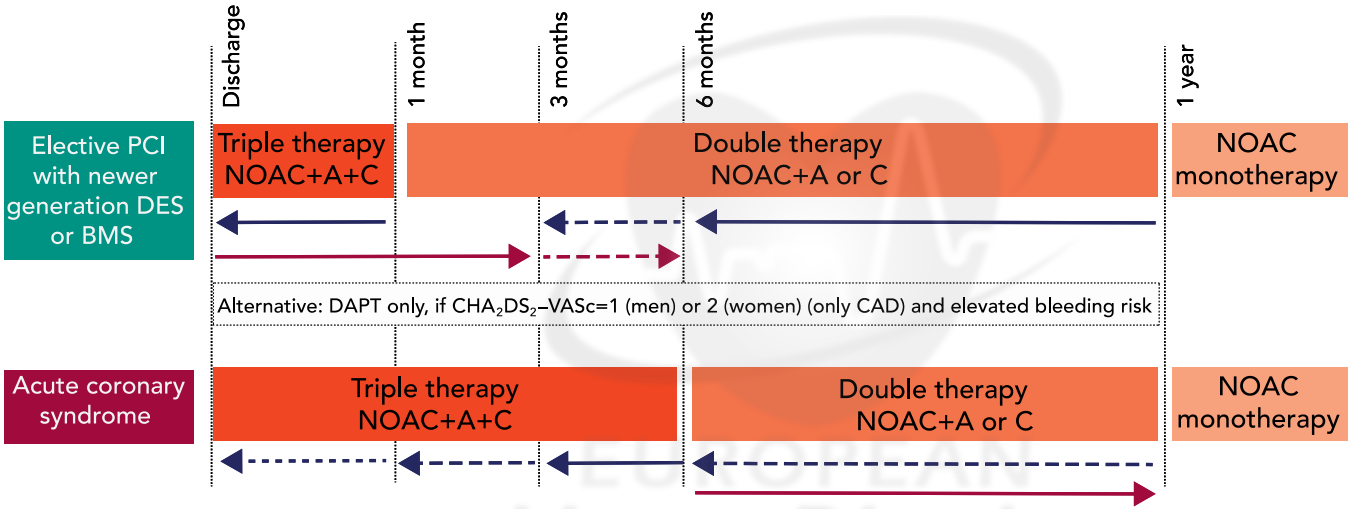
Default scenarios and criteria for adaptation for long-term treatment of patients on NOAC therapy after revascularisation or ACS



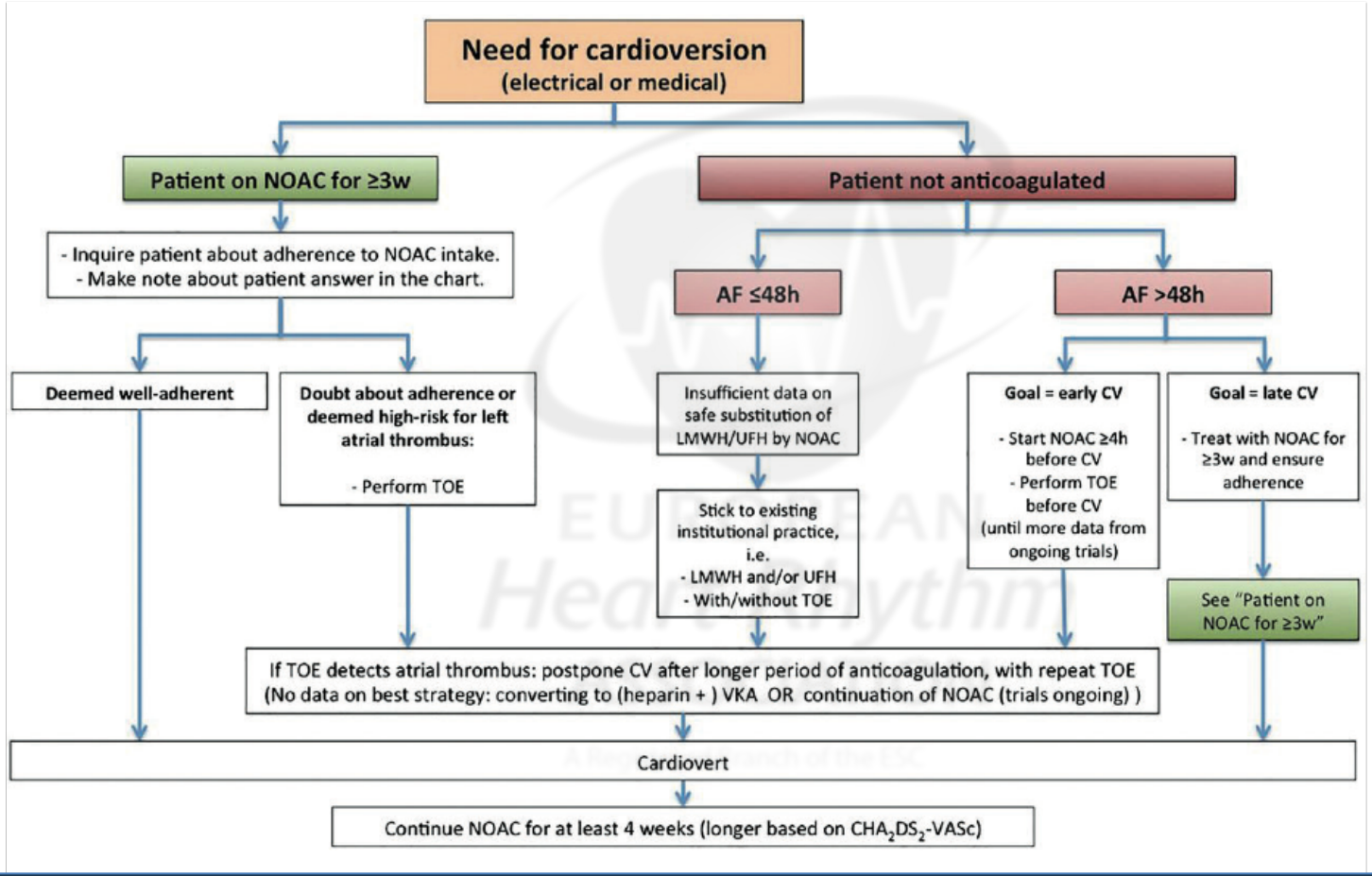
Factors to shorten combination therapy

- (Uncorrectable) high bleeding risk
- Low atherothrombotic risk (by REACH or SYNTAX score if elective?; GRACE ≥118 if ACS?)

Factors to lengthen combination therapy

- First-generation DES
- High atherothrombotic risk (scores as above ; stenting of the left main, proximal left anterior descending, proximal bifurcation; recurrent MIs, etc.) and low bleeding risk

Cardioversion in a NOAC-treated patient: different scenarios



14. Patients presenting with acute stroke while on NOACs

Acute haemorrhagic stroke

- Use same approach as for life-threatening bleeding but note that this strategy needs further evaluation in clinical studies.

Acute ischaemic stroke

- Thrombolytic therapy cannot be given within 24(–48 h) of last NOAC dose.
- Only in exceptional cases with reliable coagulation assessment may the use of fibrinolytic agents be considered.
- Mechanical recanalisation of occluded vessels may be considered but few prospective data exist in the context of NOAC therapy.

Stroke patients – Management of post-acute phase

Haemorrhagic stroke

- If cardioembolic risk high and risk of new haemorrhage low, carefully reconsider restarting NOACs 4–8 weeks after intracerebral haemorrhage.
- A history of spontaneous intracerebral bleed is a contraindication against anticoagulation unless bleeding risk has been reversed.
- Consider nonpharmacological strategies instead of NOACs (e.g. ablation or occlusion of the atrial appendage).

Stroke patients – Management of post-acute phase

Ischaemic stroke

- If infarct size not expected to increase risk of secondary intracerebral bleeding, re-initiate NOAC:
  - in patients with TIA after 1 day
  - small, non-disabling infarct after 3 days
  - moderate stroke after 6 days
  - large infarcts not before 2 weeks.

Stroke patients – Management of post-acute phase

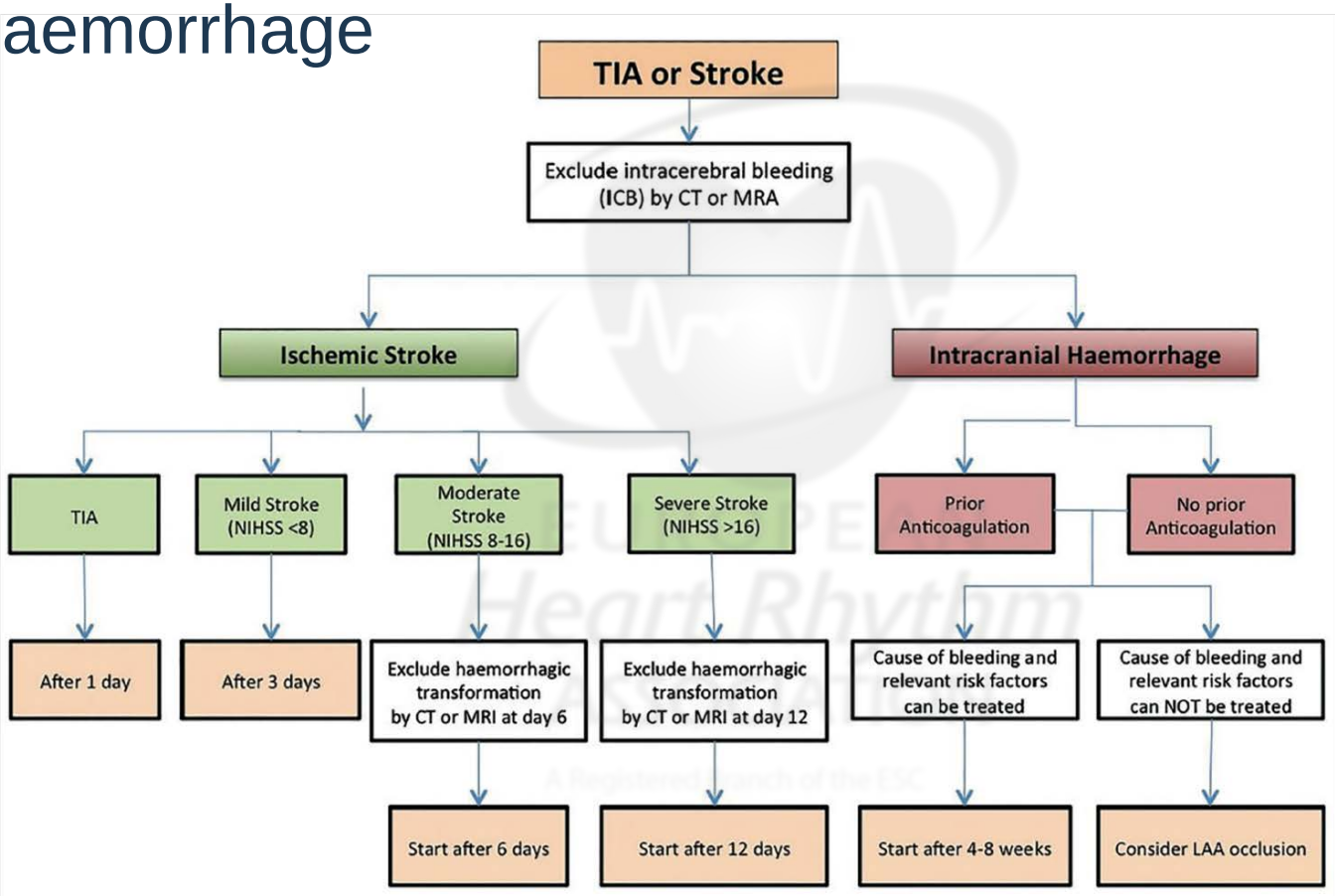
TIA of cardioembolic origin

- (Re)start NOACs as soon as possible.
- Bridging with LMWH not required.
- Aspirin is not an alternative option.

Patients with AF and significant carotid stenosis

- Carotid endarterectomy and not stenting recommended to avoid triple therapy.
- Mild to moderate asymptomatic stenosis can be treated with anticoagulants only, without addition of APT.

Flowchart for the initiation or re-initiation of anticoagulation after TIA/stroke or intracerebral haemorrhage



NOACs in AF patients with a malignancy

- When new anticoagulant initiation is needed, consider VKA over NOACs: more clinical experience.
- Malignancy in patients with AF increases stroke risk. Established anticoagulant therapy (including NOACs) should therefore be maintained, especially in patients receiving moderately myelosuppressive therapies: patient on NOAC can be continued.
- In patients undergoing myelosuppressive chemotherapy or radiation therapy, consider temporary dose reduction or cessation of NOACs. Monitor blood counts, bleeding signs and liver and renal function.
- Consider gastric protection with PPI or H_2 blockers in all patients treated with NOACs.