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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

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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

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www.NOACforAF.eu

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Eligibility for NOACs

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)	Some patients included in some NOAC trials
PTAV and TAVI	No prospective data yet May require combination with single or dual antiplatelet therapy
Hypertrophic cardiomyopathy	Few data, but patients may be eligible for NOACs

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EHRA universal NOAC card (1)

Physician or clinic coordinating NOAC treatment

Name of physician:

Adress

Tel:

Emergency information

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

Name:

Tel:

Name:

Tél:

Important patient instructions

- A non-vitamin K antagonist anticoagulant (NOAC) thins the blood and reduces the risk of getting dangerous blood clots.
- Not taking the drug means no protection!
- Take your drug exactly as prescribed (once or twice daily).
- Do not skip a prescribed dose to ensure optimal protection from blood clots and stroke!
- Do not stop your medication without consulting your physician.
- After a trauma or bleeding event, consult with your physician regarding further management.
- Do not add any other medication without consulting your physician, not even short-term painkillers that you can get without prescription.
- Alert your dentist, surgeon or other physician before an intervention.

It is important to carry this card with you at all times.Please show this card to every physician, dentist, pharmacist or other healthcare providers.

What to do in certain occasions

When should I contact a healthcare provider?

Bleeding is the most common side effect of an anticoagulant. However, the reduction in the risk for stroke outweighs the bleeding risk. Contact your healthcare provider if you have any signs or symptoms of bleeding such as:

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

What should I do if I missed a dose?

You should still take that dose, unless the time until your next dose is less than the time after your missed dose.

What if I accidently took two doses?

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

Information for healthcare providers

- Twice daily NOAC: you can opt to forgo the next planned dose and restart after 24 h.
- NOACs act as a direct thrombin inhibitor (dabigatran) or direct factor Xa inhibitor (apixaban, edoxaban, rivaroxaban).
- Check contraindications for NOACs: mechanical heart valve; rheumatic mitral stenosis; severe kidney dysfunction.
- Standard tests (such as INR, PT or aPTT) do not quantitatively reflect level of anticoagulation.
- In case of major bleeding events, NOAC should be stopped immediately.
- For certain procedures, NOAC should be stopped in advance (for timing see NOAC Practical Guide).

Recommended follow-up

Check each visit:

1. Adherence (pt. should bring remaining meds)
2. Thromboembolic events
3. Bleeding events
4. Other side effects
5. Co-medications / over-the-counter drugs
6. Need for blood sampling
7. Modifiable risk factors
8. Optimal NOAC and correct dosing

(see **www.NOACforAF.eu** for more information)

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EHRA universal NOAC card (2)

Concomitant medication

Name:	Dose:

Concomitant antiplatelet(s): type, indication, start & stop dates:

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

Information for healthcare providers Blood sampling follow-up

Blood sampling:

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

Date	Serum creatinine	Creatinine clearance	Hemo-globin	Liver tests

Planned or unplanned visits

Provide: date, site (GP, cardiologist, clinic, pharmacist,…) visits and to-dos or findings.

Atrial Fibrillation Oral Anticoagulation Card

for non-vitamin K antagonist oral anticoagulants (NOACs)

Name of patient:

Date of birth:

Adress:

Oral anticoagulant:

Dosing: ---

Timing: ---

With or without food: ---

Started on: ---

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Structured Follow-up for NOAC treated patients

Initiator of anticoagulant treatment:

- Establishes indication for anticoagulation
- Checks baseline blood works, incl. hemoglobin, renal and liver function, full coagulation panel
- Chooses anticoagulant and correct dose
- Decides on need for proton pump inhibitor
- Provides education and hands out anticoagulation card
- Organises follow-up (when, by whom, what?)
- Remains responsible coordinator for follow-up

first FU: 1 month

Follow-up: GP; anticoagulant or AF clinic; initiator of therapy; …

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

otherwise

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

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

+/- 3 months
(1-6 months, interval depending on patient factors incl. renal function, age, co-morbidities, etc…)

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Measures to optimize adherence to NOACs

Teaching & education

Involvement of Family mambers

Pré-specified follow-up

Technology aids

Pharmacy database

Optimal adherence

Once-vs, twice daily regimens

(Remote) electronic monitoring

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Checklist during follow-up of NOAC patients (1)

	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 patient 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. • Careful interval history: also temporary use can be risky.

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Checklist during follow-up of NOAC patients (2)

	Interval	Comments
6. Blood sampling (incl. Hb, renal and liver function)	Yearly	In all patients except those below.
	6-monthly	≥ 75 y (especially if on dabigatran), or frail.
	x-monthly	If renal function CrCl ≤ 60 ml/min: recheck interval = CrCl / 10.
	If needed	If intercurrent condition that may impact renal or hepatic function.
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.

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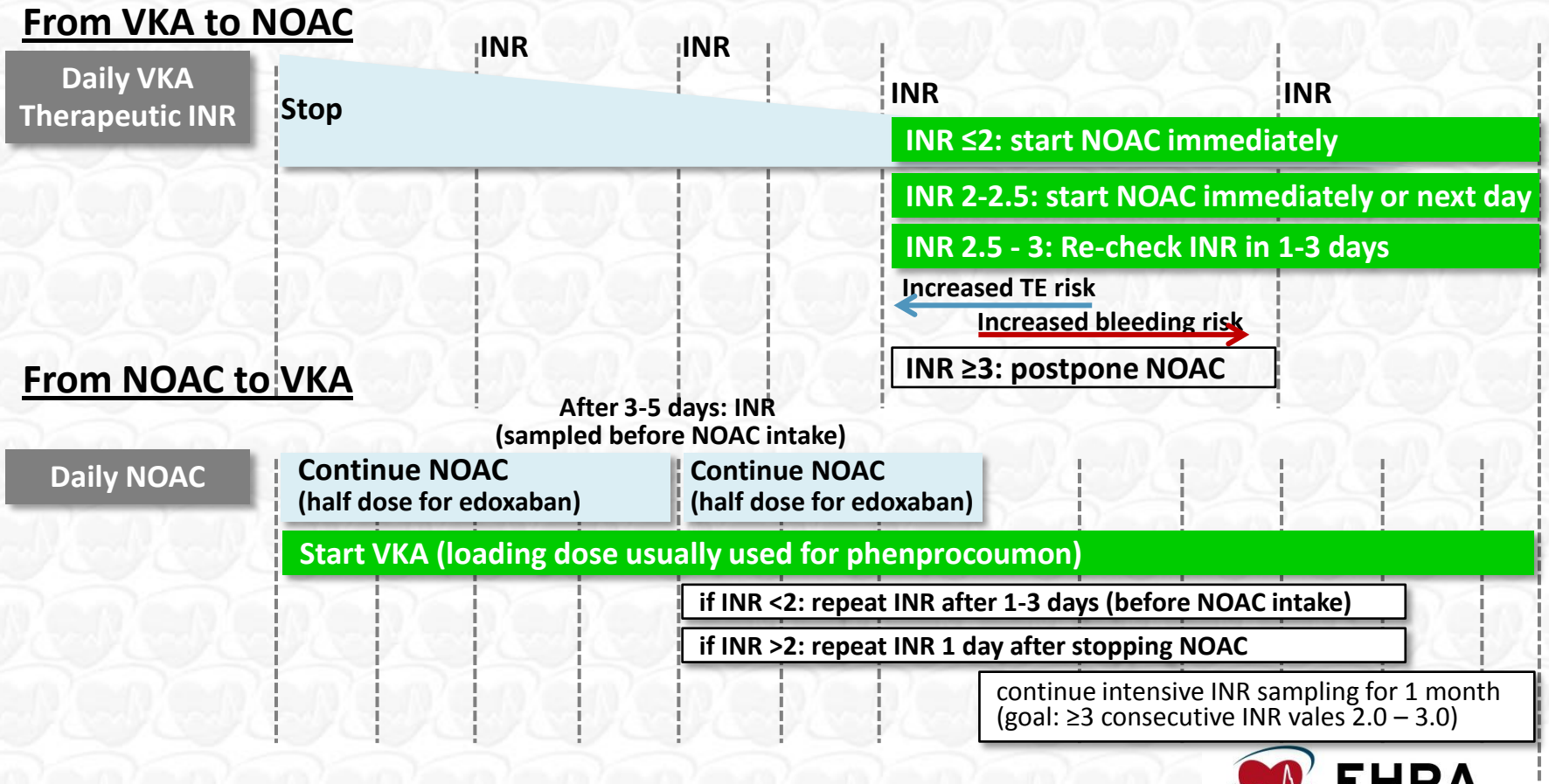
Switching to and from NOACs



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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 dialyzable	Not dialyzable
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 (see above)
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)

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Peak/trough levels of NOACs and effect on routine 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	↑↑(↑)	(↑)	↑	↑
ACT	↑(↑)	↑	↑	↑
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)

Vast majority of patients: NO plasma level measurements!

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Kidney function considerations

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

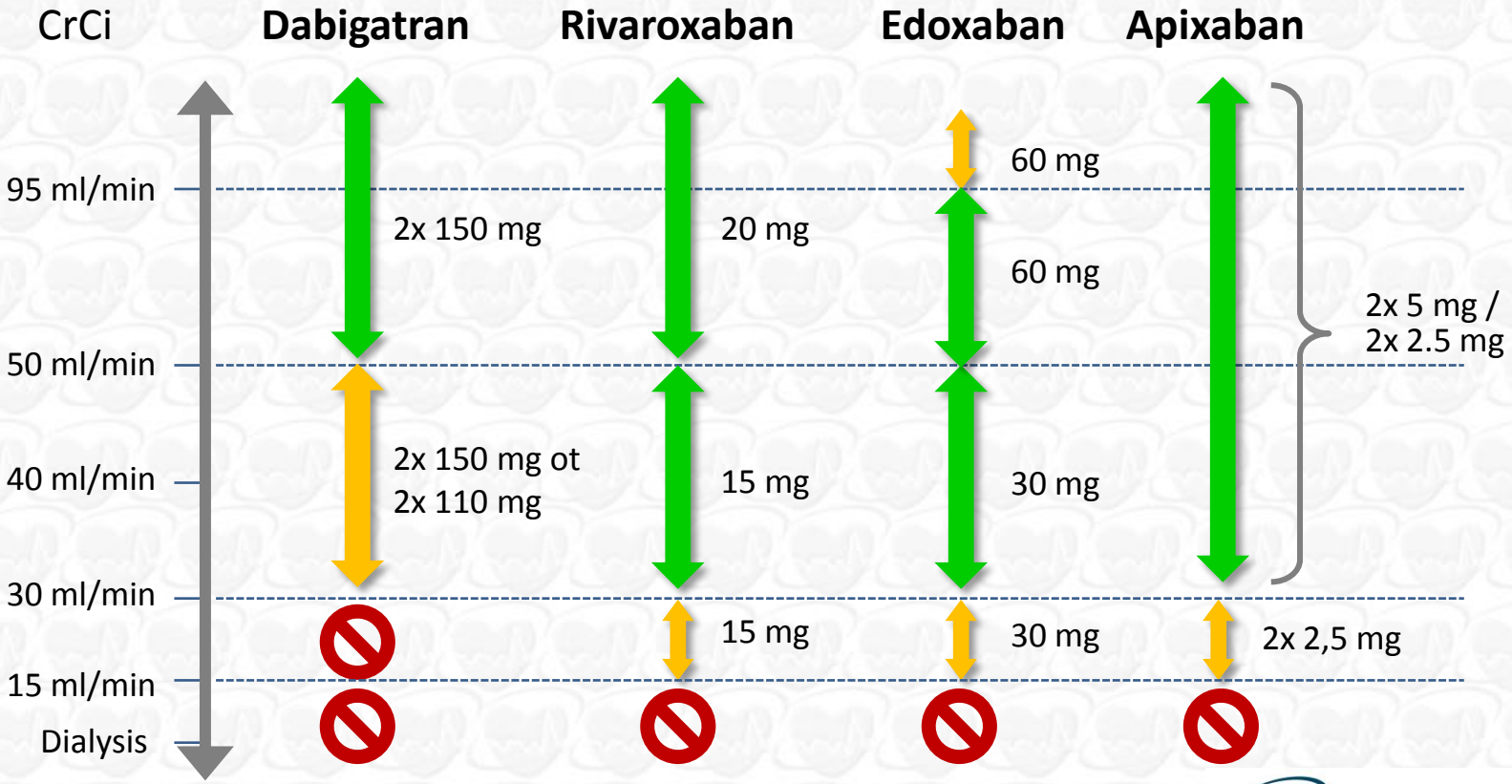
GFR category	CKD stage	GFR *	Description
G1	1	≥90	Normal or high
G2	2	60-89	Mildly decreased
G3a	3	45-59	Mildly to moderately decreased
G3b		30-44	Moderately to severely decreased
G4	4	15-29	Severely decreased
G5	5	<15	Kidney failure requires renal replacement therapy

* [ml/min/1.73m^2]

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

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

NOACs in renal insufficiency



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NOACs in patients with 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 cautiously**	**Use cautiously**	**DO NOT USE**
C (10-15 points)	**DO NOT USE**	**DO NOT USE**	**DO NOT USE**	**DO NOT USE**

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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 coadministration 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.

Interactions of commonly used drugs with NOACs (1)

	via	Dabigatran etexilate	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 to 60%	No PK data	40%	Minor effect
Digoxin	P-gp competition	No effect	No effect 444	No effect	No effect
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect	+40% 147	No data yet	No effect
Dronedarone	P-gp competition and CYP3A4 inhibition	**+70 to 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 to 180% (take simultaneously)	No PK data	+53% (SR) (No dose reduct. Req. by label)	No effect

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Interactions of commonly used drugs with NOACs (2)

	via	Dabigatran etexilate	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 2 h 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%	minus 35%, but with compensatory increase of active metabolites	Up to minus 50%

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Interactions of commonly used drugs with NOACs (3)

	Via	Dabigatran etexilate	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				

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Other factors with (potential) influence on NOAC plasma levels

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Other factors:					
Age ≥ 80 years	Potential for Increased plasma levels		#	%	
Age ≥ 75 years	Potential for Increased plasma levels			%	
Weight ≤ 60 kg	Potential for Increased plasma levels		#	#	
Renal function	Increased plasma level				
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)			

#: Dose reduction based on published .
%: age had no significant effect after adjusting for weight and renal function.

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Possible (!) interactions of anti-cancer drugs with NOACs (1)

	Via	Dabi	Apix	Edo	Riva
P-gp substrate		**Yes**	**Yes**	**Yes**	**Yes**
CYP3A4 substrate		**No**	**≈25%**	**<4%**	**≈18%**
Antimitotic agents					
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				

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Possible (!) interactions of anti-cancer drugs with NOACs (2)

	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				
Ciclophosphamide	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				
Platinum-based agents					
Cisplatin, Carboplatin, Oxaliplatin	No relevant interaction anticipated				

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Possible (!) interactions of anti-cancer drugs with NOACs (3)

	Via	Dabi	Apix	Edo	Riva
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				
Monoclonal antibodies					
Brentuximab	CYP3A4 competition; No relevant interaction anticipated				
Rituximab, Alemtuzumab, Cetuximab, Trastuzumab, Bevacizumab	No relevant interaction assumed				

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Possible (!) interactions of anti-cancer drugs with NOACs (4)

	Via	Dabi	Apix	Edo	Riva
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				
Raloxifene, Leuprolide, Mitotane	No relevant interaction anticipated				

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Possible (!) interactions of anti-cancer drugs with NOACs (5)

	Via	Dabi	Apix	Edo	Riva
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	Strong-to-moderate P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC			
Prednisone	Moderate CYP3A4 induction; CYP3A4 competition				
Temsirolimus, Sirolimus	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Everolimus	CYP3A4 competition; No relevant interaction anticipated				

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Possible (!) interactions of anti-epileptic drugs with NOACs

	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				

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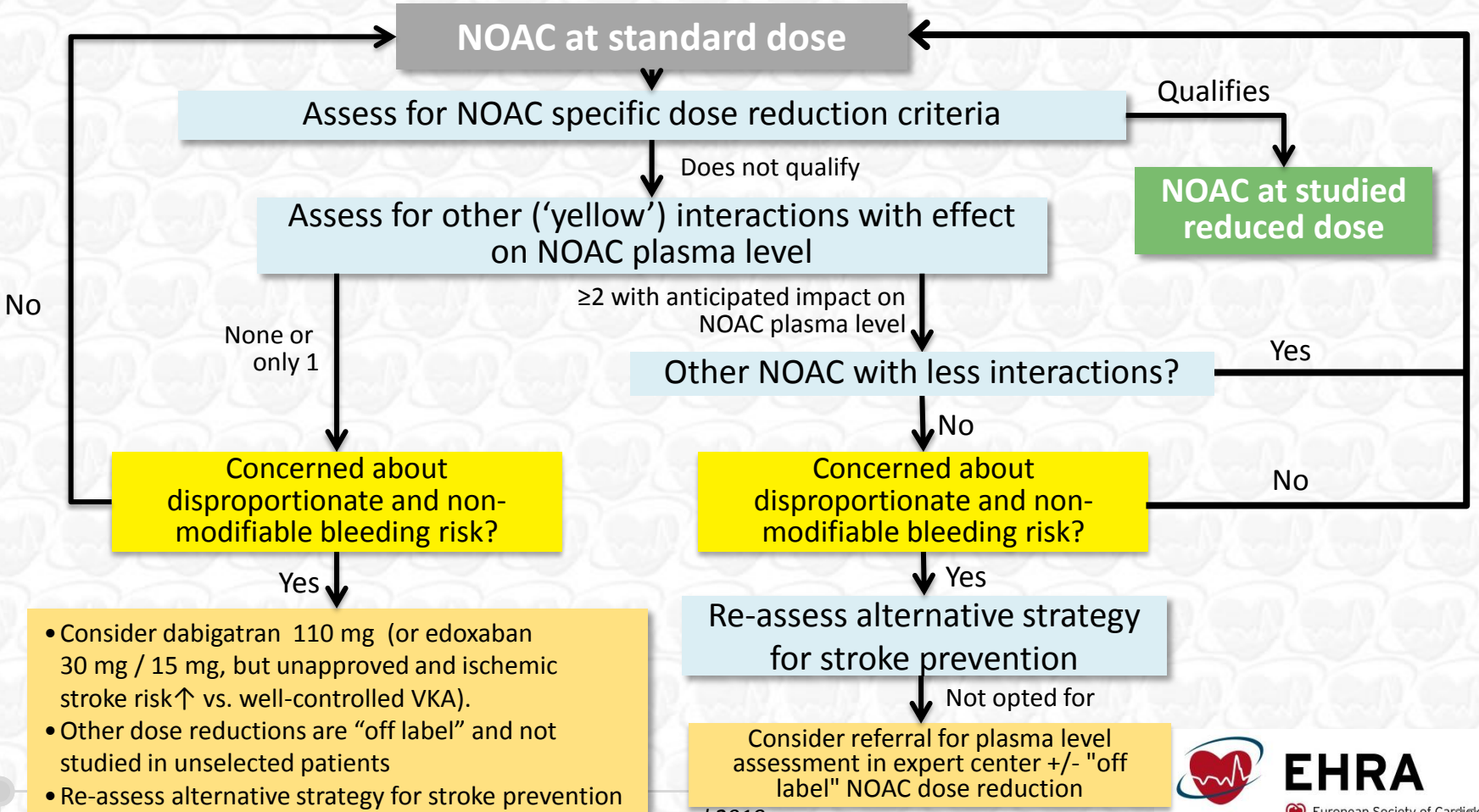
Choosing a NOAC based on drug-drug interaction



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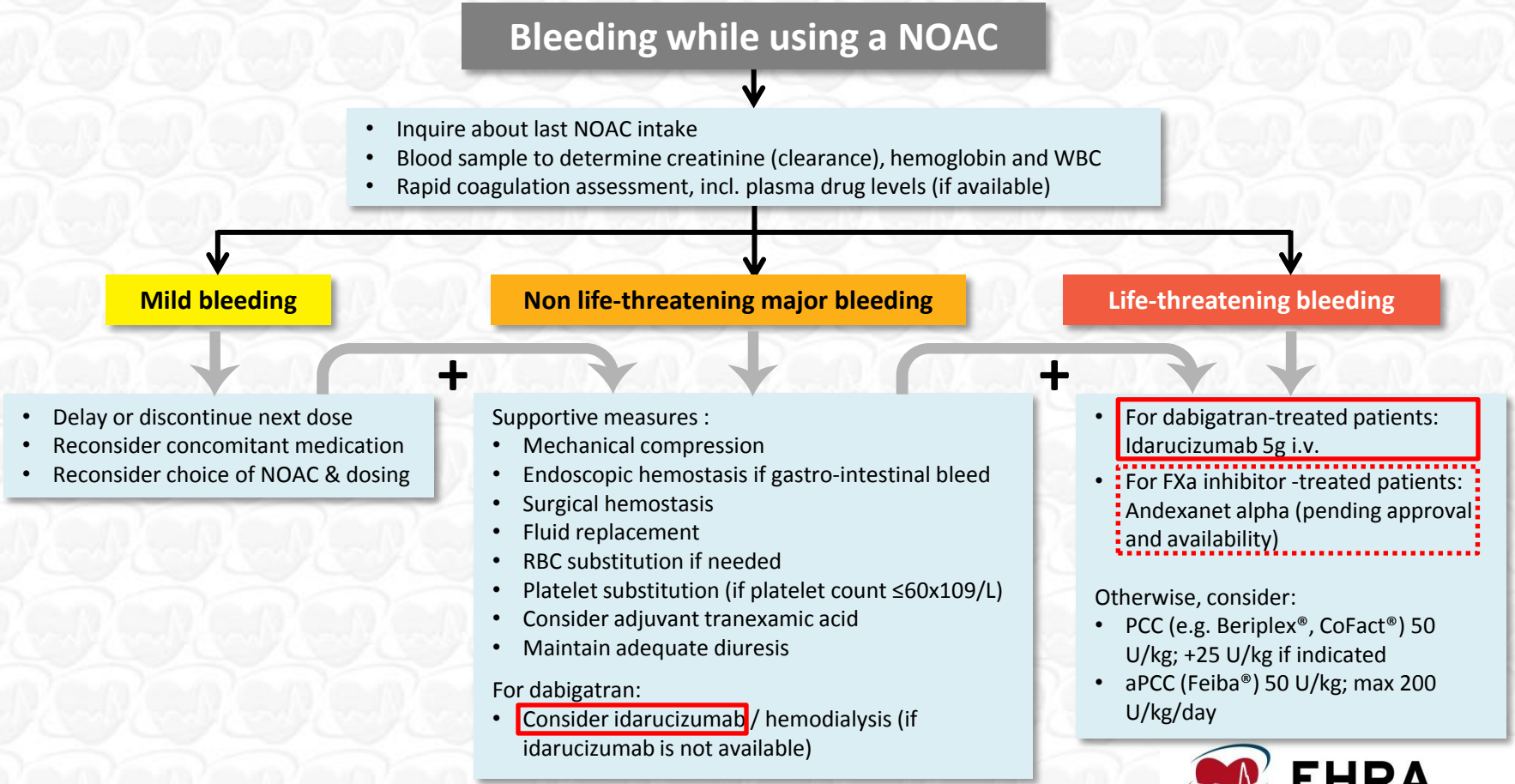
Management of bleeding while on NOAC



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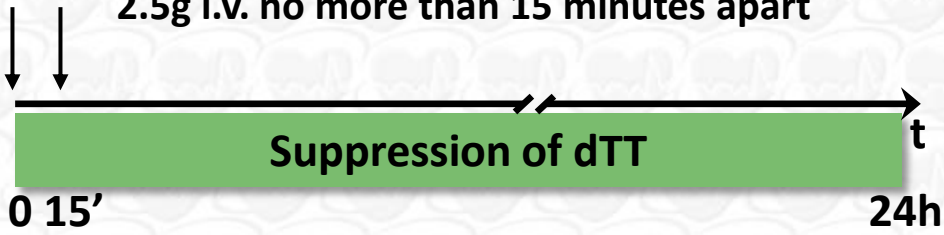
Application of NOAC reversal agents

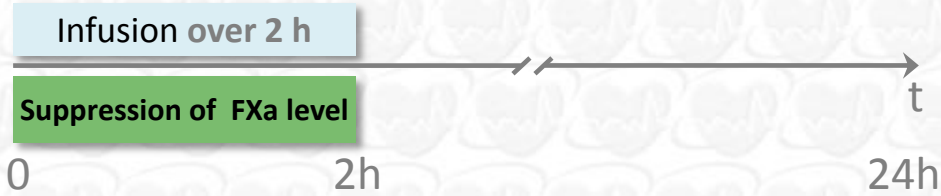
Application of Idarucizumab

Reversal of dabigatran: 5g i.v. in two doses at 2.5g i.v. no more than 15 minutes apart



Application of Andexanet Alpha (if approved and available)

- Reversal of rivaroxaban (last intake >7h before) or apixaban: 400mg bolus, 480mg infusion at 4mg/min
- Reversal of rivaroxaban (last intake <7h before or unknown), enoxaparin or edoxaban: 800mg bolus, 960mg infusion at 8mg/min



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Stroke prevention post GI bleeding

Continuing / Restarting NOAC?
Consider factors favouring withholding (✓) vs. (re-) starting anticoagulation

- Unidentifiable site of bleeding
- Multiple angiodysplasias in the GI tract
- No reversable / treatable cause?
- Bleeding during treatment interruption
- Chronic alcohol abuse
- Need for dual antiplatelet therapy after PCI
- Ider age

↓

Net assessment in favour of withholding anticoagulation according to a multidisciplinary decision

Yes ↓

Consider no anticoagulation vs. LAA occlusion

No ↓

(Re-) initiate (N)OAC as early as feasible (after 4-7 days)

If >75 years old, consider NOAC other than dabigatran, rivaroxaban or higher-dose edoxaban as the first choice

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Perioperative management of NOACs

	Dabigatran		Apixaban - Edoxaban - Rivaroxaban	
	No important bleeding risk and/or adequate 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 50-79 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			
No bridging with LMWH/UFH				
Resume full dose of NOAC ≥ 24 h post low bleeding risk interventions and 48 (-72) h post high-bleeding risk interventions				
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)				

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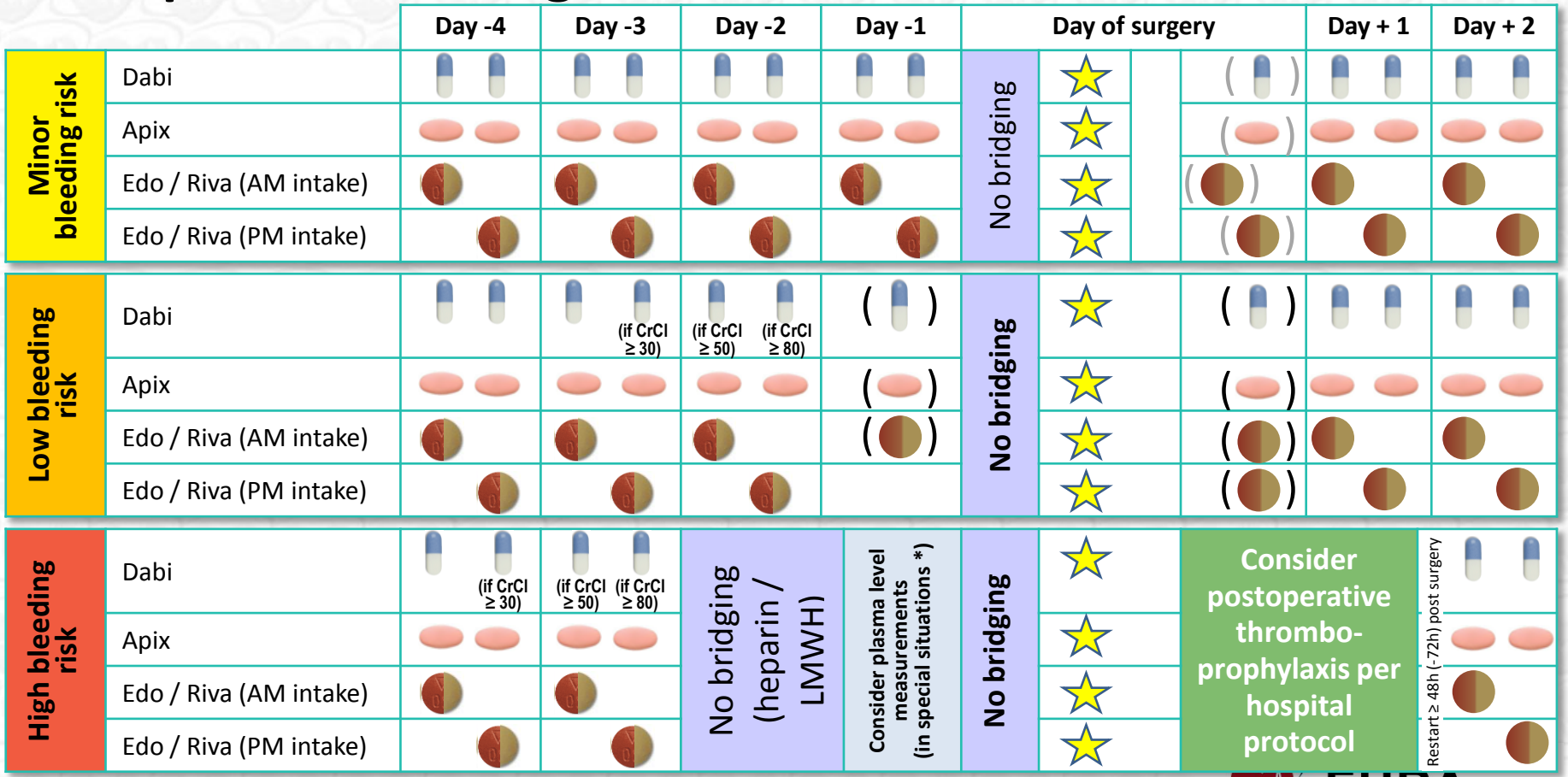
Perioperative management on NOACs



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

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 12)
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)

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

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)

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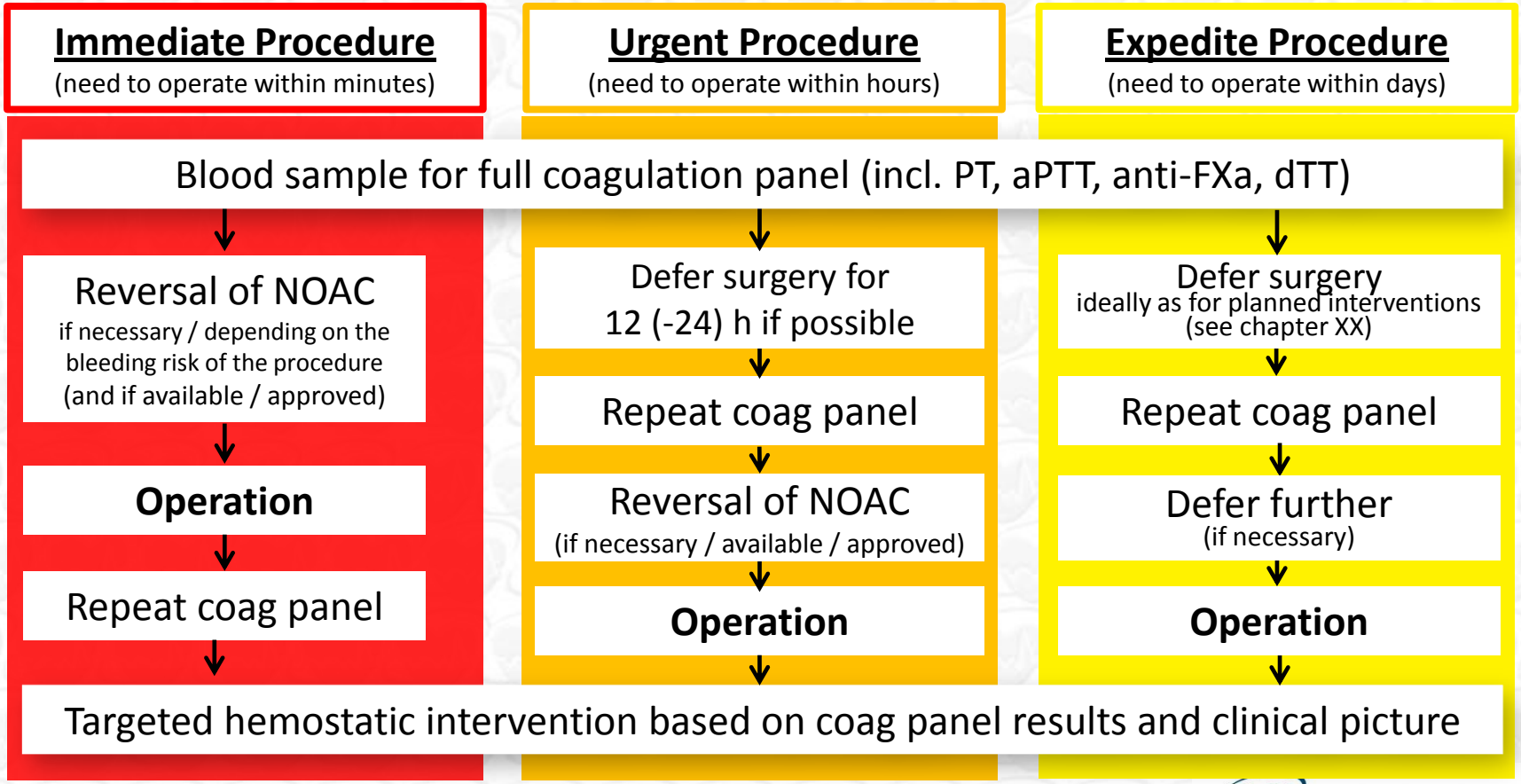
Patient requiring unplanned surgery on NOAC



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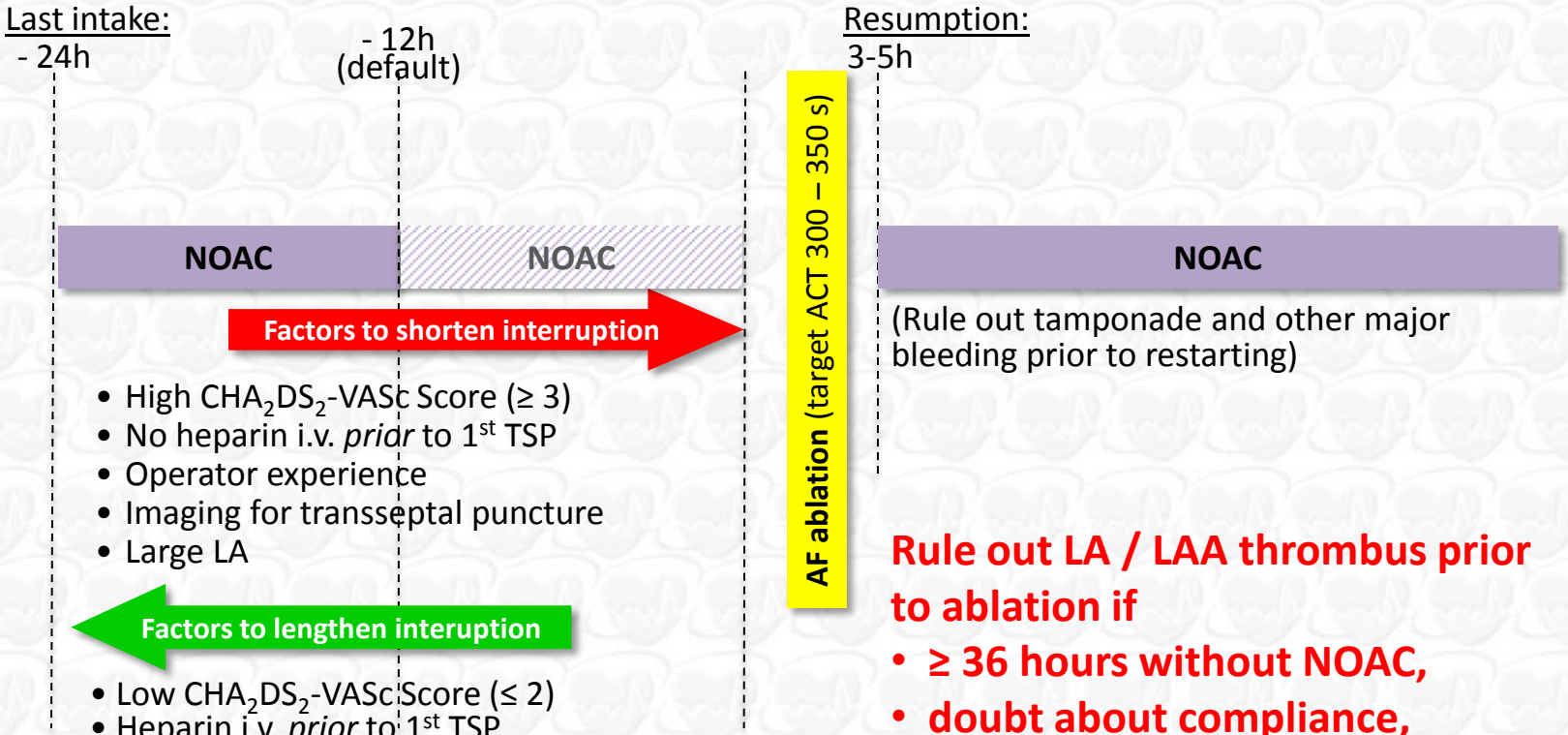
Patient on NOAC undergoing AF ablation



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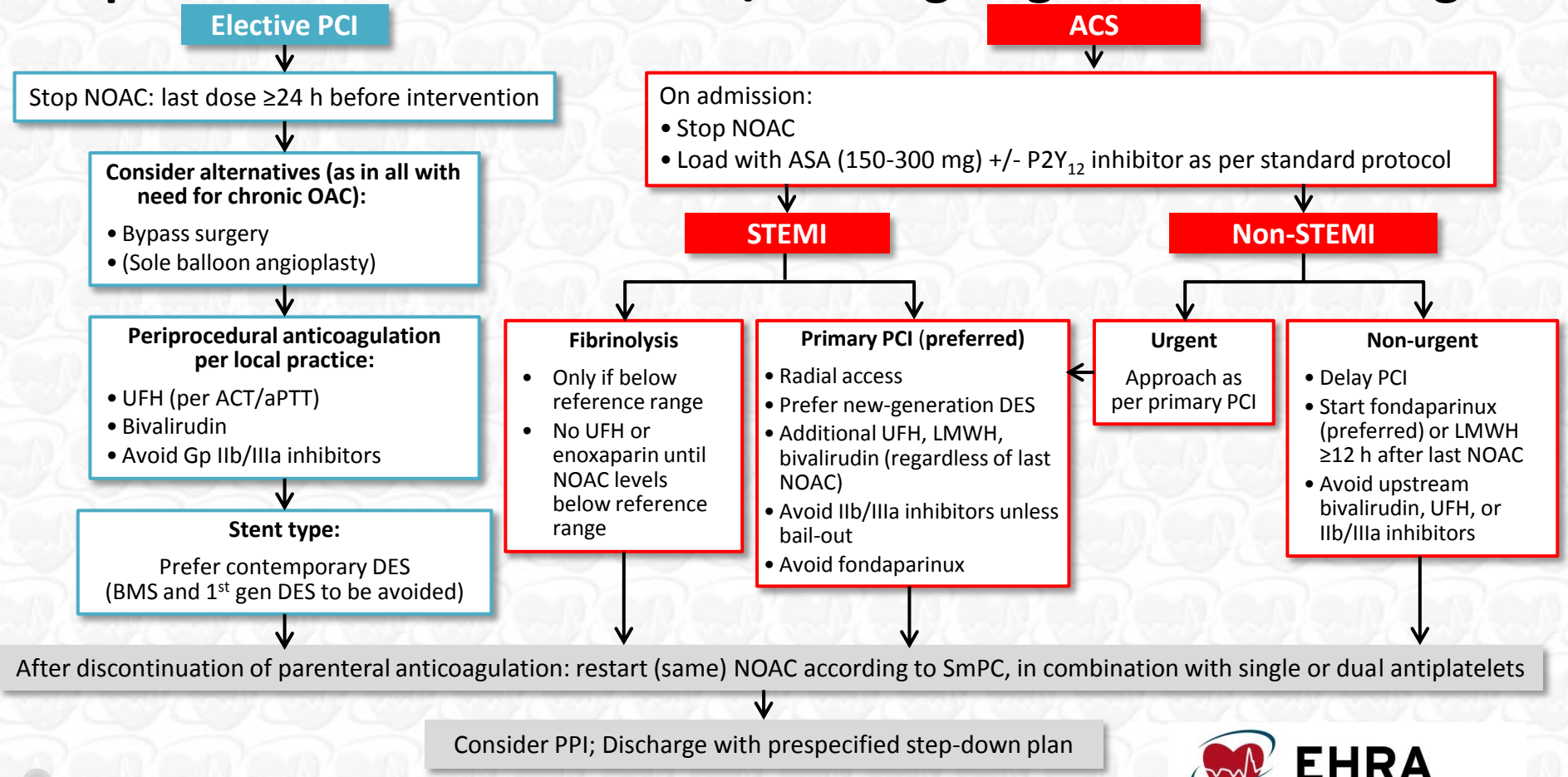
AF patient on NOAC with ACS / undergoing elective stenting



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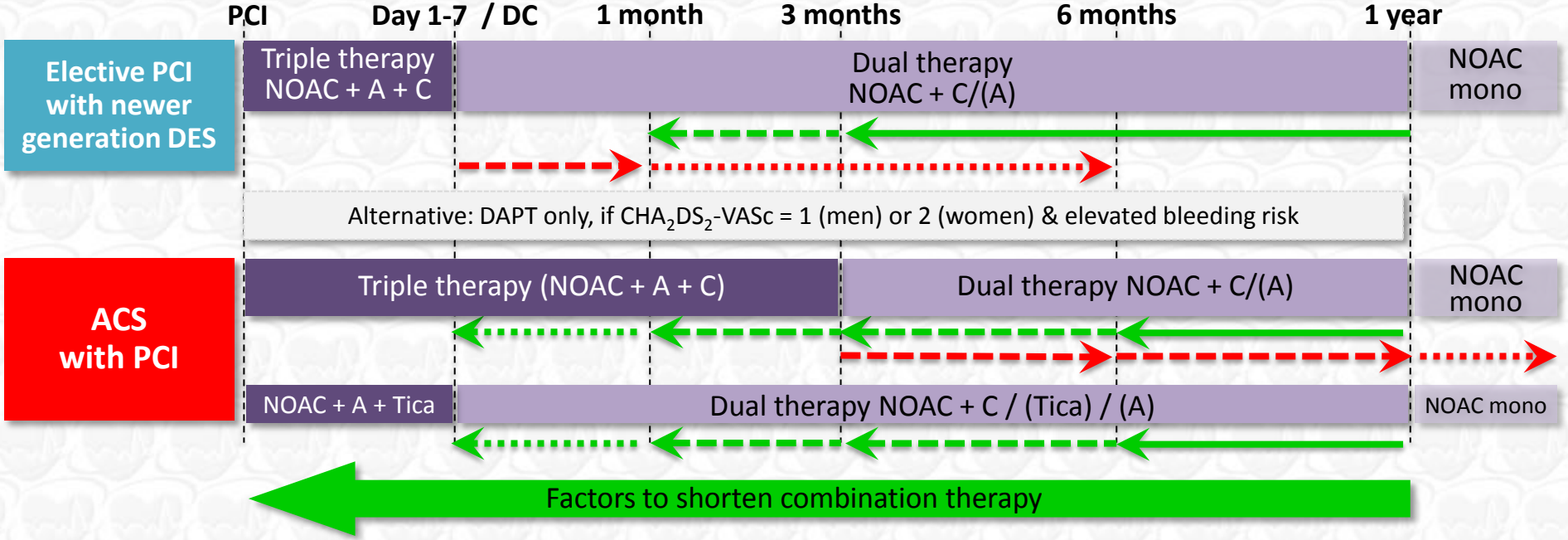
Anticoagulation post PCI / ACS (+ NOAC)



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

Factors to lengthen combination therapy

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

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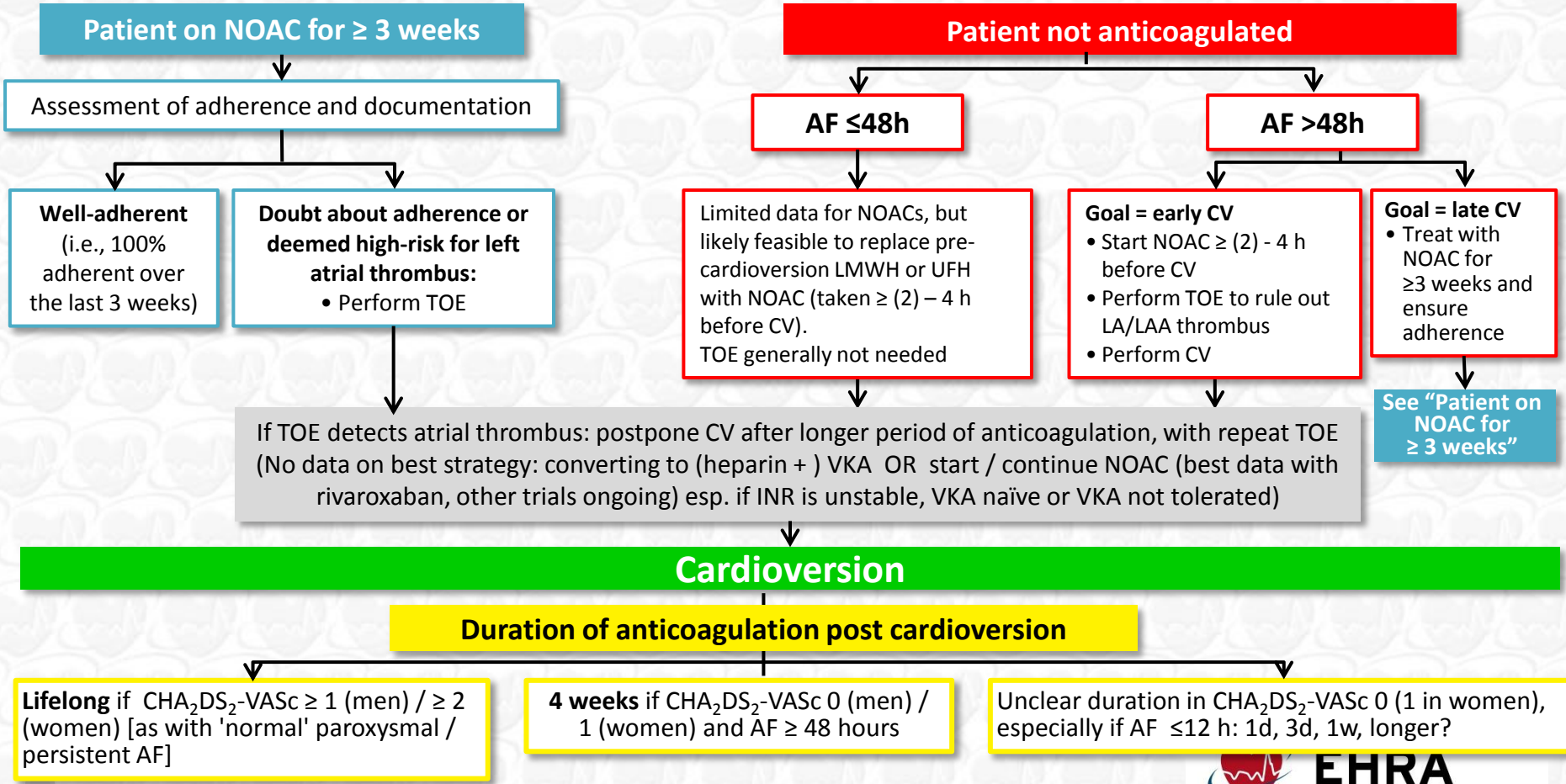
Patient undergoing cardioversion



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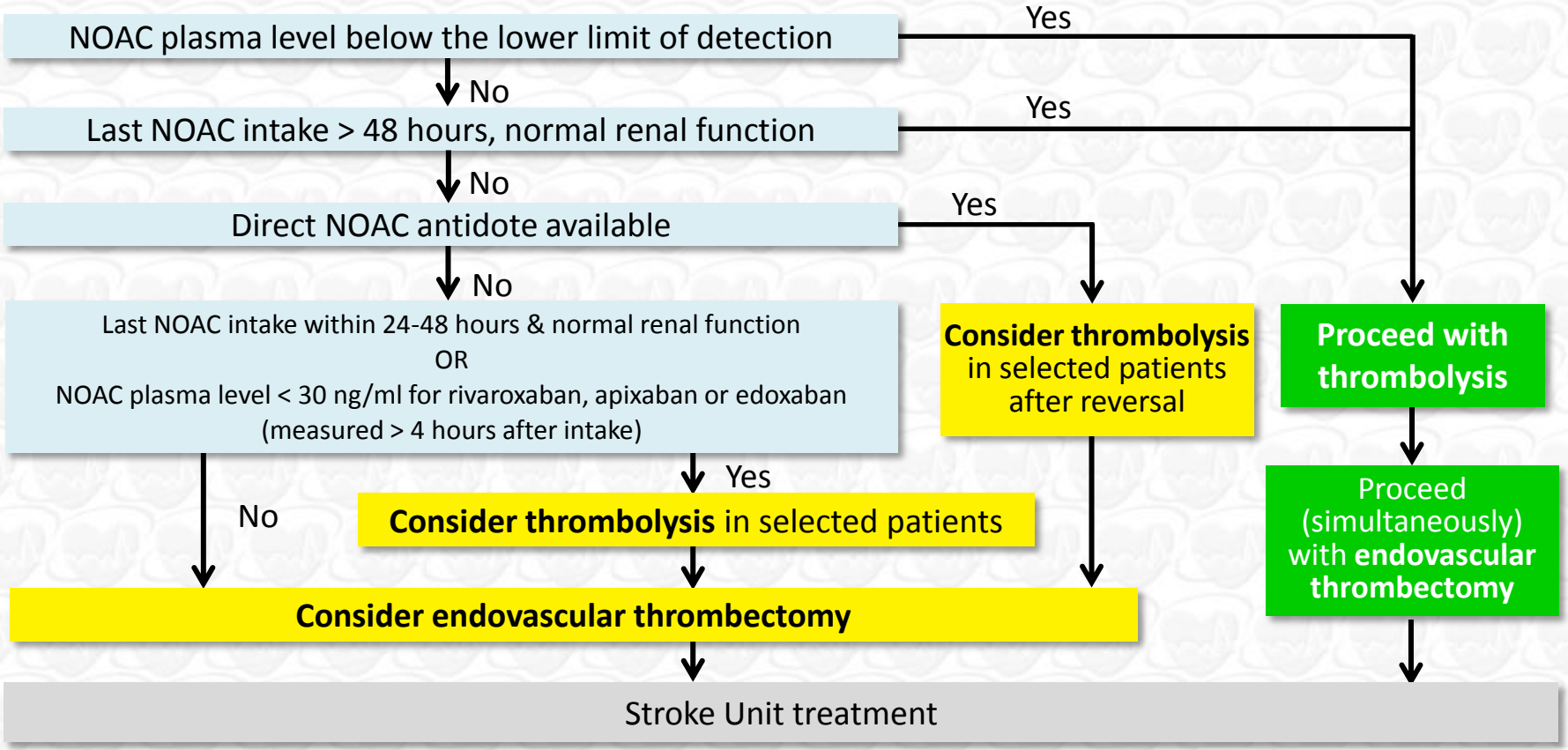
Management of acute ischemic stroke* on NOAC



** with relevant neurological deficit*

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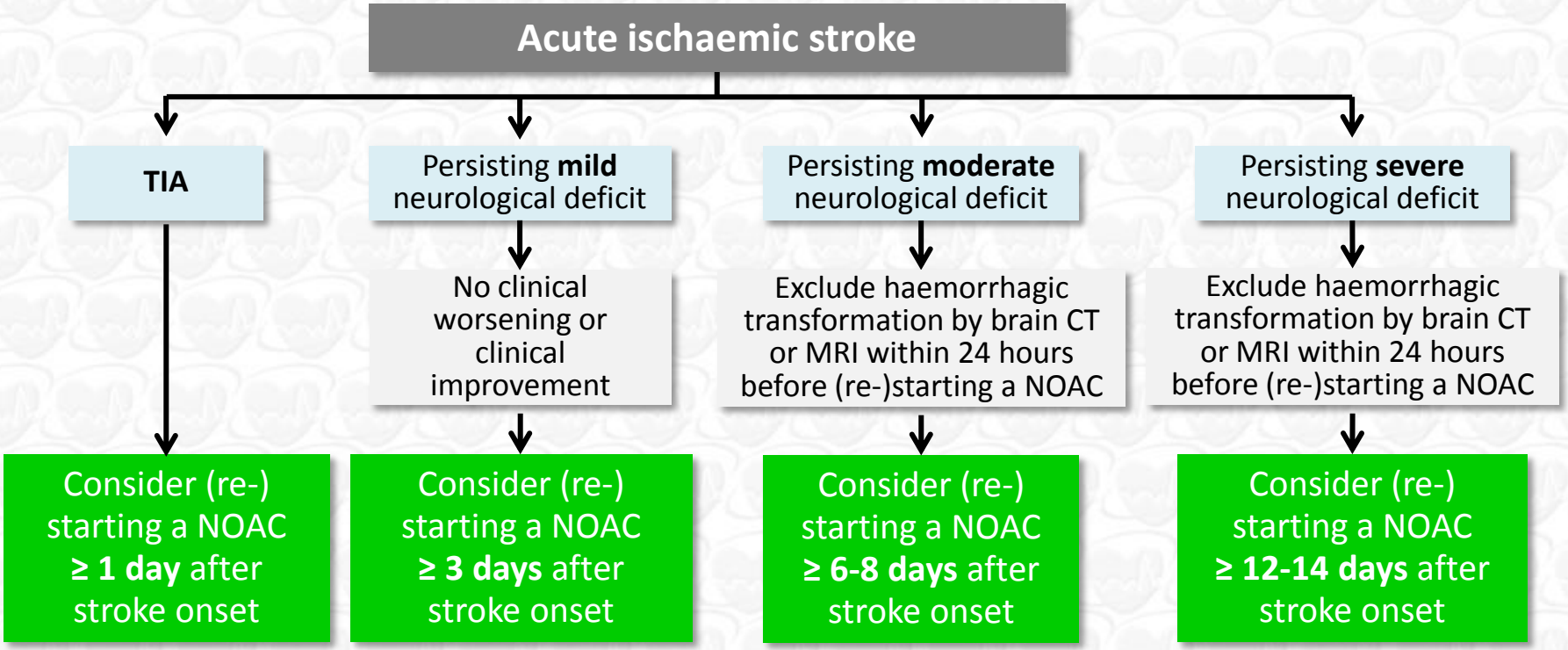
(Re-)starting anticoagulation post ischemic stroke



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Patient post intracranial hemorrhage

Consider factors favoring withholding (✓) vs. (re-) starting oral anticoagulation

- Severe intracranial bleed
- Multiple cerebral microbleeds (e.g. >10)
- No reversible/treatable cause of bleeding
- Older age
- Bleeding during interruption of anticoagulation
- Bleed on adequately or underdosed NOAC
- Uncontrolled hypertension
- Chronic alcohol abuse
- Need for dual antiplatelet therapy after PCI

↓

Net assessment in favour of withholding anticoagulation according to a multidisciplinary decision

Yes ↓ **Consider no anticoagulation vs. LAA occlusion#**

No ↓ (Re-) initiate (N)OAC after 4-8 weeks*

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NOAC dosing in AF / treatment of VTE (1)

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 y, concomitant verapamil, increased risk of GI bleeding

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NOAC dosing in AF / treatment of VTE (2)

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 y, 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)*

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NOACs in long-term prevention of VTE / post orthopedic surgery (1)

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 y, concomitant verapamil (both based on PK/PD analyses; not studied in this setting)

[**] SmPc: 1x 20 mg in patients at high risk of recurrence

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NOACs in long-term prevention of VTE / post orthopedic surgery (2)

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; concomit. verapamil, amiodarone, quinidine; age >75 y

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NOACs post PCI

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

** As outlined in detail in chapter 14, 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.*

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NOACs in atherosclerotic disease (*without AF*)

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

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Assessment of falls risk

A) High risk of falls[1]

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[2]

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%

[1]*Steffel et al., JACC 2016*

[2]*Tiedemann et al., J Gerontol A Biol Sci Med Sci 2010*

Optimizing VKA treatment for out-of-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

Based on Van Spall et al., Circulation 2012

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