EHRA
European Heart
Rhythm Association

EHRA KEY MESSAGES

Afib series

UPDATE

2021 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

www.escardio.org/EHRA

ESC
European Society
of Cardiology

2021 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. NOAC eligibility and dosing

Selected indications and contra-indications

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

Hatched – Limited data

NOAC indications and dosing for stroke prevention in atrial fibrillation (SPAF)

Stroke prevention in Atrial Fibrillation (SPAF)		
	Standard dose	**Comments / dose reduction**
Apixaban	5 mg BID	2.5 mg BID if 2 out of 3: • Weight ≤60 kg • Age ≥80 yrs •serum Creatinine ≥133 µmol/l (1.5 mg/dl)or single criterion: if CrCl 15-29 ml/min
Dabigatran	150 mg BID /or 110 mg BID	No pre-specified dose-reduction criteria in phase III trial *SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding*
Edoxaban	60 mg QD	30 mg QD if: • Weight ≤60 kg • CrCl 15-49 ml/min • concomitant therapy with strong P-Gp inhibitor
Rivaroxaban	20 mg QD	15 mg QD if CrCl ≤15-49 ml/min

NOAC dosing in AF patients post ACS / PCI*		
	Standard dose	**Comments / dose reduction**
Apixaban	5 mg BID	Dose reduction as for SPAF
Dabigatran	150 mg BID or 110 mg BID	110mg as for SPAF
Edoxaban	60 mg QD	Dose reduction as for SPAF
Rivaroxaban	15 mg QD	Dose reduction to 10 mg QD if CrCl 30-49 ml/min

*in addition to single / dual antiplatelet therapy, where applicable. See page 49 for details.

NOAC indications and dosing (DVT/PE)

Treatment of deep vein thrombosis / pulmonary embolism		
	Initial Therapy	**Comments / dose reduction**
Apixaban	10 mg BID, 7 days	5 mg BID, no dose reduction
Dabigatran	Heparin / LMWH	150 mg BID, no dose reduction#
Edoxaban	Heparin / LMWH	60 mg QD, same dose reduction as for SPAF! (see above)
Rivaroxaban	15 mg BID, 21 days	20 mg QD, no dose reduction**

Per SmPC: 110mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding (based on pharmacokinetic / pharmacodynamic (PK/PD) analyses; not studied in this setting)
** Per SmPC: 15 mg if risk of bleeding outweighs risk for recurrent DVT and PE (based on PK/PD analyses; not studied in this setting)

Long-term prevention of DVT / PE		
	Standard dose	**Comments / dose reduction**
Apixaban	2.5 mg BID	
Dabigatran	150 mg BID	No pre-specified dose-reduction criteria in clinical trial#
Edoxaban	60 mg QD*	
Rivaroxaban	10 mg QD	**

SmPC: 110mg BID if age ≥80 years, concomitant verapamil (both based on pharmacokinetics / pharmacodynamics analyses; not studied in this setting)
* not specifically studied, follow up data available up to 12 months in phase III trial
** SmPC: 20mg QD in patients at high risk of recurrence

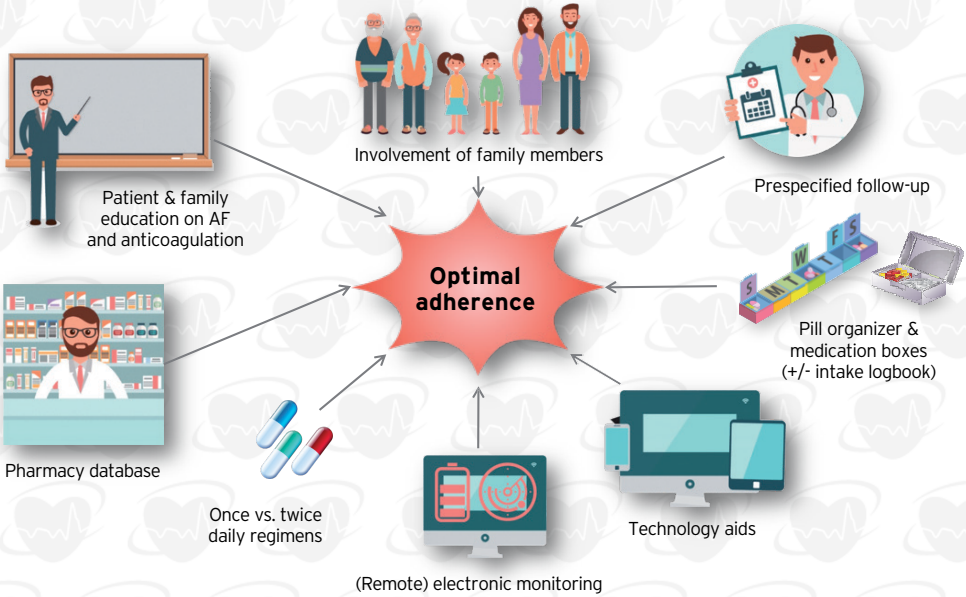
NOAC indications and dosing in patients without indication for OAC (i.e., no AF / DVT / PE)

Secondary prevention of atherothrombotic events post ACS		
	Standard dose	**Comments / dose reduction**
Rivaroxaban	2.5 mg BID	In addition to aspirin +/- $P2Y_{12}$ inhibitor

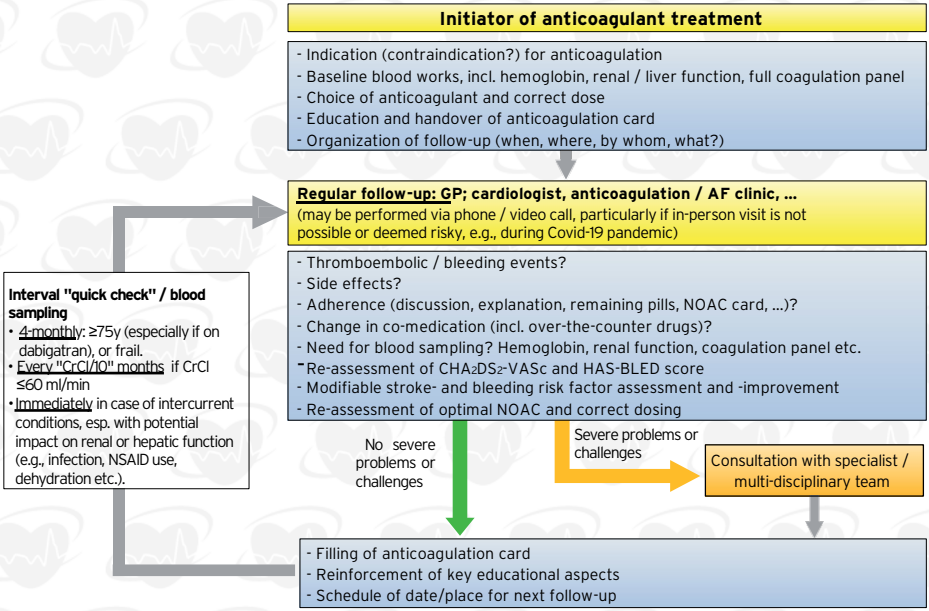
Secondary prevention of atherothrombotic events in CCS and / or symptomatic PAD		
	Standard dose	**Comments / dose reduction**
Rivaroxaban	2.5 mg BID	In addition to aspirin

2. Practical considerations for initiation and follow-up

Measures to optimize adherence to NOACs



Structured Follow-up for NOAC treated patients



Checklist during follow-up contacts of AF patients on anticoagulation

	Interval	Comments
1. Adherence	Each visit	• Instruct patient to bring NOAC card and complete list of medication: make note and assess adherence. • Re-educate on importance of strict intake schedule. • Inform about adherence aids (special boxes; smartphone applications; ...). Consider specific adherence-measuring interventions (see page 6) • Inform about minor bleeding (gum, epistaxis, small ecchymosis) and instruct not to skip any dose • Assess cognitive function
2.Thromboembolism	Each visit	• Systemic circulation (TIA, stroke, peripheral). • Deep vein thrombosis, pulmonary embolism
3. Bleeding	Each visit	• For every bleeding: Look for reason. Cancer? Ulcer? Other causes, lesions etc.? Treatment or prevention possible? • "Nuisance" bleeding: Reason? Treatment / prevention (see above)? • Assess impact on quality of life.
4. Other side effects	Each visit	• Carefully assess relation with NOAC: decide for continuation (and motivate) or change NOAC.
5. Co-medications	Each visit	• Prescription drugs; over-the-counter drugs. • Careful interval history (also temporary use, e.g., NSAIDs)
6. Blood sampling (incl. Hb, renal / liver function)	Yearly	In all patients except those below
	4-monthly	≥75 yrs (especially if on dabigatran), or frail.
	Variable	If renal function CrCl ≤60 ml/min: CrCl / 10 = minimum recheck interval [in months]
	If needed	In case of intercurrent conditions, especially with potential impact on renal or hepatic function (e.g., infection, NSAID use, dehydration etc.)

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

	Interval	Comments
7. Re-assess stroke risk	Each visit	CHA_2DS_2-VASc score, as recommended by current guidelines
8. Assessing and minimizing 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 • Falls
9. Assessing for optimal NOAC and correct dosing	Each visit	Especially based on the above, re-assess whether - The chosen NOAC is the best for the patient - The chosen dose is correct

Missed dose, double dose, uncertainty about dose intake

Missed dose

- A forgotten dose may be taken until half of the dosing interval has passed.
- BID dosing regimen: forgotten dose can be taken up until 6 h after the scheduled intake.
- QD dosing regimen: forgotten dose can be taken up until 12 h after the scheduled intake.
- After these time points, the dose should be skipped, and the next scheduled dose should be taken.

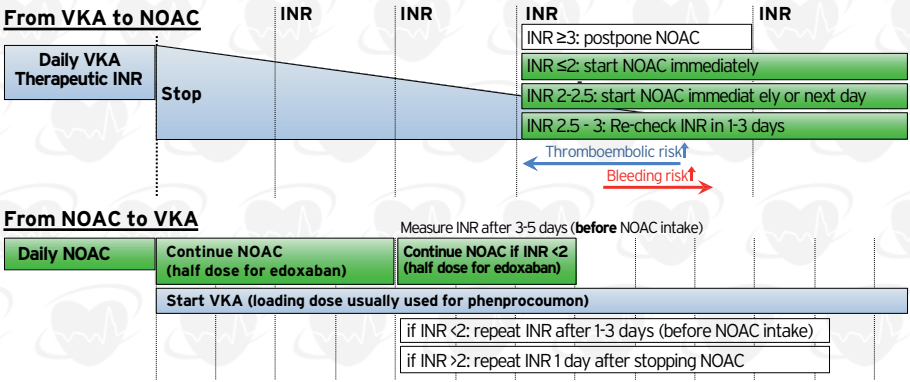
Double dose

- BID dosing regimen: next planned dose (i.e. after 12 h) may be skipped, regular BID dosing regimen restarted 24 h after the double dose intake.
- QD dosing regimen: Continue normal dosing regimen, i.e. without skipping the next daily dose.

Uncertainty about dose intake

- BID dosing regimen: generally not advisable to take another tablet / capsule. Continue with regular dose regimen, i.e. starting with the next dose at the 12 h interval.
- QD dosing regimen:
  - High thromboembolic risk (e.g., CHA_2DS_2-VASc ≥ 3): take another tablet 6-8 hours after the original (uncertain) intake, then continue with normal dose regimen
  - Low thromboembolic risk (e.g., CHA_2DS_2-VASc ≤ 2): wait until the next scheduled dose.

Switching NOACs to and from VKA



Switching NOACs to and from other NOACs / heparin

From unfractionated heparin to NOAC

From NOAC to unfractionated heparin

Start UFH 12 (BID NOAC) - 24 (QD NOAC) hours after last NOAC intake (or earlier if indicated, e.g., in ACS)

From BID NOAC to QD NOAC

From BID NOAC to LMWH

From QD NOAC to BID NOAC

From QD NOAC to LMWH

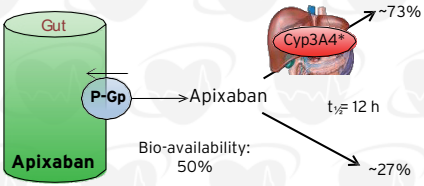
3. Pharmacokinetics and drug-drug interactions of NOACs

Absorption and metabolism of NOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bio-availability	3-7%	50%	62%	15 mg / 20 mg: 66% without food, 100% with food.
Prodrug	Yes	No	No	No
Clearance non-renal / renal of absorbed dose	20% / 80%	73% / 27%	50% / 50%	65% / 35%
Plasma protein binding	35%	87%	55%	95%
Dialysability	50-60% (in part dialysable)	14% (not dialysable)	n.a. (not dialysable)	n.a. (not dialysable)
Metabolism	Glucoronic acid conjugation	CYP3A4 (25%), CYP1A2, CYP2J2, CYP2C8, CYP2C9 CYP2C19	CYP3A4 (<4% of elimination)	CYP2A4 (18%), CYP2J2
Absorption with food	No effect	No effect	6-22% more; minimal effect on exposure	+39% more (see above)
Absorption with H_2B/PPI	-12-30% (not clinically relevant)	No effect	No effect	No effect
Time to peak levels [h]	3	3	2-4	2-4
Elimination half-life [h]	12-17	12	10-14	5-9 (young) 11-13 (elderly)

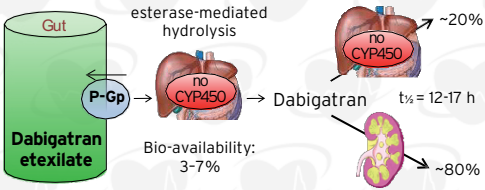
NOAC metabolism

Apixaban

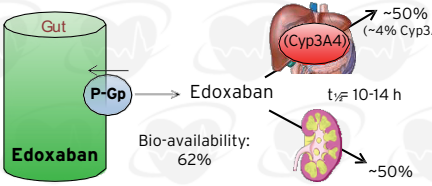


*also via CYP1A2, CYP2J2, CYP2C8, CYP2C9, and CYP2C19

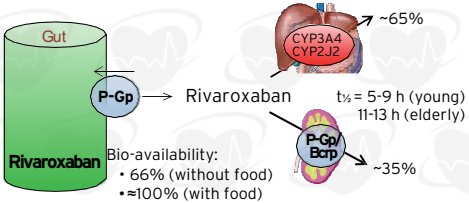
Dabigatran



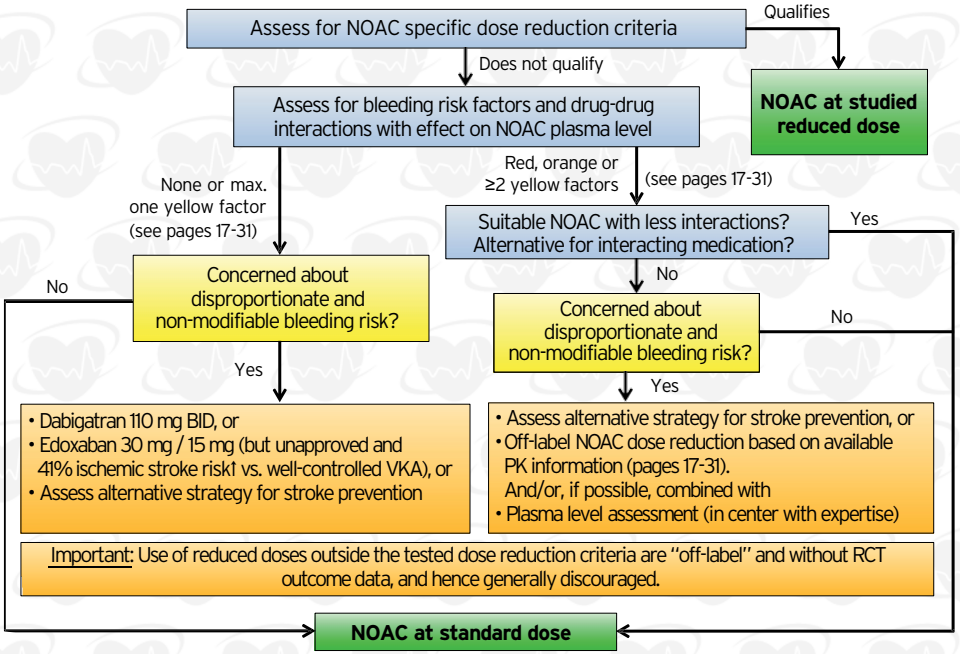
Edoxaban



Rivaroxaban



Choosing a NOAC 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 5) 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

Effect of drug-drug interactions and clinical factors on NOAC plasma levels and anticoagulant effects

Color coding is based on the respective NOAC SmPC, drug interaction databases, or expert opinion. Some of the color codes will likely require adaptation as more data become available over time.

White	No relevant drug-drug interaction anticipated.
Yellow	Caution required, especially in case of polypharmacy or in the presence of ≥2 yellow / bleeding risk factors (see page 15).
Orange	Lower dose (dabigatran) or dose reduction (edoxaban) recommended according to label as indicated. Otherwise consider avoiding concomitant use, careful monitoring required if combined (see page 15).
Red	Contraindicated / not advisable due to increased plasma levels.
Blue (light)	Caution required, especially in case of polypharmacy or in the presence of ≥2 light blue interactions due to reduced NOAC plasma levels.
Blue (dark)	Contraindicated due to reduced NOAC plasma levels.
Pink	No information retrievable (only page 31, Covid-19 medication).
Hatched color coding indicates no clinical or PK data available.	

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	+12–60%	No PK data	+40%	Minor effect
Digoxin	P-gp competition	No effect	No effect	No effect	No effect
Diltiazem	Weak P-gp and CYP3A4 inhibition	No effect	+40%	No data yet	No effect
Dronedarone	P-gp and CYP3A4 inhibition	+70 to 100%	With caution	+85% (dose reduction to 30 mg once daily by label)	Moderate effect; should be avoided
Quinidine	P-gp inhibition	+53%	No data yet	+77% (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp inhibition and weak CYP3A4 inhibition	+12 to 180% (if taken simultaneously) (110 mg BID by label)	No PK data	+53% (SR) (No dose reduction required by label)	+40% (probably not relevant)

Interactions of commonly used drugs with NOACs (2)

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Other cardiovascular drugs					
Atorvastatin	P-gp inhibition and CYP3A4 competition	No relevant interaction	No data yet	No effect	No effect
Ticagrelor (see also page 49)	P-gp inhibition	+24 to 65% (give loading dose 2h after dabigatran)	No data – carefully monitor	No data – carefully monitor	No data – carefully monitor
Antibiotics					
Clarithromycin; Erythromycin	P-gp inhibition and strong CYP3A4 inhibition	Clarithromycin: +19% AUC; +15% Cmax	Clarithromycin: +60% AUC; +30% Cmax	Erythromycin: +85% AUC; +68% Cmax (dose reduction to 30 mg once daily by label)	Clarithromycin: +50% AUC; +40% Cmax Erythromycin: +30% AUC; +30% Cmax
Rifampicin	P-gp/ BCRP and CYP3A4 induction	minus 66% AUC; minus 67% Cmax	minus 54% AUC; minus 42% Cmax	minus 35% AUC, (but with compensatory increase of active metabolites	minus 50% AUC; minus 22% Cmax

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	Variable increase / decrease	Strong increase	No data yet	+153% AUC +55% Cmax (Ritonavir 600 BID)
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% AUC; +30% Cmax (if given systemically)
Itraconazole; Ketoconazole	Potent P-gp and BCRP competition; strong CYP3A4 inhibition	+140 to 150% (ketoconazole) (US: 2 x 75 mg if CrCl 30-50 ml/min)	+100% AUC; +64% Cmax (ketoconazole)	+87% AUC; +89% Cmax(dose reduction to 30 mg once daily by label) (ketoconazole)	+160% AUC; +72% Cmax (ketoconazole)
Voriconazole	Strong CYP3A4 inhibition	No data yet		No data yet	
Posaconazole	Mild to moderate P-gp inhibition, strong CYP3A4 inhibition				

Interactions of commonly used drugs with NOACs (4)

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Other drugs					
H_2-blockers; PPI; Al- Mg-hydroxide	GI absorption	Minor effect, not clinically relevant	No effect	Minor effect, not clinically relevant	No effect
SSRIs; SNRIs	Pharmacodynamic effect on platelets				
St. John's wort	P-gp/ BCRP and CYP3A4 induction	Should be avoided (per SmPC)	"With caution" (per SmPC)	"With caution" (per SmPC)	Should be avoided (per SmPC)
Naproxen	P-gp competition; pharmacody-namically (increased bleeding time)	No data yet	+55% AUC; +61% Cmax	No difference in AUC	No relevant increase of AUC

Other factors with potential impact on NOAC plasma levels / anticoagulant effect

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Age ≥80 years	Potential for increased plasma levels	110mg BID (per SmPC)			
Age ≥75 years	Potential for increased plasma levels				
Weight ≤60 kg (see page 56)	Potential for increased plasma levels			Dose reduction according to label	
Weight ≥120 kg (see page 56)	Potential for decreased plasma levels				
Chronic kidney disease	Potential for increased plasma levels				
Other factors with potentially increased bleeding risk		E.g.,: • Concomitant antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants • Severe Frailty / falls risk • H/o bleeding or predisposition (anemia, thrombocytopenia)			

Interactions of commonly used anticancer drugs (1)

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
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	CYP3A4/P-gp competition				
Antimetabolites					
Methotrexate	P-gp competition; no relevant interaction anticipated				
Pemetrexed, Purine ana-logs, Pyrimidine analogs	No relevant interaction anticipated				

Interactions of commonly used anticancer drugs (2)

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Topoisomerase inhibitors					
Topotecan	No relevant interaction anticipated				
Irinotecan	CYP3A4/P-gp competition; no relevant interaction anticipated				
Etoposide	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Alkylating agents					
Ifosfamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Cyclophos-phamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Lomustine	Mild CYP3A4 inhibition				
Busulfan	CYP3A4 competition; no relevant interaction anticipated				
Bendamustine	P-gp competition; no relevant interaction anticipated				

Interactions of commonly used anticancer drugs (3)

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Alkylating agents (continued)					
Chlorambucil, Melphalan, Carmustine, Procarbazine, Dacarbazine, Temozolomide	no relevant interaction anticipated				
Platinum-based agents					
Cisplatin, Carboplatin, Oxaliplatin	No relevant interaction anticipated				
Monoclonal antibodies					
Brentuximab	CYP3A4 competition; no relevant interaction anticipated				
Rituximab, Alemtuzumab, Cetuximab, Trastuzumab, Bevacizumab	No relevant interaction assumed				

Interactions of commonly used anticancer drugs (4)

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
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				
Intercalating agents					
Bleomycin, Dactinomycin	No relevant interaction anticipated				
Mitomycin C	P-gp competition; no relevant interaction anticipated				

Interactions of commonly used anticancer drugs (5)

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
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 inhibition; CYP3A4 competition				
Erlotinib, Gefitinib	CYP3A4 competition; no relevant interaction anticipated				

Interactions of commonly used anticancer drugs (6)

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
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				

Interactions of commonly used anticancer drugs (7)

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

Interactions of commonly used antiepileptic drugs

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Brivaracetam	--	No relevant interaction known/assumed			
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	-29%	-50%		
Ethosuximide	CYP3A4 competition	No relevant interaction known/assumed			
Gabapentin	--	No relevant interaction known/assumed			
Lacosamide	--	No relevant interaction known/assumed			
Lamotrigine	P-gp competition	No relevant interaction known/assumed			
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/possible P-gp induction				
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition				
Pregabalin	--	No relevant interaction known/assumed			
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction/inhibition				
Zonisamide	CYP3A4 competition; weak P-gp inhibition	No relevant interaction known/assumed			

Anticipated effects of common herbal medicines on NOAC plasma levels

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Curcumin	P-gp inhibition				
Echinacea purpurea	Mild CYP3A4 inhibition				
Garlic	Mild CYP3A4 inhibition; anticoagulation / antiplatelet effect				
Ginger	Anticoagulation / antiplatelet effect				
Ginkgo biloba	P-gp inhibition; anticoagulation / antiplatelet effect				
Ginseng	Anticoagulation / antiplatelet effect				
Green Tea	P-gp inhibition; anticoagulation / antiplatelet effect				
Horse chestnut	Anticoagulation / antiplatelet effect				
St. John's wort	P-gp/ BCRP and CYP3A4 induction	Should be avoided (per SmPC)	"With caution" (per SmPC)	"With caution" (per SmPC)	Should be avoided (per SmPC)
Valerian	Mild CYP3A4 inhibition				

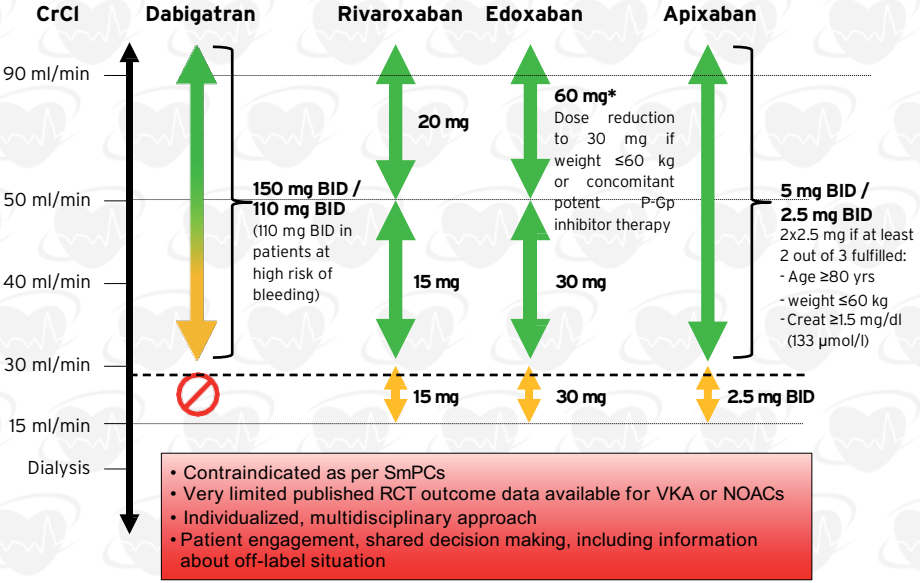
Important: Several hypothetical pharmacokinetic and pharmacodynamic pathways, various unknown mechanisms of interaction, inherent variation in composition.

Interactions of drugs used in the treatment of COVID-19

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Azithromycin	P-gp inhibition	No PK data	No PK data	No PK data (no dose reduction required by label)	No PK data
Atazanavir	CYP3A4 inhibition	No PK data	No PK data Consider avoiding	No PK data	No PK data Consider avoiding
Lopinavir / Ritonavir	P-gp and BCRP inhibition or induction; CYP3A4 inhibition	No PK data Consider avoiding	No PK data	No PK data Consider avoiding	+153% (ritonavir)
Darunavir / Cobicistat	CYP3A4 inhibition, P-gp and BCRP inhibition				
Ribavirin		No information retrievable			
Remdesivir		No information retrievable			
Favipiravir		No information retrievable			
Bevacizumab					
Eculizumab					
Tocilizumab		No information retrievable			
Fingolimod					
Interferon					
Pirfenidone					
Methyl-prednisolone					
Nitazoxanide		No information retrievable			

4. NOACs in patients with CKD or advanced liver disease

NOACs in Chronic Kidney Disease (CKD)



*According to EMA SmPC edoxaban should be used in "high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk".

Criteria for diagnosing CKD; estimation of renal function and categories of renal dysfunction

Decreased GFR*	- GFR <60 mL/min/1.73m²
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/1.73m²]

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

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

NOAC in patients with liver disease

Baseline assessment:

- H/o thromboembolism or bleeding?
- Relevant co-medications and over-the-counter drugs?
- CBC, liver function test, PT/INR, APTT, renal function
- High bleeding risk (e.g., H/o major bleeding (varices), uncontrolled alcohol intake, etc.)?

Highest risk patients → Consider no anticoagulation / evaluate alternative stroke prevention strategy

All other patients

Parameter	1 point	2 points	3 points
Encephalo-pathy	No	Grade 1-2	Grade 3-4
Ascites	No	Mild	≥ Moderate
Bilirubin	<2 mg/dL <34 mol/L	2-3 mg/dL 34-50 mol/L	>3 mg/dL >50 mol/L
Albumin	>3.5 g/dL >35 g/L	2.8-3.5 g/dL 28-35 g/L	<2.8 g/dL <28 g/dL
INR	< 1.7	1.71-2.30	>2.30

NOAC use recommendations in liver disease

	A (<7 pts)	B (7–9 pts)	C (>9 pts)
Dabigatran	Normal dose	Use with caution	Not recommended
Apixaban			
Edoxaban			
Rivaroxaban		Not recommended	

- ✓ Assess Child-Pugh score
- ✓ Check NOAC use recommendations in liver disease
- ✓ Check for drug-drug interactions
- ✓ Discuss in multidisciplinary team

Close follow-up **(see also page 7)**

- Signs of (occult) bleeding?
- Adherence? Side effects?
- (New) co-medications, incl. NSAIDs, aspirin, OTC?
- CBC, liver function, PT/INR, aPTT, renal function
- Continue bleeding risk minimization strategies
- Re-enforce education, incl. alcohol abstinence

5. NOAC plasma level measurements

Expected plasma levels of NOACs in patients treated for AF

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Peak levels	52 - 383	69 - 321	101 - 288	178 - 343
Trough levels	28 - 215	34 - 230	12 - 43	12 - 137

(5-95% percentiles, [ng/ml] for FXa inhibitors and 10-90% percentiles (ng/ml) for Dabigatran)

Consider plasma level measurements in case of:

- Severe or life-threatening bleeding (see pages 37, 44/45)
- Emergency operation (or high-risk elective operation – see page 40)
- Ischemic stroke on NOAC (see page 51)
- Special situations, e.g.
  - Multiple drug-drug interactions (pages 15-31)
  - Extremes of bodyweight (see page 56)
  - CKD stage 4 / 5 (see page 32)

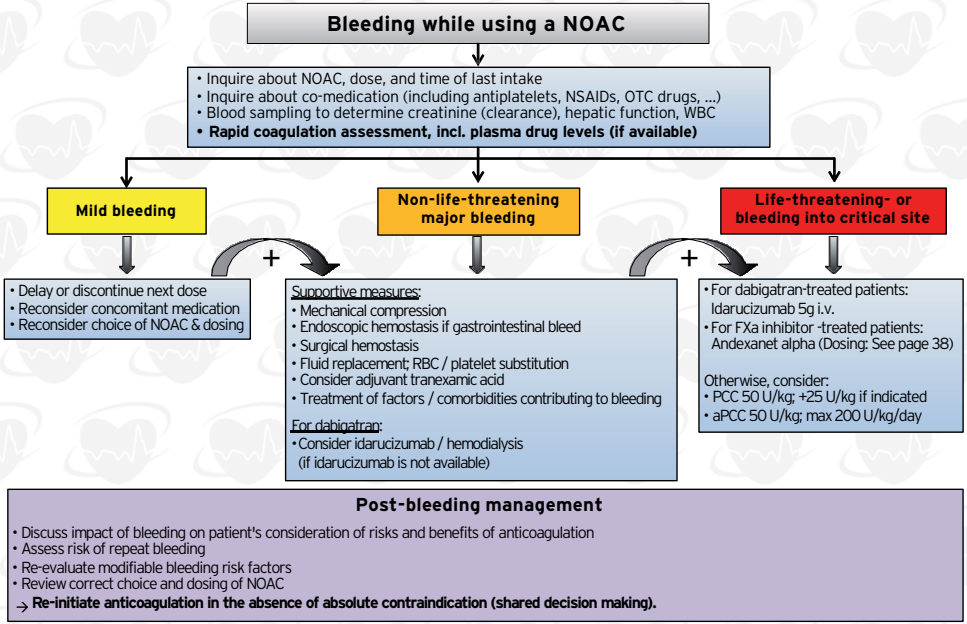
Only in centers with experience in determination and interpretation of NOAC plasma levels

Vast majority of patients: NO necessity for plasma level measurements

Expected impact of NOACs on routine coagulation tests

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
PT	(↑) at peak (↑) if supratherapeutic	(↑) at peak	•at therapeutic levels (if sensitive assay is used). Normal values do not exclude trough levels.	•at therapeutic levels (if sensitive assay is used). Normal values do not exclude trough levels.
aPTT	↑↑(↑) Normal values exclude supratherapeutic- but not therapeutic levels.	(↑) at peak	(↑) at peak	(↑) at peak
ACT	↑(↑) Consistent with effect on aPTT.	(↑)	(↑)	(↑)
TT	↑↑↑↑ Normal values exclude presence of Dabigatran.	-	-	-

6. Management of bleeding under NOAC therapy



Application of Idarucizumab

5 g i.v. in two consecutive infusions of
2.5 g i.v. over 5\10 minutes each

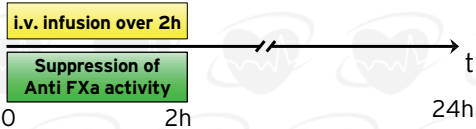
Application of Andexanet Alpha

Last dose	Timing of last dose	
	<8 hours#	≥8 hours
Apix ≤5 mg / Riva ≤10 mg / Edo ≤30 mg	Low dose	Low dose
Apix >5 mg / Riva >10 mg / Edo >30 mg	High dose	

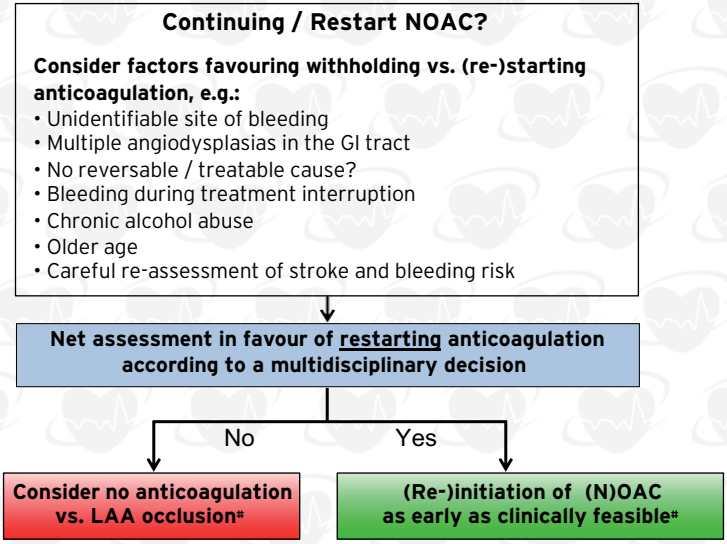
#or unknown

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

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

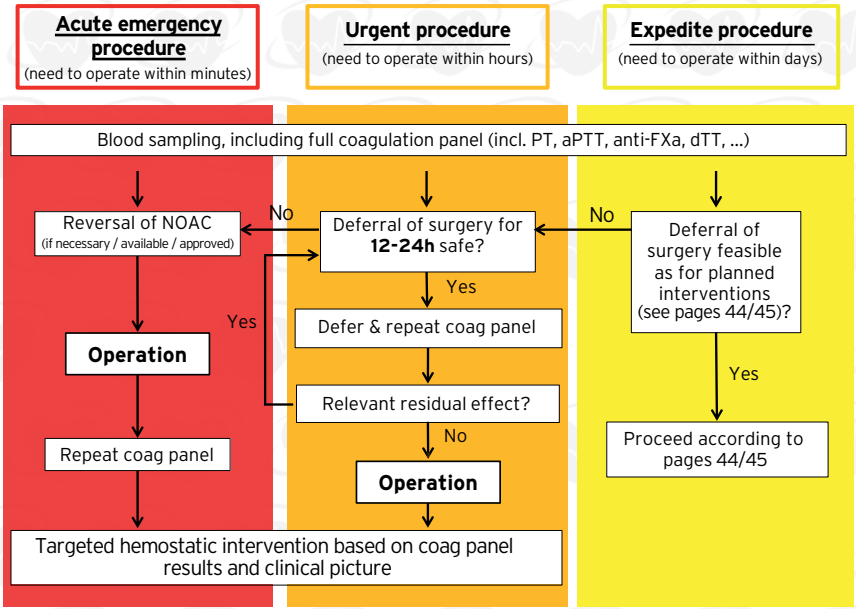


Stroke prevention after GI bleeding



Without evidence; ideally include patient in an ongoing trial

7. Patients requiring an urgent surgical intervention



8. Planned invasive procedures, surgery, or ablation

Perioperative NOAC management

1. Patient characteristics, including:

- Age
- Stroke risk
- Bleeding risk (incl. h/o post-op bleeding complications etc.)
- Recent (≤3 months) cardiovascular event
- Comorbidities, esp. renal function
- Comedications (e.g., antiplatelets, NSAIDs)

2. Surgical factors, including:

- Bleeding risk of procedure
- Consequences of bleeding complication (esp. neurosurgery, cardiac surgery, large intra-abdominal / -thoracic procedures)
- Planned anesthesia (full, spinal / epidural, local etc.)
- Anticipated restart of NOAC therapy

Determine time of last NOAC intake pre-op

Written communication of plan
(including to operator, primary care physician, anesthetist and patient)

Re-iterate no need for heparin bridging

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

Minor risk interventions (i.e., infrequent bleeding and with low clinical impact)
Dental extractions (1-3 teeth), paradontal surgery, implant positioning, subgingival scalling / cleaning
Cataract or glaucoma intervention
Endoscopy without biopsy or resection
Superficial surgery (e.g., abscess incision; small dermatologic excisions, skin biopsy)
Pacemaker or ICD implantation (except complex procedures)
Electrophysiological study or catheter ablation (except complex procedures), see also page 47
Routine elective coronary / peripheral artery intervention (except complex procedures), see also page 48
Intramuscular injection (e.g., vaccination)
Low risk interventions (i.e., infrequent bleeding or with non-severe clinical impact)
Complex dental procedures
Endoscopy with simple biopsy
Small orthopedic surgery (foot, hand, arthroscopy, ...)

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

High risk interventions (i.e., frequent bleeding and / or with important clinical impact) (continued)
Cardiac surgery
Peripheral arterial revascularization surgery (e.g., aortic aneurysm repair, vascular bypass)
Complex invasive cardiological interventions, including lead extraction, (epicardial) VT ablation, chronic total occlusion PCI etc.
Neurosurgery
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Complex endoscopy (e.g., multiple / large polypectomy, ERCP with sphincterotomy etc.)
Abdominal surgery (incl. liver biopsy)
Thoracic surgery
Major urologic surgery / biopsy (incl. kidney)
Extracorporeal shockwave lithotripsy
Major orthopedic surgery

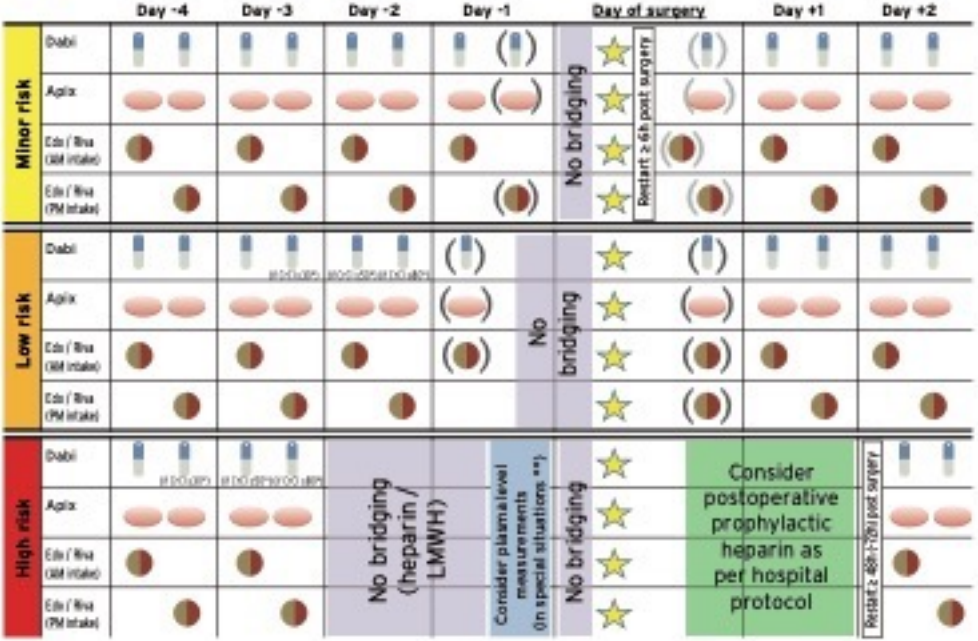
Perioperative cessation of NOACs

	Dabigatran		Apixaban - Edoxaban Rivaroxaban	
No perioperative bridging with LMWH / UFH				
Minor risk procedures: • **Perform procedure at NOAC trough level (i.e., 12 h / 24 h after last intake)** • **Resume same day or latest next day**				
	Low risk	**High risk**	**Low risk**	**High risk**
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–79 ml/min	≥36 h	≥72 h		
CrCl 30–49 ml/min	≥48 h	≥96 h		
CrCl 15–29 ml/min	Not indicated	Not indicated	≥36 h	
CrCl <15 ml/min	No official indication for use			

Important:

- Timing of interruption may require adaptation based on individual patient characteristics (page 41)
- In patients / situations with risk of NOAC accumulation (renal insufficiency, older age, concomitant medication) pausing the NOAC 12-24 hours earlier may be considered.
- Resume full dose of NOAC 24h after low-risk- and 48 (-72) h after high-risk interventions

Perioperative management on NOACs



Important: Timing of interruption may require adaptation based on individual patient characteristics (Page 41).

Perioperative management on NOACs

Yellow star = Time point of the intervention / operation

Parentheses indicate optional pre-/ postoperative intake, especially in patients not at high risk of drug accumulation / bleeding.

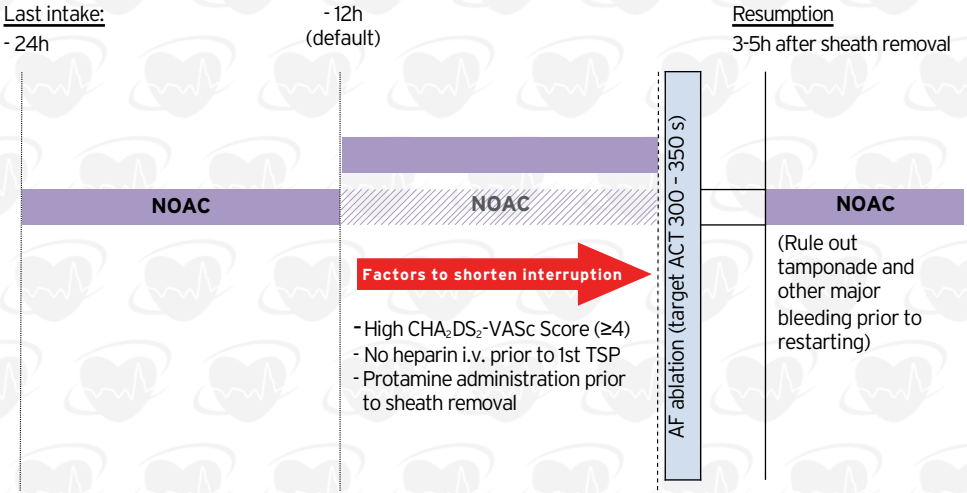
Consider +24 hours of interruption in situations likely resulting in increased plasma levels (e.g., body weight <50kg, significant interactions (see page 15))

* Intake of this dose of Dabigatran if CrCl is in the indicated range; otherwise skip this dose

** Consider measurement of plasma levels in very special situations, e.g., highest risk neurosurgery / cardiac surgery, severely impaired renal function, combination of factors predisposing to higher NOAC levels (see page 35).

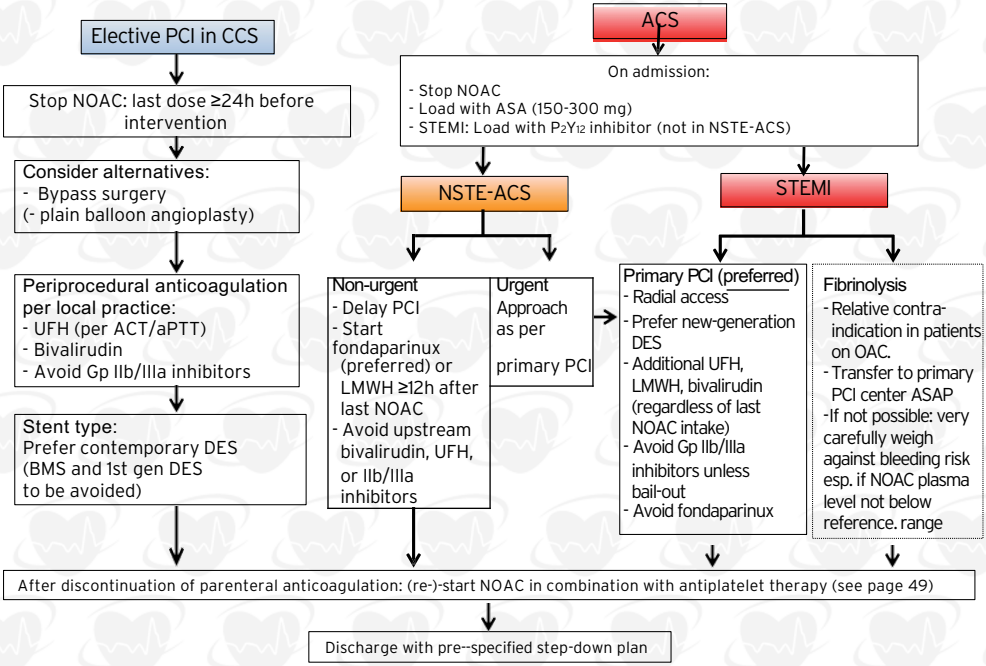
Rivaroxaban needs to be taken with food for stroke prevention in AF, which needs to be considered (also) in the post-operative setting

Patient on NOAC undergoing AF ablation

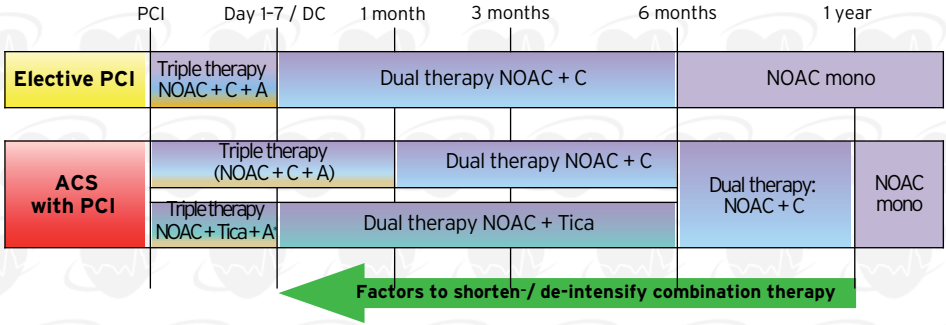


9. Patients with AF and coronary artery disease

AF patient on NOAC with ACS / elective stenting



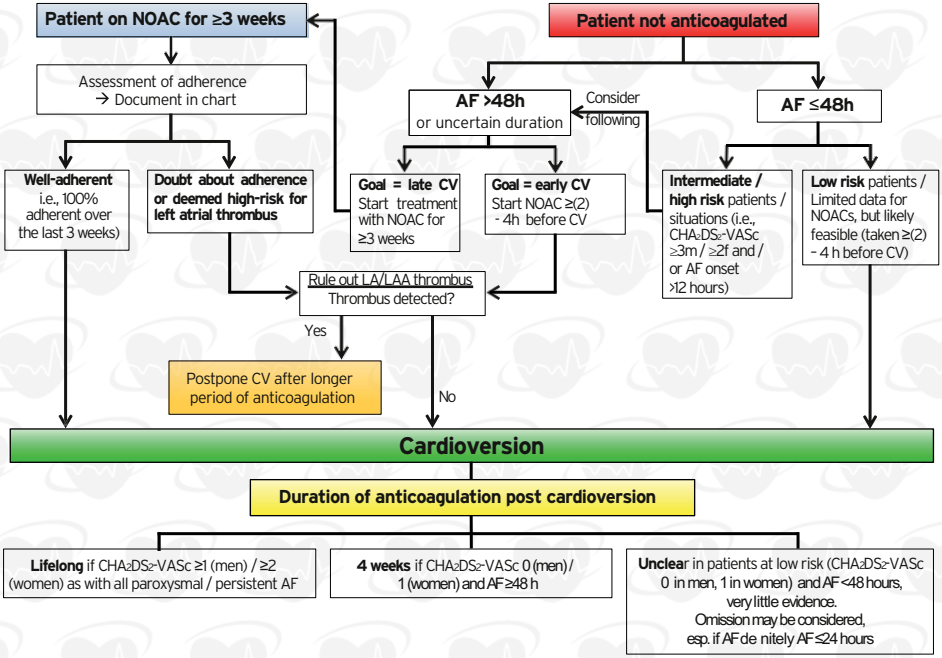
Anticoagulation post PCI / ACS



In all patients:

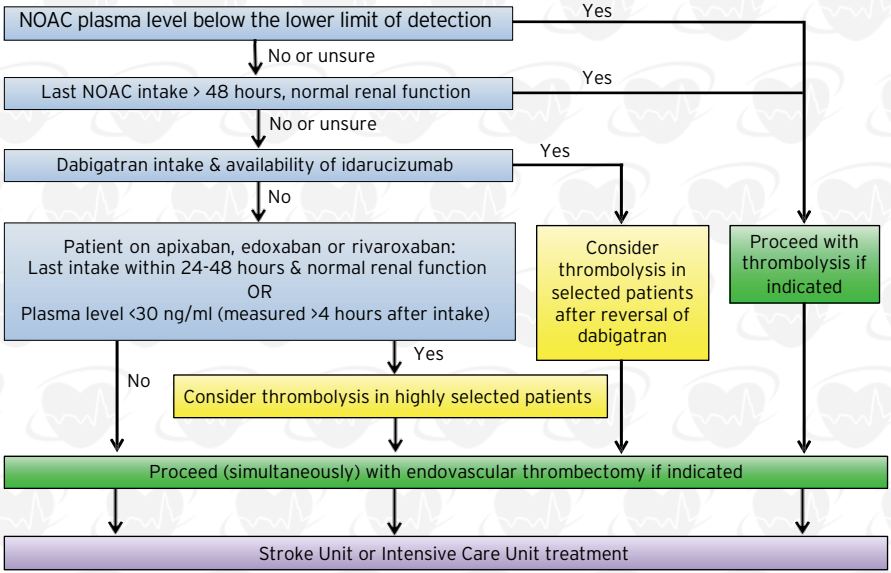
- Avoid use of BMS / first generation DES
- Use PPI if on triple (/ dual) therapy
- Minimize bleeding risk by assessing and treating modifiable bleeding risk factors (e.g., hypertension, etc.)
- Close follow-up; check for signs of (occult) bleeding

10. Cardioversion in a NOAC-treated patient

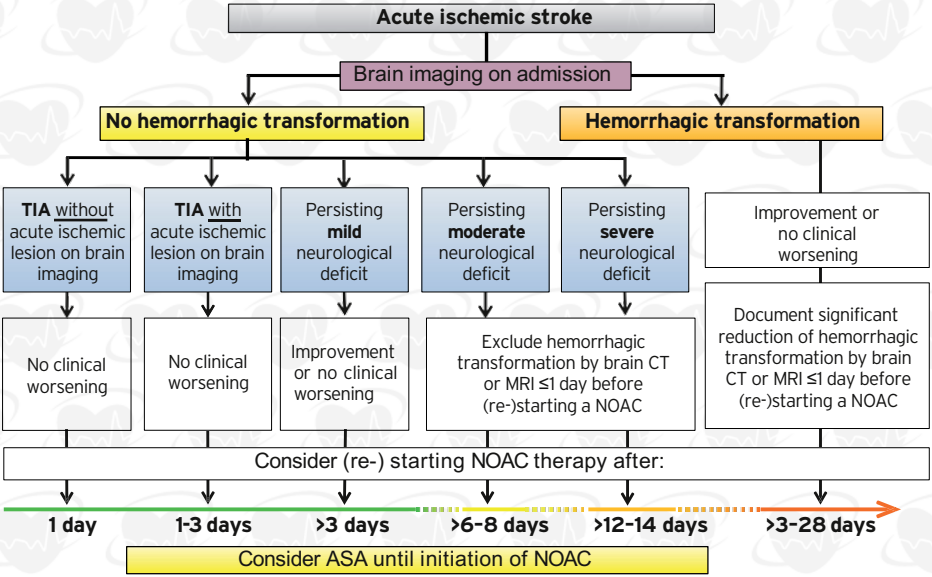


11. AF patients presenting with acute stroke on NOACs

Management of acute ischemic stroke on NOAC therapy

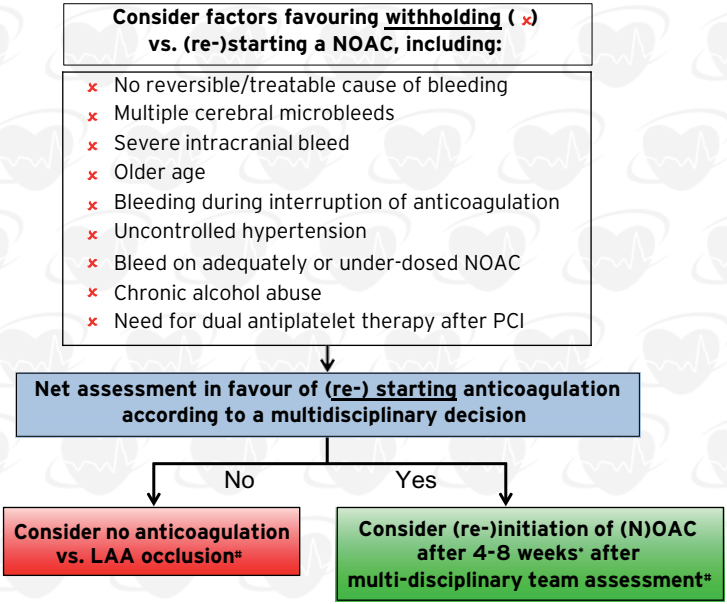


(Re-)starting NOAC after an acute ischemic stroke



Based on expert opinion! No RCT data available yet

Patient post intracerebral haemorrhage



Without RCT evidence; ideally include patient in an ongoing trial.
* Brain imaging mandatory before (re-)initiation of (N)OAC.

12. NOACs in advanced age and frailty

NOAC use in frail patients

Very Fit	Robust, active, energetic and motivated. Commonly exercise regularly. Among the fittest for their age.
Well	No active disease symptoms but less fit than category 1. Often exercise or very active occasionally, e.g., seasonally.
Managing Well	Medical problems well controlled, but not regularly active beyond routine walking.
Vulnerable	Not dependent on others for daily help, but often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.
Mildly Frail	Often with more evident slowing; need help in high order with ADLs. Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.
Moderately Frail	Need help with all outside activities and with keeping house. Often have problems with stairs and need help with bathing, might need minimal assistance with dressing.
Severely Frail	Completely dependent for personal care (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 can 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.

"Clinical Frailty scale" based on comprehensive geriatric assessment including structured interview (http://www.csha.ca and Rockwood et al., Lancet 1999; 353: 205-6.)

Examples of tools for assessing falls risk

High risk of falls*

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

Probability of falls assessment#

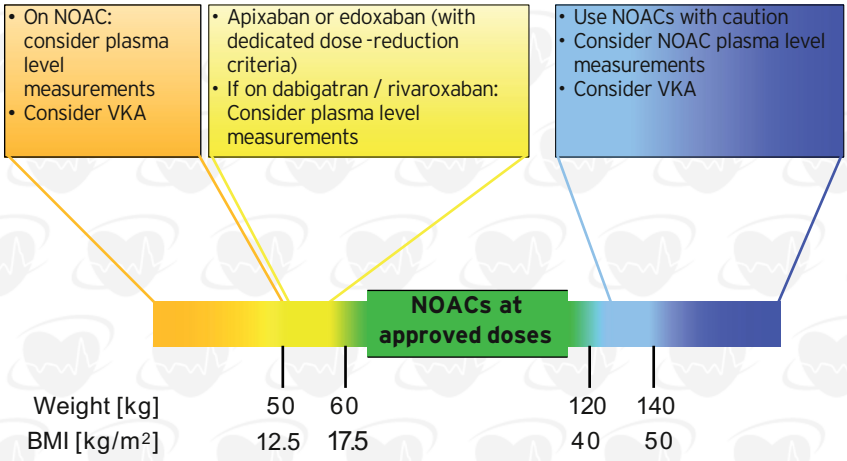
1point for each 'yes'

- 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%

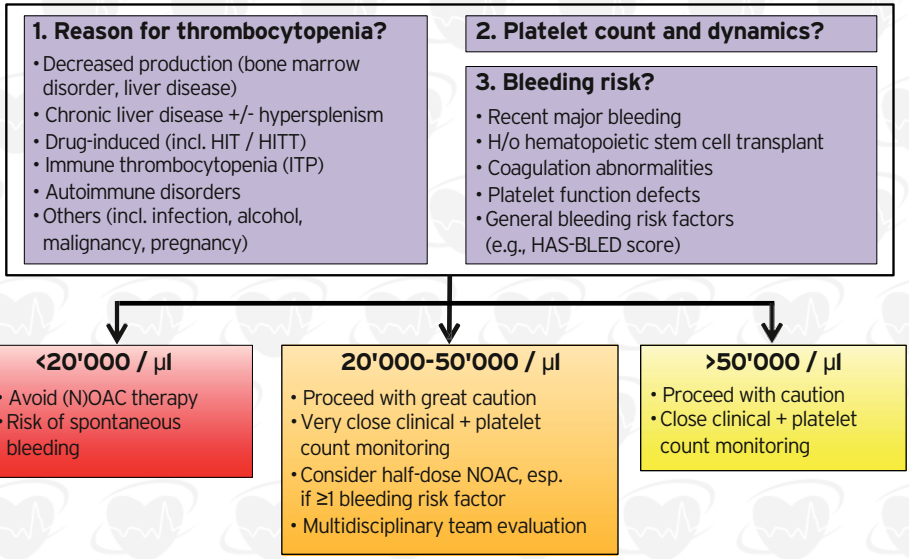
*Adapted from Steffel et al., J Am Coll Cardiol. 2016 Sep 13; 68(11):1169-1178.
#Adapted from Tiedemann et al., J Gerontol A Biol Med Sci 2010; Aug;65(8):896-903 doi;10.1093/Gerona/glq067.

13. NOACs in low- and high body weights



14. NOACs in other special populations

NOAC use in thrombocytopenic patients



15. NOACs in atrial fibrillation patients with a malignancy

Safety evaluation

- **AF-related** bleeding risk factors (e.g., by HAS-BLED or other bleeding scores)
- **Cancer-related** risk factors (actively bleeding/high-risk cancer, intracranial/liver metastases)
- **Treatment-related** risk factors (surgery, radiation, central lines, severe thrombocytopenia, etc.)

↓

Choice of anticoagulant

1. **NOAC** (unless opted against by multidisciplinary team, e.g., active GI cancer)
2. **LMWH**
3. **VKA**

↓

Patient protection

- **Close clinical follow-up**
- **Practical issues** (regular food intake? Correct dose? etc.)
- **Potential drug-drug interactions** (pages 23-28)
- **Gastric protection** (PPI/H2-blockers)
- **Assess necessity for treatment interruption** (e.g., if platelet count <20k, severe renal impairment, active bleeding etc.)

Interdisciplinary teamwork

Cardiologist – Oncologist – Haematologist/Radiologist – Other specialties

16. Optimizing dose adjustments of Vitamin-K Antagonists

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

Writing Committee

Jan Steffel[1], Ronan Collins[2], Matthias Antz[3], Pieter Cornu[4], Lien Desteghe[5,6], Karl Georg Haeusler[7], Jonas Oldgren[8], Holger Reinecke[9], Vanessa Roldan-Schilling[10], Nigel Rowell[11], Peter Sinnaeve[12], Thomas Vanassche[13], Tatjana Potpara[13], A. John Camm[14], Hein Heidbüchel[5,6]

(1) Department of Cardiology, University Hospital Zurich, Rämistrasse 100, CH-8091 Zurich, Switzerland
(2) Age-Related Health Care & Stroke-Service, Tallaght Hospital, Dublin, Ireland
(3) City Hospital Braunschweig, Braunschweig, Germany
(4) Faculty of Medicine and Pharmacy, Research Group Clinical Pharmacology and Clinical Pharmacy, Vrije Universiteit Brussel, Belgium
(5) Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium
(6) Antwerp University and University Hospital, Antwerp, Belgium
(7) Department of Neurology, Universitätsklinikum Würzburg, Würzburg, Germany
(8) Uppsala Clinical Research Center and Department of Medical Sciences, Uppsala University, Uppsala, Sweden
(9) Department of Cardiovascular Medicine, University Hospital Münster, Münster, Germany
(10) University of Murcia, Murcia, Spain
(11) Middlesbrough, UK
(12) Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium
(13) School of Medicine, Belgrade University, Belgrade, Serbia
(14) Cardiology Clinical Academic Group, Molecular & Clinical Sciences Institute, St George's University, London, UK, and Imperial College

List of topics

AFib | Syncope | Inherited / SCD / VT | Devices

External reviewer affiliations:

Gregory Y.H. Lip[1] (review coordinator), Thomas Deneke[2], Nikolaos Dagres[3], Giuseppe Boriani[4], Tze-Fan Chao[5], Eue-Keun Choi[6], Mellanie True Hills[7], Itamar de Souza Santos[8], Deirdre A. Lane[9], Dan Atar[10], Boyoung Joung[11], Oana Maria Cole[12], Mark Field[12]

(1) Liverpool Centre for Cardiovascular Science, University of Liverpool; Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
(2) Clinic for Interventional Electrophysiology, Heart Center RHÖN-KLINIKUM Campus Bad Neustadt, Germany
(3) Department of Electrophysiology, Heart Center Leipzig at University of Leipzig, Leipzig, Germany
(4) Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy
(5) Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan & Institute of Clinical Medicine and Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan
(6) Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea
(7) StopAfib.org, PO Box 541, TX 76246-0541 Greenwood, Texas United States of America
(8) Centro de Pesquisa Clínica e Epidemiológica, Hospital Universitário, Universidade de São Paulo & Departamento de Clínica Médica, Faculdade de Medicina, Universidade de São Paulo
(9) Liverpool Centre for Cardiovascular Science, University of Liverpool; Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
(10) Dept. of Cardiology, Oslo University Hospital, Ullevål, Oslo, Norway, and Institute of Clinical Sciences, University of Oslo, Norway
(11) Yonsei University College of Medicine, Cardiology Department, Seoul, Korea (Republic of)
(12) Liverpool Heart and Chest Hospital, Liverpool, UK & Liverpool Centre for Cardiovascular Sciences, Liverpool UK

The authors thank the EHRA Scientific Document Committee:

Dr. Nikolaos Dagres, Prof. Thomas Deneke, Prof. Arthur Wilde, Prof. Frank R. Heinzel, Prof. Christian Meyer, Prof. Lucas Boersma, Prof. Radoslaw Lenarczyk, Prof. Luigi Di Biase, Dr. Elena Arbelo, Dr. Avi Sabbag, Prof. Pierre Jais, Prof. Milos Taborsky, Asso. Prof. Markus Stühlinger

Funding

This article and derived educational materials (slide set, website, booklet and NOAC card) were produced by and under the sole responsibility of the European Heart Rhythm Association, and supported by BayerPharma AG, Bristol-Myers Squibb, and PfizerAlliance and Daiichi-Sankyo Europe GmbH in the form of an unrestricted educational grant.

EHRA
European Heart
Rhythm Association
European Society of Cardiology

European Society of Cardiology
European Heart Rhythm Association (EHRA)
2035, route des Colles - Les Templiers
CS 80179 Biot
06903 Sophia Antipolis - FRANCE

Tel: +33 (0)4 92 94 76 00
Fax: +33 (0)4 92 94 86 46
Email: ehra@escardio.org

www.escardio.org/EHRA