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KEY MESSAGES

AFib Series

EHRA Practical Guide on the use of new oral anticoagulants (NOAC) in patients with non-valvular atrial fibrillation

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EUROPEAN Heart Rhythm ASSOCIATION
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EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

Table of Contents

Introduction

New oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with non-valvular atrial fibrillation (AF). This guide wants to help to use these new drugs effectively and safely in clinical practice, by presenting 15 clinical settings that require decisions on dosing, temporary interruption etc.
Please visit the associated EHRA Web site www.NOACforAF.eu for related and updated information, and to provide feedback to the authors of the Practical Guide.

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

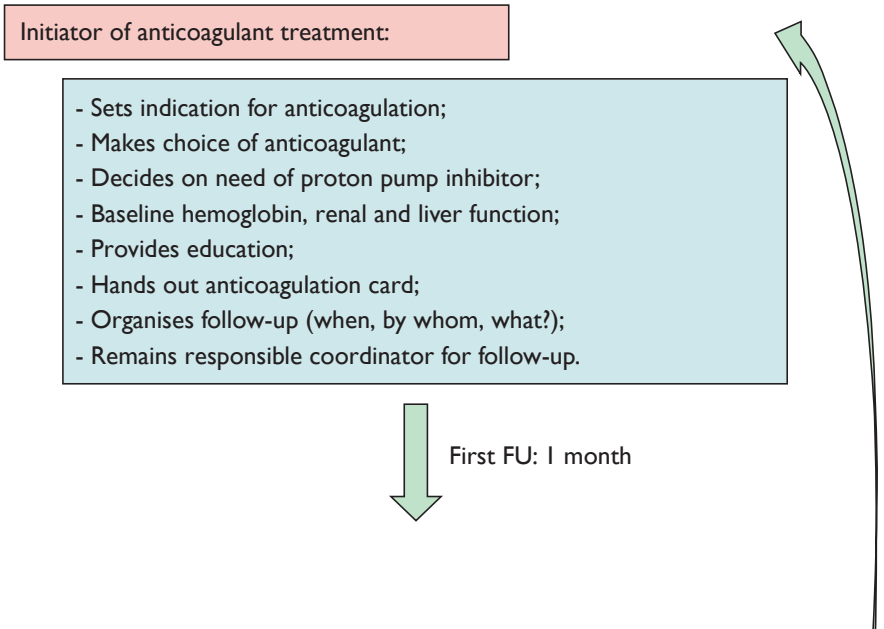
Table 1 lists the NOACs approved or under evaluation for stroke prevention in patients with non-valvular AF, and considered in this practical guide. The choice of NOAC may depend on clinical factors or co-medications taken by the patient (see Section 3). The responsibilites of the initiator of anticoagulant therapy, and the proposed flow of follow-up are summarised in Figure 1. Table 2 contains a checklist of items to do during a follow-up visit. A patient information card is crucial, both for the patient (instructions on correct intake; contact information in case of questions) as for health care workers (other care-takers are involved; renal function; follow-up schedule; concomitant medication…). A generic and universal NOAC anticoagulation card is proposed in Figure 2 (and can be downloaded from the Web site) to facilitate structured follow-up of patients: it is intended to document each planned visit, each relevant observation or checklist examination, and any medication change, so that every person following up the patient is well-informed in a concerted manner. Nurse-coordinated AF clinics may be very helpful in this regard.

Table 1 New anticoagulant drugs (NOACs), approved or under evaluation for prevention of systemic embolism or stroke in patients with non-valvular atrial fibrillation

	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Action	Direct thrombin inhibitor (DTI)	Activated factor Xa (FXa) inhibitor	Activated factor Xa (FXa) inhibitor	Activated factor Xa (FXa) inhibitor
Dose	150 mg BID 110 mg BID	5 mg BID 2.5 mg BID	60 mg QD 30 mg QD 15 mg QD	20 mg QD 15 mg QD
Phase 3 clinical trial	RE-LY	ARISTOTLE AVERROES	ENGAGE-AF	ROCKET-AF

*: no EMA approval yet. Needs update after finalisation of SmPC.
BID = twice daily; QD = once daily.
See further Tables and text for discussion on dose considerations. Hatching: not yet approved by EMA.

Figure 1 Scheme for structured follow-up of patients on NOACs



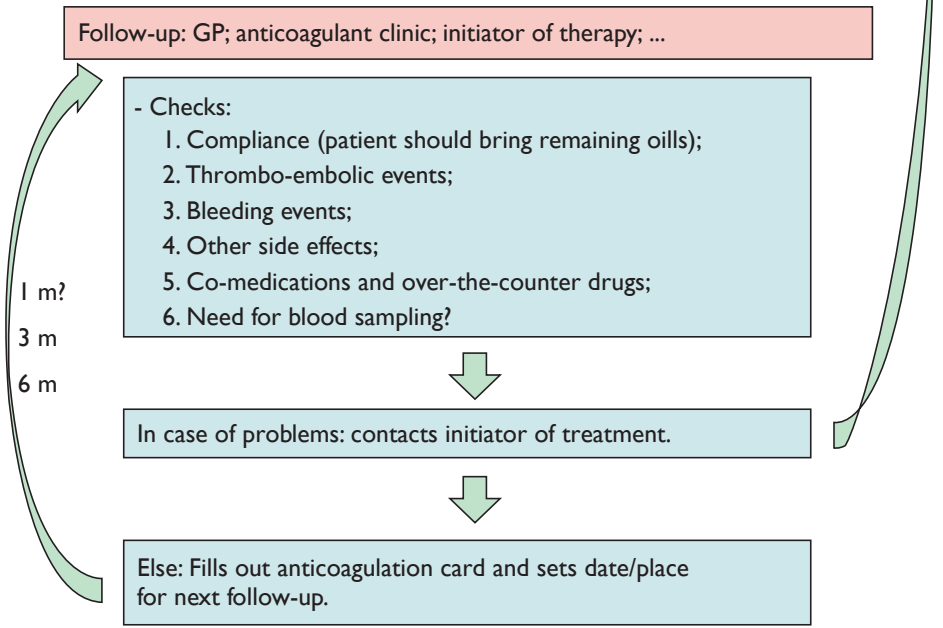

Follow-up: GP; anticoagulant clinic; initiator of therapy; ...
- Checks:
1. Compliance (patient should bring remaining oills);
2. Thrombo-embolic events;
3. Bleeding events;
4. Other side effects;
5. Co-medications and over-the-counter drugs;
6. Need for blood sampling?
1 m?
3 m
6 m
In case of problems: contacts initiator of treatment.
Else: Fills out anticoagulation card and sets date/place for next follow-up.

Table 2 Checklist during follow-up contacts of AF patients on anticoagulation		
	Interval	**Comments**
1. Compliance	Each visit	- Instruct patient to bring remaining medication: note and calculate average adherence. - Re-educate on importance of strict intake schedule. - Inform about compliance aids (special boxes; smartphone applications; …)
2.Thrombo-embolism	Each visit	- Systemic circulation (TIA, stroke, peripheral) - Pulmonary circulation
3. Bleeding	Each visit	- "Nuisance" bleeding: preventive measures possible? (PPI; haemorrhoidectomy; …). Motivate patient to diligently continue anticoagulation. - Bleeding with impact on quality-of-life or with risk: prevention possible? Need for revision of anticoagulation indication or dose?
4. Other side effects	Each visit	- Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation (with bridging), or change of anticoagulant drug.
5. Co-medications	Each visit	- Prescription drugs; over-the-counter drugs (see Section 3). - Careful interval history: also temporary use can be risk!
6. Blood sampling	Yearly 6-monthly 3-monthly on indication	- Haemoglobin, renal and liver function - Renal function if CrCl 30-60 ml/min, or if on dabigatran and >75y or fragile. - If CrCl 15-30 ml/min - If intercurring condition that may impact renal or hepatic function.

CrCl = creatinine clearance (preferably measured by the Cockroft method); PPI = proton pump inhibitor; TIA = transient ischemic attack.

Figure 2 Uniform patient card for patients treated with NOAC for AF

Important patient instructions

Take your drug exactly as prescribed (once or twice daily).
No drug is no protection!

Never stop your medicine without consulting your physician.

Never 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.

Concomitant medication

Name:	Dose:

Emergency information

Standard tests do not quantitatively reflect level of anticoagulation!

Name & telephone of patient relative to contact if emergency:

Patient blood group (+ physician signature):

Atrial Fibrillation Oral Anticoagulation Card

for non-vitamin-K anticoagulants

Patient name: DOB:

Patient address:

Oral anticoagulant, dosing, timing, with or without food:

Treatment indication:

Treatment started:

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

Figure 2 Uniform patient card for patients treated with NOAC for AF (continued)

Planned or unplanned visits

Date (or date range):	Site (GP; clinic; cardiologist; …):	To do / findings:

Recommended follow-up

(see EHRA at **www.NOACforAF.eu** for information & practical advice)

Check each visit:

1. **Compliance (pt. should bring remaining meds)?**
2. **Thrombo-embolic events?**
3. **Bleeding events?**
4. **Other side effects?**
5. **Co-medications and over-the-counter drugs.**

Blood sampling:

- **monitoring of anticoagulation level is not required!**
- **yearly:** Hb, renal and liver function
- **if CrCl 30-60 ml/min, >75y, or fragile:** 6-monthly renal function
- **if CrCl 15-30 ml/min:** 3-monthly renal function
- **if intercurring condition that may have impact:** renal and/or liver function

Date	Serum creatinine	Creatinine clearance	Hemo-globin	Liver tests

2. How to measure the anticoagulant effect of NOACs?

NOACs do not require routine monitoring of coagulation. However, the quantitative assessment of the drug exposure and the anticoagulant effect may be needed in emergency or special situations. When interpreting a coagulation assay in a patient treated with a NOAC: the maximum effect of the NOAC will occur approximately 3 hours after intake for each of these drugs, with an elmination half-life of about 12 or 24 hours in normal conditions (e.g. normal renal function). An overview of the interpretation of all the coagulation tests for different NOACs can be found in **Table 3**. The activated partial thromboplastin time (aPTT) may provide a qualitative assessment of the presence of dabigatran (albeit with a curvilinear relation, see **Figure 3**) and the prothrombin time (PT) for factor Xa inhibitors (albeit with a higly variable sensitivity of the different PT reagents, see **Figure 4**), but these respective tests are not sensitive for the quantitative assessment of the NOAC. Quantitative tests for direct thrombin inhibitors (DTI) and FXa inhibitors do exist, but they may not (yet) be routinely available in most hospitals. Even so, there are no data on a cut-off of these quantitative tests below which elective or urgent surgery is 'safe', and therefore their use in this respect cannot be recommended at this time (see also Sections 10 and 11).

Table 3 Interpretation of coagulation assays in patients treated with different NOACs

	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Plasma peak level	2 h after ingestion	1-4 h after ingestion	1-2 h after ingestion	2-4 h after ingestion
Plasma trough level	12-24 h after ingestion	12-24 h after ingestion	12-24 h after ingestion	16-24 h after ingestion
PT	Cannot be used	Cannot be used	Prolonged but no known relation with bleeding risk	Prolonged: may indicate excess bleeding risk but local calibration required.
INR	Cannot be used	Cannot be used	Cannot be used	Cannot be used

Table 3 Interpretation of coagulation assays in patients treated with different NOACs (continued)				
	Dabigatran	**Apixaban**	**Edoxaban***	**Rivaroxaban**
aPTT	At trough: >2x ULN suggests excess bleeding risk	Cannot be used	Prolonged but no known relation with bleeding risk	Cannot be used
dTT	At trough: >200 ng/ml = >65 sec: excess bleeding risk	Cannot be used	Cannot be used	Cannot be used
anti-FXa chromogenic assays	Not applicable	No data yet	Quantitative; no data on threshold values for bleeding or thrombosis	Quantitative; no data on threshold values for bleeding or thrombosis
Ecarin clotting time (ECT)	At trough: ≥3x ULN: excess bleeding risk	Not affected	Not affected	Not affected

*: no EMA approval yet. Needs update after finalisation of SmPC.
Routine monitoring is not required. Assays need cautious interpretation for clinical use in special circumstances, as discussed in the text.
aPTT = activated partial thromboplastin time; dTT = diluted thrombin time; INR = international normalised ratio; PT = prothrombin time; ULN = upper limit of normal.

Figure 3 Curvilinear relation between aPTT and dabigatran plasma levels

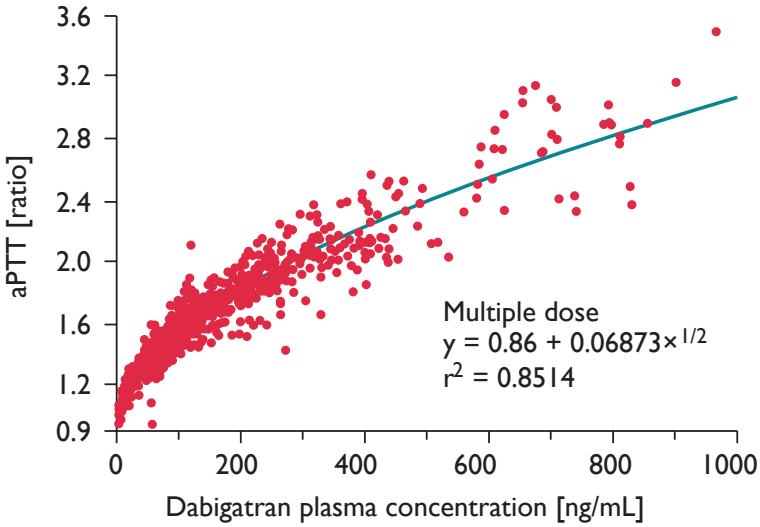
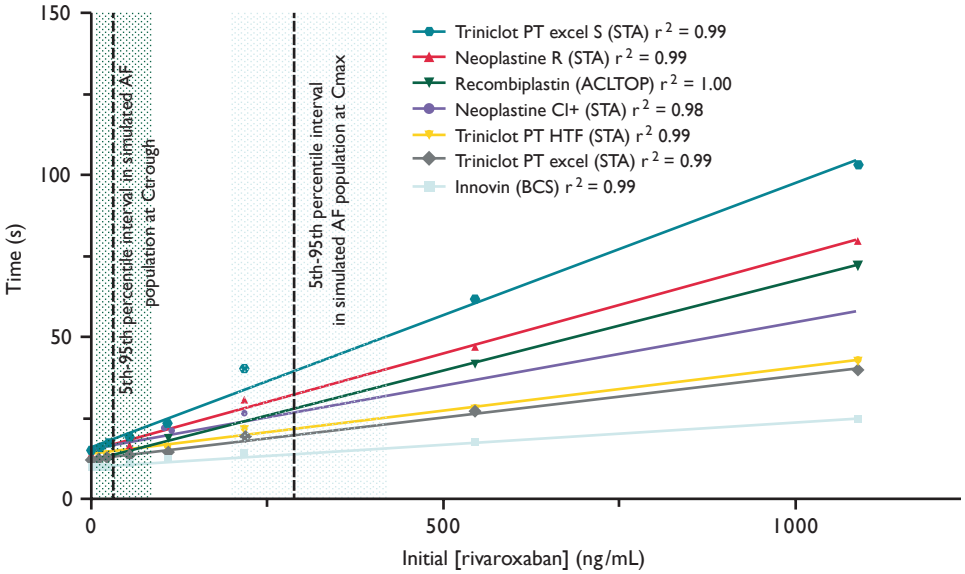


Figure 4 Relation between PT and FXa inhibitor (rivaroxaban) plasma levels



3. Drug-drug interactions and pharmacokinetics of NOACs

There are some drug-drug interactions that may affect the NOAC plasma levels and/or effect, and that need to be taken into account in combination with patient related factors. Sometimes, a dose reduction of the NOAC is warranted, or there may even be a contraindication for its use. The uptake, metabolisation and elimination of the different NOACs are graphically depicted in **Figure 5** and summarised in **Table 4**. We have chosen an approach with 3 levels of alert for drug-drug interactions or other clinical factors, as shown in **Table 5**:

1) "red" interactions (i.e. 'contraindication' or 'discouragement' for use),

2) "orange" interactions (dose adaptation), and

3) "yellow" interactions requiring evaluation: in combination with other "yellow" factors they may result in "orange" or even "red".

Only for rivaroxaban there is an official recommendation to take rivaroxaban with food.

Concomitant use of proton-pump inhibitors (PPI) and H2-blockers does not constitute a contraindication for NOAC use.

Association of NOACs with (dual) antiplatelet drugs requires active measures to reduce time on double and triple therapy: see Section 12.

Figure 5 Absorption, metabolism and elimination of the different NOACs

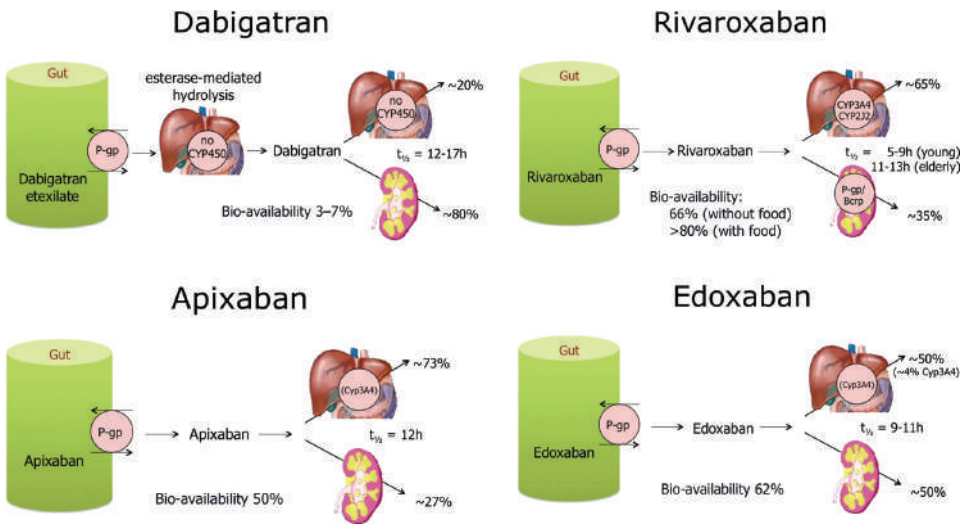


Table 4 Absorption and metabolism of the different NOACs				
	Dabigatran	**Apixaban**	**Edoxaban***	**Rivaroxaban**
Bio-availability	3-7%	50%	62%	66% without food almost 100% with food
Prodrug	Yes	No	No	No
Clearance non-renal / renal of absorbed dose (if normal renal function; see also Section 7)	20% / 80%	73% / 27%	50% / 50%	65% / 35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination; minor CYP3A4 contribution)	Minimal (<4% of elimination)	Yes (elimination)
Absorption with food	No effect	No effect	6-22% more	+39% more
Intake with food recommended?	No	No	No official recommendation yet	Mandatory
Absorption with H2B/PPI	-12% to -30%	No effect	No effect	No effect
Asian ethnicity	+25%	No effect	No effect	None
GI tolerability	Dyspepsia 5-10%	No problem	No problem	No problem
Elimination half-life	12-17 h	12 h	9-11 h	5-9 h (young) 11-13 h (elderly)

*: no EMA approval yet. Needs update after finalisation of SmPC.
GI = gastro-intestinal; H2B = H2-blocker; PPI = proton-pump inhibitor.

Table 5 Effect on NOAC plasma levels ("area under the curve, AUC") from drug-drug interactions and recommendations towards NOAC dosings

	Via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%	No data yet	No effect	No effect
Digoxin	P-gp competition	No effect	No data yet	No effect	No effect
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180% (reduce dose and take simultaneously)	No data yet	+53% (SR) (Reduce dose by 50%)*	Minor effect (use with caution if CrCl 15-50 ml/min)
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)
Quinidine	P-gp competition	+50%	No data yet	+80% (Reduce dose by 50%)§	+50%
Amiodarone	P-gp competition	+12-60%	No data yet	No effect	Minor effect (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70-100% (US: 2 x 75 mg)	No data yet	+85% (Reduce dose by 50%)*	No data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 x 75 mg)	+100%	No data yet	Up to +160%

Table 5 Effect on NOAC plasma levels ("area under the curve, AUC") from drug-drug interactions and recommendations towards NOAC dosings (continued)

	Via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)
Cyclosporin; tacrolimus	P-gp competition	No data yet	No data yet	No data yet	+50%
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition	+15-20%	No data yet	No data yet	+30-54%
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%
Rifampicin; St. John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	-66%	-54%	-35%	Up to -50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	-12% to -30%	No data yet	No effect	No effect

Table 5 Effect on NOAC plasma levels ("area under the curve, AUC") from drug-drug interactions and recommendations towards NOAC dosings (continued)

	Via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Other factors:					
Age ≥ 80 years	Increased plasma level			No data yet	
Age ≥75 years	Increased plasma level			No data yet	
Weight ≤ 60 kg	Increased plasma level				
Renal function	Increased plasma level	See Table 7			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active 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 BID to 110 mg BID for dabigatran; from 20 mg to 15 mg QD for rivaroxaban; from 5 mg BID to 2.5 mg BID for apixaban)
Yellow = consider dose reduction if another 'yellow' factor is present.
Hatching = no data available; recommendation based on pharmacokinetic considerations.
*: no EMA approval yet. Needs update after finalisation of SmPC.
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 = gastro-intestinal
§: prespecified dose reduction has been tested in Phase 3 clinical trial (to be published).

4. Switching between anticoagulant regimens

Especially the switch from a NOAC to VKA requires careful attention, since there is a high likelihood of undertreatment and hence thrombo-embolic risk for the patient. Due to the slow onset of action of VKAs, it may take 5 to 10 days before an INR in therapeutic range is obtained, with large individual variations. Therefore, the NOAC and the VKA should be administered concomitantly until the INR is in a range that is considered appropriate. Moreover, since NOACs may have an additional impact on the INR (especially the FXa inhibitors), influencing the measurement while on combined treatment during the overlap phase, it is important 1) that the INR be measured just before the next intake of the NOAC during concomitant administration, and 2) be re-tested 24 hours after the last dose of the NOAC (i.e. sole VKA therapy) to assure adequate anticoagulation. It is also recommended to closely monitor INR within the first month until stable values have been attained (i.e. 3 consecutive measurements should have yielded values between 2.0 and 3.0).

When switching from VKA to NOAC, the NOAC can immediately be initiated once the INR is lower than 2.0. If the INR is 2.0 – 2.5, NOACs can be started immediately or the next day. For INR > 2.5, the actual INR value and the half-life of the VKA needs to be taken into account to estimate the time when the INR value will likely drop to below this threshold value. A confirmatory INR sampling may be planned.

A parenteral anticoagulant (UFH, LMWH) can be initiated when the next dose of the NOAC is due, or vice versa. The same holds true for switching from one NOAC to another.

5. Ensuring compliance with NOAC intake

Monitoring of the NOAC anticoagulant effect is not required to guide therapy, unless in unusual clinical situations, since they have a very predictable effect. However, the anticoagulant effect fades rapidly 12 to 24 hours after the last intake. Therefore, strict therapy compliance with drug intake is crucial. Although a once daily (QD) dosing regimen is related to greater adherence versus a twice daily (BID) regimen in cardiovascular patients in general, it is unknown whether any regimen is superior in guaranteeing the clinical effect of NOACs, as seen in the clinical trials, into daily practice. E.g, forgetting a single intake of a BID drug may constitute less 'unprotected' time than for a QD drug. Anyway, all means to optimise compliance should be considered, including:

1. Patient education (using leaflets, a patient NOAC card, group sessions, and potentially new electronic means of communication like online patient groups).
2. Involvement of family members.
3. A clearly prespecified follow-up schedule (GP, cardiologist, electrophysiologist, and/or nurse-coordinated AF centres).
4. Other technological aids being explored: format of the blisters; medication boxes (conventional or with electronic verification of intake); smartphone applications and/or SMS messages that alert the patient about the next intake. One tool may not fit all patients and individualisation of these aids should be considered.
5. Some patients may prefer INR monitoring to no monitoring. Patient preference counts.
6. Networked pharmacy database, tracking NOAC prescriptions to individual patients.
7. Conversion to VKAs if patient shows low compliance.

6. How to deal with dosing errors?

Provide co-workers with clear instructions on how to advise when patients call in with dosing error questions, which occurs often. Prevent by recommending well-labeled weekly pill containers.

Missed dose

No double dose should be taken to make up for missed individual doses. The patient should still take a forgotten dose up till half of the interval between doses (e.g. 6h or 12h for a BID resp. QD drug). If that is not possible anymore, the dose should be skipped and the next scheduled dose should be taken.

Double dose

For NOACs with a BID dosing regimen, one could opt to forgo the next planned dose (i.e. after 12 hours), and restart BID intake from after 24 hours. For NOACs with a QD dosing regimen, the patient should continue the normal dosing regimen, i.e without skipping the next daily dose.

Uncertainty about dose intake

Sometimes, the patient is not sure about whether a dose has been taken or not.
For NOACs with a BID dosing regimen, one could advise to just continue the planned dose regimen, i.e. starting with the next dose at the 12 hour interval.
For NOACs with a QD dosing regimen, one could advise to take another pill and then continue the planned dose regimen.

Overdose

Depending on the amount of suspected overdose, hospitalisation for monitoring or urgent measures should be advised. For further discussion, see Section 8.

7. Patients with chronic kidney disease

In the context of NOAC treatement, CrCl is best assessed by the Cockroft method, as this was used in most NOAC trials. All NOAC have some degree of renal clearance, as shown in **Table 4** and **Table 7. Table 6** lists the estimated drug half-lives and effect on area under the curve for NOAC plasma concentrations in different stages of chronic kidney disease. Rivaroxaban and apixaban have been approved also for use in patients with CKD stage IV, i.e. CrCl 15 – 30 ml/min, with the lower dose regimen. However, there are no outcome data for NOACs in this group of patients, and the current ESC Guidelines recommend against NOAC use in such patients. The approved European labeling and dosing in chronic kidney disease are listed for all NOAC in **Table 7**. Not any NOAC is approved for use in dialysis patients.

There are no comparative studies that the risks from CKD differ among the NOACs. In light of the potential impact of further renal function fluctuations, dabigatran, which is primarily cleared renally, may not be the NOAC of first choice in patients with known CKD, especially stage III or higher. On the other hand, there was no significant interaction between the relative risk/benefit of dabigatran vs. VKA in relation to kidney function. Therefore, careful balancing of the clinical benefits and risks may justify its choice in stable patients.

In patients on all NOACs, renal function needs to be monitored carefully, at least yearly, to detect changes in renal function and adapt the dose accordingly: see **Table 2** for concrete interval proposals.

Table 6 Estimated drug half-lives and effect on area under the curve NOAC plasma concentrations in different stages of chronic kidney disease compared to healthy controls

	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
CrCl ≥60 ml/min CKD Stage I & II	~14 h	No data	~8.6 h	~8.5 h
CrCl 30-60 ml/min CKD Stage III	~18 h	No data	~9.4 h	~9 h
CrCl 15-30 ml/min CKD Stage IV	~28 h	No data	~16.9 h	~9.5 h
CrCl ≤15 ml/min CKD Stage V	No data	No data	No data	No data

*: no EMA approval yet. Needs update after finalisation of SmPC.
CKD = chronic kidney disease; CrCl = creatinine clearance.

Table 7 NOACs in renal dysfunction: Approved European labels and dosing in chronic kidney disease

	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Fraction renally excreted of absorbed dose	80%	27%	50%	35%
Bio-availability	3-7%	50%	62%	66% without food almost 100% with food
Fraction renally excreted of administered dose	4%	14%	37%	33%
Approved for CrCl ≥ ...	≥30 ml/min	≥15 ml/min	Not available	≥15 ml/min
Dosing recommendation	CrCl ≥50 ml/min: no adjustment (i.e. 2 x 150 mg/d)	Serum creatinine ≥1.5 mg/dl: no adjustment (i.e. 2 x 5 mg/d)	Not available	CrCl ≥50 ml/min: no adjustment
Dosing if CKD	When CrCl 30-49 ml/min, 150 mg BID is possible (SmPC) but 110 mg BID if 'high risk of bleeding' (SmPC) or 'recommended' (GL update) Note: 75 mg BID approved in US only: - if CrCl 15-30 ml/min - if CrCl 30-49 ml/min and other orange factor Table 5 (e.g. verapamil)	CrCl 15-29 ml/min: 2.5 mg BID Serum creatinine ≥ 1.5 mg/dl in combination with age ≥80 years or weight ≤60 kg, or with other 'yellow' factor (Table 5): 2.5 mg BID	Not available	15 mg OD when CrCl 15-49 ml/min
Not recommended if	CrCl <30 ml/min	CrCl <15 ml/min	Not available	CrCl <15 ml/min

*: no EMA approval yet. Needs update after finalisation of SmPC.

$: no EMA indication. FDA recommendation based on pharmacokinetics. Carefully weigh risks and benefits of this approach. Note that 75 mg capsules are not available on the European market for AF indication.

CKD = chronic kidney disease; CrCl = creatinine clearance; BID = twice daily; OD = once daily; SmPC = summary of product characteristics.

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

In terms of management, distinguish between an overdose with and without bleeding complication.
In case of bleeding complications, see Section 9.

If no ongoing bleeding and in the case of recent acute ingestion or an overdose, the use of activated charcoal to reduce absorption may be considered for any NOAC (with a standard dosing scheme for adults of 30 to 50 g). Currently there are no specific antidotes for NOACs, although development is ongoing. Given the relatively short plasma half life of the NOAC drugs, a 'wait-and-see' management is advocated in most cases.

In case of an overdose suspicion, coagulation tests can help to determine its degree and possible bleeding risk (see Section 2 for the interpretation of coagulation tests). If a more aggressive normalisation of plasma levels is deemed necessary, or rapid normalisation is not expected (e.g. major renal insufficiency) the steps outlined in Section 9 can be taken.

9. Management of bleeding complications

Studies have shown that the bleeding profile of NOACs, in particular with respect to intracranial and other life-threatening bleeding, is more favourable than that of warfarin, despite the absence of antidotes and rapid (routine) quantitative measurements of the anticoagulant effect. Current recommendations on bleeding management are more based on experts' opinions and laboratory endpoints than on clinical data.

Non life-threatening bleeding

See **Table 8** for detailed and stepwise instructions, which are slightly different for dabigatran and the factor Xa inhibitors. **Figure 6** shows a graphical flowchart for management of bleeding complications. After cessation of treatment, restoration of haemostasis is to be expected within 12 to 24 hours after the last taken dose, given plasma half-lifes of around 12 hours for most NOACs. This underscores the importance to inquire about the used dosing regimen, the exact time of last intake, factors influencing plasma concentrations (like P-gp therapy, chronic kidney disease, and others, see also **Tables 4, 5 and 6**), and other factors influencing haemostasis (like concomitant use of anti-platelet drugs).

Although dabigatran can be dialysed (in a small study, dialysis removed 62% at 2 hours and 68% at 4 hours), it should be noted that there is only limited clinical experience in using dialysis in this setting (cf. risks of bleeding at puncture sites for dialysis vs. risk of waiting). Whether enhanced removal of dabigatran is possible via haemoperfusion over a charcoal filter is under evaluation. At this moment, the latter cannot be recommended in patients. Dialysis has not been shown to be an option in patients treated with any of the FXa inhibitors.

Life-threatening bleeding

Based on (scarce) experimental data and without clinical data that they affect clinical outcome (i.e. that they reduce blood loss and improve outcome), the administration of PCC (also called PPSB; some brand names are Cofact®, Confidex®, Octaplex®, and Beriplex®) or aPCC (also called FEIBA; brand name Feiba®) can be considered in a patient with life-threatening bleeding if immediate haemostatic support is required. The choice may depend on their availability and the experience of the treatment center. The place of recombinant activated factor VIIa (NovoSeven®, 90 µg/kg) needs further evaluation.

Fresh frozen plasma is of no help to reverse NOAC anticoagulation, but may be indicated to expand plasma volume in patients who require massive transfusion.

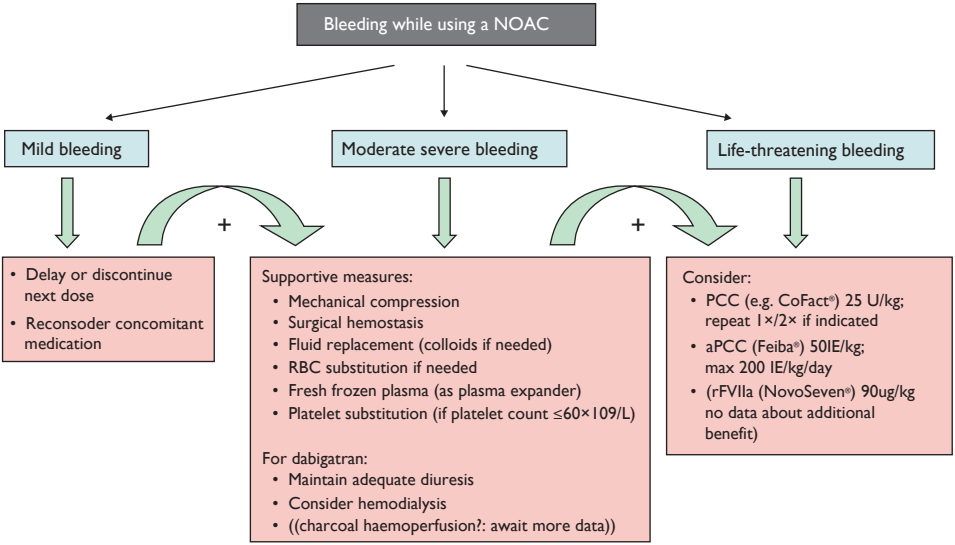
We recommend development of a hospital-wide policy concerning bleeding management based on input among cardiologists, haemostatis experts and emergency physicians. Such policy should be communicated well, and be easily accessible for emergency use (e.g. on an Intranet site or in pocket-sized leaflets).

Table 8 Possible measures to take in case of bleeding (continued)		
	Direct thrombin inhibitors (dabigatran)	**FXa inhibitors** (apixaban, edoxaban, rivaroxaban)
None life-threatening bleeding	Inquire last intake + dosing regimen. Estimate normalisation of haemostasis: Normal renal function: 12-24h CrCl 50-80 ml/min: 24-36h CrCl 30-50 ml/min: 36-48h CrCl <30 ml/min: ≥48h Maintain diuresis. Local haemostatic measures. Fluid replacement (colloids if needed). RBC substitution if necessary. Platelet substitution (in case of thrombocytopenia ≤ 60 x 109/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 (preliminary evidence: -65% after 4h). Charcoal haemoperfusion not recommended (no data).	Inquire last intake + dosing regimen. Normalisation of haemostasis: 12-24h Local haemostatic measures. Fluid replacement (colloids if needed). RBC substitution if necessary. Platelet substitution (in case of thrombocytopenia ≤ 60 x 109/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)

Table 8 Possible measures to take in case of bleeding (continued)		
	Direct thrombin inhibitors (dabigatran)	**FXa inhibitors (apixaban, edoxaban, rivaroxaban)**
Life-threatening bleeding	All of the above. Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence). Activated PCC 50 IE/kg; max 200 IE/kg/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)	All of the above. Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence). Activated PCC 50 IE/kg; max 200 IE/kg/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)

CrCl = creatinine clearance; PCC = Prothrombin complex concentrate; RBC = red blood cells.

Figure 6 Management of bleeding in patients taking NOACs



10. Patients undergoing a planned surgical intervention or ablation

When to stop the NOACs?

Bridging is not necessary in NOAC treated patients since the predictable waning of the anticoagulation effect allows properly timed short-term cessation and reinitiation of NOAC therapy before and after surgery. This needs to be timed well, however, as proposed in **Table 9**. Again, the development of an institutional guideline is recommended. **Table 10** provides a classification of elective surgical interventions according to bleeding risk.

For interventions **without clinically important bleeding risk**, the procedure can be performed at trough concentration of the NOAC (i.e. 12 or 24 hours after the last intake, depending on twice or once daily dosing). It may be more practical to have the intervention scheduled 18 to 24 hours after the last intake, and then restart 6 hours later, i.e. with skipping 1 dose for BID NOAC.

For procedures **with a minor and major bleeding risk**, it is recommended to discontinue NOACs 24 respectively 48 hours before the elective procedure in patients with a normal kidney function. These time intervals need to be prolonged in case of renal dysfunction, especially for dabigatran (Table 9).
Although the aPTT and PT may provide a semi-quantitative assessment of dabigatran and FXa inhibitors, respectively (see Section 2), a strategy that includes normalization of the aPTT or PT prior to elective/urgent interventions has not been validated.

When to restart the NOACs?

For procedures with immediate and complete haemostasis, the NOAC can be resumed 6 – 8 hours after the intervention. For many surgical interventions, however, resuming full dose anticoagulation within the first 48 to 72 hours after the procedure may carry a bleeding risk that could outweighs the risk of cardio-embolism. For procedures associated with immobilisation, one could administer a reduced venous thromboprophylactic or intermediate dose of low molecular weight heparins (LMWH) 6 to 8 hours after surgery, whereas restarting NOACs is deferred 48 to 72 hours after the invasive procedure. There are no data on the safety and efficacy of the post-operative use of a reduced dose of the NOACs (such as used for the prevention of VTE after hip/knee replacement) in patients with AF undergoing a surgical procedure.

Special considerations concerning AF ablation procedures

There is data showing that if a strategy of timed cessation of NOAC is appropriately executed along the guidance of Table 9, with a restart after 6 to 22 hours after the ablation, and bridged with administration of UFH and LMWH per- and immediately post-ablation respectively, it results in comparable bleeding and cardioembolic complications as ablation under un-interrupted VKA therapy. A too aggressively shortened periprocedural cessation of NOACs and/or no bridging may be less safe.

Table 9 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban*		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12h or 24h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 50-80 ml/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 30-50 ml/min§	**≥48 h**	**≥96 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 15-30 ml/min§	Not indicated	Not indicated	**≥36 h**	**≥48 h**	No data	No data	**≥36 h**	**≥48 h**
CrCl <15 ml/min	No official indication for use							

*: no EMA approval yet. Needs update after finalisation of SmPC.

Low risk = surgery with low risk of bleeding; High risk = surgery with high risk of bleeding. See also **Table 10**. CrCl: creatinine clearance.

§: many of these patients may be on the lower dose of dabigatran (i.e. 2x110 mg/d) or apixaban (i.e. 2x2.5 mg/d), or have to be on the lower dose of rivaroxaban (15 mg/d).

Table 10 Classification of elective surgical interventions according to bleeding risk
Interventions not necessarily requiring discontinuation of anticoagulation
Dental interventions
Extraction of 1 to 3 teeth
Paradontal surgery
Incision of abscess
Implant positioning
Ophthalmology
Cataract or glaucoma intervention
Endoscopy without surgery
Superficial surgery (e.g. abscess incision; small dermatologic excisions; …)
Interventions with low bleeding risk
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single transseptal puncture)
Angiography
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)

Table 10 Classification of elective surgical interventions according to bleeding risk (continued)
Interventions with high bleeding risk
Complex left-sided ablation (pulmonary vein isolation;VT ablation)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy

For each patient, individual factors relating to bleeding and thrombo-embolic risk need to be taken into account, and be discussed with the intervening physician.

11. Patients undergoing an urgent surgical intervention

The NOAC should be discontinued and surgery deferred, if possible, until at least 12 hours and ideally 24 hours after the last dose. Evaluation of common coagulation tests (aPTT for DTI; sensitive PT for FXa inhibitors) or of specific coagulation test (dTT for DTI; chromogenic assays for FXa inhitibors) can be considered if there is concern about the pharmacokinetic waning of the anticoagulant effect (e.g. renal insufficiency and/or concomitant conditiions as in **Table 4**; see also Section 2). Nevertheless, such strategy has never been evaluated, cannot be recommended, and should not be used routinely.

12. Patient with AF and coronary artery disease

The combination of atrial fibrillation and coronary heart disease not only is a common clinical setting, it is also a complex situation on how to deal with anticoagulation and antiplatelet therapy, and it is associated with significantly higher mortality rates. Unfortunately, there is not sufficient data available to optimally guide clinical practice in such settings. Moreover, new antiplatelet agents have entered the market for acute coronary syndromes (ACS), adding to uncertainty on how to use those in combination with VKAs or NOACs. We have defined three clinical scenarios. For background information and key scientific data that form the basis of the guidance spelled out here, we refer to the full text.

Scenario 1: Acute coronary syndrome management in AF patients on NOACs (see also **Table 11**)

Combining antiplatelet with anticoagulant agents significantly increases the risk of major bleeding. The type and level of anticoagulation as well as single vs. dual antiplatelet therapy and its duration need to be highly personalized, based on atherothrombotic risk, cardioembolic risk and bleeding risk using validated scores.

Because of the relatively short half-life of NOACs, the timing of the last intake of these agents has an impact on the choice and timing of anticoagulation for ACS and during invasive management.

NOACs should preferably be temporarily discontinued upon presentation with ACS.

In the absence of contraindications, all ACS patients should receive low-dose aspirin immediately at admission, as well as a P2Y12 inhibitor. In patients at high bleeding risk, aspirin only might be a safer initial therapy awaiting invasive management. Unless for patients allergic to aspirin, monotherapy with clopidogrel is not recommended in the acute setting.

In case a PCI is performed:

1. A radial approach is strongly recommended.
2. In primary PCI, it is recommended to use additional parenteral anticoagulation, regardless of the timing of the last dose of NOAC. Given its short-lasting action and lower bleeding risk, bivalirudin might be the preferred over unfractionated heparin or enoxaparin.

3. If a coronary angiography is not urgent, the NOAC should be discontinued before patients are taken to the cath lab (24h or longer). Peri-procedural anticoagulation should be used per local practice.
4. If possible, bare-metal stents (BMS) are preferred above drug-eluting stents (DES) in order to shorten exposure to dual or triple therapy.

In stabilized patients, anticoagulation can be restarted after parenteral anticoagulation is safely stopped.

1. It is reasonable to restart the same NOAC in patients who had an indication for a NOAC over VKA.
2. When restarting NOAC consider dose reduction according to bleeding and atherothrombotic risk.

The period of additional antiplatelet therapy should probably be kept as short as possible.

1. 1 month for a bare metal stent to 6 or even 3 months for DES after PCI.
2. After that, monotherapy with VKA or NOAC could be considered in patients with low-to-intermediate atherothrombotic risk and moderate-to-high bleeding risk.

For patients requiring ticagrelor or prasugrel, caution is necessary when adding VKA; it may be prudent to avoid NOACs in such patients.

Table 11 Recommendations concerning management of AF patients on NOACs who present with an acute coronary syndrome (ACS)
1. Temporarily discontinue NOAC upon presentation.
2. Immediately initiate dual antiplatelet therapy (DAPT) upon presentation unless in frail patients with a high bleeding risk (only aspirin; delay DAPT until complete waning of the anticoagulative effect of NOAC). Unless for patients allergic to aspirin, monotherapy with clopidogrel is not recommended in the acute setting.
3. Low dose of aspirin (150-300 mg loading; 75-100 mg/d later), preferably combined with an ADP receptor inhibitor (ticagrelor or prasugrel preferred over clopidogrel).
4. After waning of the anticoagulative effect of NOAC, parenteral anticoagulation should be initiated. Fondaparinux is preferred in NSTE-ACS because of its lower bleeding risk.
5. In case of an STEMI, primary PCI is strongly recommended over fibrinolysis.
a) If fibrinolysis is the only available reperfusion therapy: avoid unfractionated heparin (UFH) or enoxaparin until the NOAC effect has disappeared.
6. In case of NSTE-ACS:
a) If not urgent, delay coronary angiography until complete waning of NOAC effect.
b) Peri-procedural anticoagulation per local practice (preferrably UFH or bivaluridin).
7. In case of PCI:
a) A radial approach is preferred as it reduces at least the risk of access site bleeding.
b) If possible and indicated, a balloon angioplasty without stenting significantly reduces the need for (prolonged) triple therapy.
c) Bare-metal stents minimize the duration of dual or triple therapy and are generally preferred.
d) Use additional parenteral anticoagulation, regardless of the timing of the last dose of NOAC.

Table 11 Recommendations concerning management of AF patients on NOACs who present with an acute coronary syndrome (ACS) (continued)
e) Because of its short half-time and reduced bleeding risk, periprocedural bivalirudin is preferred. Discontinue immediately after PCI.
f) Avoid glycoprotein IIb/IIIa inhibitors unless for bail-out situations.
8. In patients requiring (extensive) revascularization, bypass surgery might be preferred to avoid prolonged triple therapy.
9. When restarting NOAC consider dose reduction according to bleeding and atherothrombotic risk and aim at shortest necessary duration of dual or triple therapy.
10. The newer platelet inhibitors prasugrel and ticagrelor have not been evaluated with OAC or NOAC. It may be prudent to await further data before combining these platelet inhibitors and NOAC

ACS = acute coronary syndrome; NSTE = non-ST elevation; PCI = percutaneous coronary intervention.

Scenario 2: Management of the patient with a recent ACS (<1y) who develops new-onset AF (see also **Table 12**)

In patients with low atherothrombotic risk, VKA or NOAC in monotherapy could be considered after 1 to 3 months (or 6 months in case of recent DES), especially when their bleeding risk is elevated (HAS-BLED ≥3).

Temporary dual antiplatelet therapy without additional anticoagulation can be a safe and effective alternative for patients with a low CHA2DS2-VASc (i.e. ≤1), especially in those with a high residual risk for recurrent ACS.

Table 12 Recommendations concerning new onset AF in patients with a recent (<1 year) ACS

1.	In patients with low or moderate atherothrombotic risk (GRACE risk <118), VKAs in monotherapy could be considered after 1 to 3 months (or 6 months in case of DES), especially when the bleeding risk is elevated (HAS-BLED ≥3).
2.	In patients with high atherothrombotic risk (GRACE risk >118), additional single antiplatelet therapy (preferably clopidogrel) might be necessary, especially when their bleeding risk is acceptable (HAS-BLED <3).
3.	Dual antiplatelet therapy without additional anticoagulation might be an alternative for patients with a low CHA2DS2-VASc score (i.e. ≤1) but high residual atherothrombotic risk (i.e. GRACE risk score >118)
4.	If a NOAC would be indicated, a FXa inhibitor might be preferred in view of the small and insignificant increase in the risk of myocardial infarction (MI) with dabigatran, but this needs to be weighed against the overall perceived clinical effect (which was not negated for dabigatran).
5.	If dabigatran would be indicated, a lower dose (110 mg BID) might be preferred, in combination with low-dose aspirin or with clopidogrel.
6.	Ultra-low dose rivaroxaban (2x2.5 mg/d or 2x5 mg/d) in combination with DAPT has not been evaluated in the setting of AF and can currently not be recommended.

ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy

Scenario 3: A stable CAD patient (ACS >1y ago; elective BMS>1m; DES>6m) develops AF (see also **Table 13**).

It is likely that the advantages of NOACs (in monotherapy) over VKAs are preserved in CAD patients with AF.

In patients on dabigatran with low bleeding risk and high atherothrombotic risk, one might consider adding low-dose aspirin in patients, accepting that this will increase the bleeding risk by approximately 60%.

Table 13 Recommendations concerning new onset AF in patients with a remote (>1 year) ACS

1.	Since VKAs alone are superior to aspirin post-ACS, anticoagulation without additional antiplatelet agents is considered sufficient for most AF patients with stable CAD.
2.	As the advantages of NOACs over VKAs are likely to be preserved in stable CAD patients with AF, NOACs may be safe and effective alternatives to VKAs.
3.	In general, no preference is given to either one of the NOACs.
4.	If dabigatran is chosen, a lower dose (110 mg BID) plus low-dose aspirin might be a sensible option (or clopidogrel in case of allergy to aspirin).

ACS = acute coronary syndrome; BID = twice daily; CAD = coronary artery disease.

13. Cardioversion in a NOAC treated patient

Although data is limited it appears that cardioversion under NOAC is as safe as under warfarin. However, a prior TEE should be considered if there is doubt about NOAC intake compliance. Prospective registries and randomised trials on this topic are ongoing to better guide patient management in the future. Please check on www.NOACforAF.eu for updates.

14. Patients presenting with acute stroke while on NOACs

The acute phase

Patients with acute haemorrhagic stroke

Data concerning treatment of intracerebral haemorrhage (ICH) under NOACs are missing yet. The same approaches as discussed in Section 9 should be applied but the efficacy and safety of this strategy applied for ICH needs to be further evaluated in clinical studies.

Patients with acute ischemic stroke

According to current guidelines, thrombolytic therapy with recombinant tissue plasminogen activator (rtPA), which is approved within a 4.5 hour time window from onset of stroke symptoms, is not recommended in patients under therapy with anticoagulants. Therefore, it cannot be given within 48 hours after the last administration of NOAC (corresponding to 4 plasma half lives). The use of thrombolytics in situations with uncertainty about the anticoagulaton status is discouraged. Only in exceptional single cases in which reliable coagulation assessment (with specific tests, see Section 2) is within the normal reference range, the use of fibrinolytic agents can be considered.
Alternatively, mechanical recanalization of occluded vessels may be considered as an alternative treatment option, but no prospective data exist in this regard.

Management of the post-acute phase

Haemorrhagic stroke

Administration of NOACs may be restarted 10-14 days after intracerebral haemorrhage if cardioembolic risk is high and the risk of new intracerebral haemorrhage is estimated to be low. In practice, however, the same factors that are predictive for embolic stroke (age, hypertension, previous stroke and others) are also predictive for haemorrhages. Moreover, according to the labelling of VKAs and NOACs, a history of a spontaneous intracerebral bleed constitutes a contraindication against anticoagulation, unless the cause of the intracerebral bleed has been reversed. This is also true for extracerebral, intracranial haemorrhages such as sub- or epidural haemorrhages, both spontaneous or traumatic. Non-pharmacological prevention strategies such as ablation or occlusion of the atrial appendage should be considered as potential substitutes.

Ischemic stroke

The 1-3-6-12 day rule could serve as a rule of thumb, with re-institution of anticoagulation in patients with a TIA after 1 day, with small, non-disabling infarct after 3 days, with a moderate stroke after 6 days, while large infarcts involving large parts of the arterial territory will be treated not before 2 (or even 3) weeks.
Alternative causes for ischemic stroke should be investigated, especially in compliant patients.

Patients with transient ischemic attack (TIA) of cardioembolic origin

In this case, anticoagulation treatment with NOACs can be started as soon as possible. Bridging with LMWH is not required. Aspirin is no alternative option.

Patients with AF and significant carotid stenosis.

In these patients carotid endarterectomy and not stenting is recommended to avoid triple therapy which is associated with considerably increased bleeding, as discussed in Section 12.

15. NOACs vs. VKAs in AF patients with a malignancy

There is very little controlled data for NOAC therapy in AF patients with malignancy. Antithrombotic therapy in patients with AF and suffering a malignancy needs discussion between cardiologist and oncologis, since patients with malignancies are at increased risk for thromboembolic events, but cancer therapy also inflicts bleeding risks, be it through surgery, irradiation, or chemotherapy. Oncologists can best estimate the coagulation side effects of a specific planned therapy.

When anticoagulant therapy needs to be newly initiated in a patient with malignancy, therapy with VKAs or heparins should be considered over NOACs, because of the clinical experience with these substances, the possibility of close monitoring, and reversal options.

The presence of a malignancy in patients with AF increases stroke risk. Established anticoagulant therapy should therefore be continued, including NOAC therapy, whenever possible, especially in patients who receive moderately myelosuppressive therapies. The NOAC dose may need adaptation to anticipate therapy-induced changes in organ function (especially liver and renal function). Moreover, gastric protection with PPI or H2 blockers should be considered in all patients treated with anticoagulants.

When a myelosuppressive chemotherapy or radiation therapy is planned, the interdisciplinary team should consider temporary dose reduction or cessation of NOAC therapy, as well as specific monitoring modalities including repetitive full blood counts including platelets, careful clinical examination for bleeding signs, and regular monitoring of liver and renal function.

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