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Guidelines

European Heart Rhythm Association practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Summary of the document prepared by the Czech Society of Cardiology

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Contents

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1. Introduction

New oral anticoagulants (NOACs) have emerged as an alternative for vitamin K antagonists (VKAs) for thrombo-embolic prevention in patients with non-valvular atrial fibrillation (AF). Although very promising in many regards (predictable effect without need for monitoring, fewer food and drug interactions, shorter plasma half-life, and an improved efficacy/safety ratio), the proper use of NOACs will require new approaches in many daily aspects. While the 2010 ESC Guidelines (and the 2012 Update) mainly discuss the indications for anticoagulation in general (based on the CHA2DS2-VASc score) and of NOAC in particular, they guide less on how to deal with NOAC in specific clinical situations. The European Heart Rhythm Association (EHRA) set out to coordinate a unified way of informing physicians on the practical use of the different NOACs, in a text that supplements the AF Guidelines as a guidance tool for safe, effective use of NOAC when prescribed.

Please note that all drugs discussed in this document may not already be EMA approved for the non-valvular AF indication, and/or may not be available in the different constituent EU countries at the time of publication of this document. Since new information is becoming available at a rapid pace, an EHRA web site with the latest updated information accompanies this text (http://www.NOACforAF.eu, which links to http://www.escardio.org/ COMMUNITIES/EHRA, under 'Publications'). Any item that has been changed from the original printed version will be highlighted in the future.

2. Practical start-up and follow-up scheme for patients on new oral anticoagulants

Before prescribing a NOAC (Table 1) to a patient with AF, a risk–benefit analysis should be made concerning anti-

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

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa 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

[a] 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, as (being) studied in Phase 3 clinical trial; not yet approved by EMA.

coagulation in general and the choice of the specific anticoagulant on the basis of approved indications and on the preference of the patient after discussion of the different options. Concerning the choice of a given NOAC, it is also important to consider the clinical profile of the patient and co-medications, some of which may be contraindicated or

Fig. 1 – European Heart Rhythm Association proposal for a universal NOAC anticoagulation card. 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…). We present a generic and universal card that could serve all patients under NOAC therapy.

pose unfavourable drug–drug interactions. As for users of VKAs, it is equally important that those treated with NOACs carry details about their anticoagulant therapy to alert any (para-)medical participant in their care. We propose a uniform card to be completed and carried by each patient (Fig. 1). It can be downloaded in digital form at http://www.NOACforAF.eu. The goal of the card is not only to list demographic and medication information, and to educate the patient, but mainly to structure a coordinated follow-up of the patient by different caregivers. The structure of initiation and follow-up is shown in Fig. 2. A checklist for actions during the follow-up contacts is presented in Table 2. Therapy with this new class of drugs requires vigilance, also because this is a fragile patient population and NOACs are drugs with potentially severe complications. Patients should return on a regular basis for on-going review of their treatment, preferably every 3 months. This review may be undertaken by general practitioners provided that they have good guidance on what to do and when. The card also lists the appropriate timing of laboratory testing, taking the patient profile into considera tion. Renal function should be assessed more frequently in patients receiving dabigatran, or in potentially compromised patients such as the elderly, otherwise frail patients, or in those where an intercurring condition may affect renal function, since all NOACs require dose reductions depending on renal function.

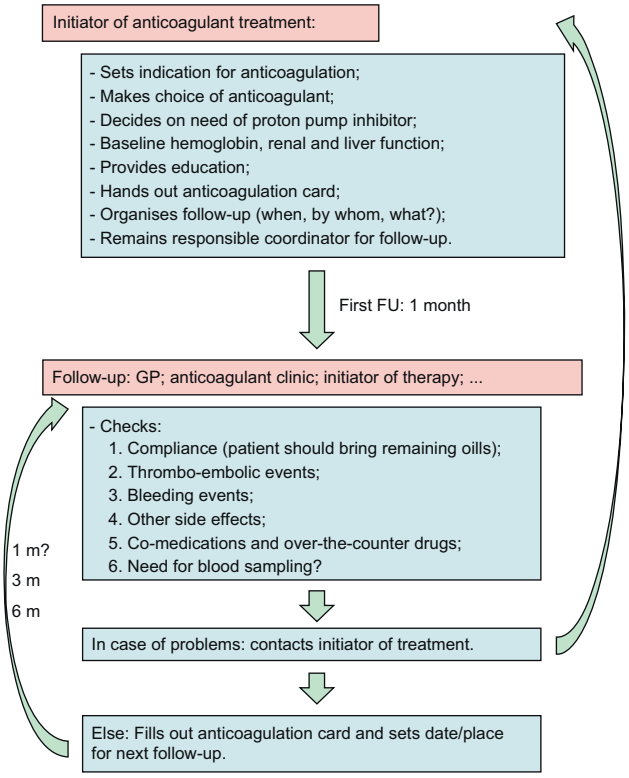

Fig. 2 – Structured follow-up of patients on NOACs. It is mandatory to ensure safe and effective drug intake. The anticoagulation card, as proposed in Fig. 1, is intended to document each planned visit, each relevant observation or examination, and any medication change, so that every person following up the patient is well-informed. Moreover, written communication between the different (para)medical players is required to inform them about the follow-up plan and execution.

3. How to measure the anticoagulant effect of new oral anticoagulants?

New oral anticoagulants do not require routine monitoring of coagulation: neither the dose nor the dosing intervals should be altered in response to changes in laboratory coagulation parameters. However, the quantitative assessment of the drug exposure and the anticoagulant effect may be needed in emergency situations. When interpreting a coagulation assay in a patient treated with a NOAC, in contrast to VKA coagulation monitoring, it is paramount to know exactly when the NOAC was administered relative to the time of blood sampling. The time delay between intake and blood sampling should, therefore, be carefully recorded when biological monitoring is performed. A complete overview of the effect on common coagulation assays by direct thrombin inhibitors (DTI) and FXa inhibitors can be found in Table 3. The activated partial thromboplastin time (aPTT) may provide a qualitative assessment of the presence of dabigatran. If the aPTT level at trough (i.e. 12–24 h after ingestion) still exceeds two times the upper limit of normal, this may be associated with a higher risk of bleeding, and may warrant caution especially in patients with bleeding risk factors. The prothrombin time (PT) may provide a qualitative assessment of the presence of factor Xa inhibitors. Like the aPTT for dabigatran, these respective tests are not sensitive for the quantitative assessment of the NOAC effect! Quantitative tests for DTI and FXa inhibitors do exist (diluted thrombin-time and chromogenic assays, respectively), but they may not (yet) be routinely available in most hospitals. Moreover, there are no data on a cut-off of these specific tests below which elective or urgent surgery is 'safe', and therefore their use in this respect cannot be recommended at this time. Point of care tests to assess the international normalised ratio (INR) should not be used in patients on NOACs.

4. Drug–drug interactions and pharmacokinetics of new oral anticoagulants

Despite high expectations of less food interactions with the NOAC drugs, physicians will have to consider pharmacokinetic effects of accompanying drugs and of comorbidities when prescribing NOACs, especially when a combination of interfering factors is present. The absorption and metabolism of different NOACs is summarised in Table 4. There is a good rationale for reducing the dose of NOACs in patients with a high bleeding risk and/or when a higher plasma level of the drug can be anticipated. We have chosen an approach with three levels of alert for drug–drug interactions or other clinical factors that may affect NOAC plasma levels or effects (Table 5): (1) 'red' interactions reclude the use of a given NOAC in combination (i.e. 'contraindication' or 'discouragement' for use), (2) 'orange' interactions refer to the recommendation to adapt the NOAC dose, since they result in

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 4) 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 >75 years of fragile If CrCl 15–30 ml/min If intercurring condition that may impact renal or hepatic function

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

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

	Dabigatran	Apixaban	Edoxaban[a]	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
aPTT	At trough: >2× 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 or >65 s: 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
ECT	At trough: ≥3× ULN: excess bleeding risk	Not affected	Not affected	Not affected

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

changes of the plasma levels or effect of NOACs that could potentially have a clinical impact, and (3) 'yellow' interactions with the recommendation to keep the original dose, unless two or more concomitant 'yellow' interactions are present. Two or more 'yellow' interactions need expert evaluation, and may lead to the decision of not prescribing the drug ('red') or of adapting its dose ('orange'). Unfortunately, for many potential interactions with drugs that are often used in AF patients no detailed information is available yet. These have been shaded in the Table. It is prudent to abstain from using NOACs in such circumstances until more information is available.

Table 4 – Absorption and metabolism of the different NOACs.

	Dabigatran	Apixaban	Edoxaban[a]	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 8)	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	−12–30%	No effect	No effect	No effect
Asian ethnicity	+25%	No effect	No effect	No effect
Gl 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)

H2B, H2-blocker; PPI, proton pump inhibitor; Gl, gastro-intestinal.
[a] No EMA approval yet. Needs update after finalisation of SmPC.

Since food intake has an impact on the absorption and bioavailability of rivaroxaban (area under the curve plasma concentrations increase by 39%), rivaroxaban should be taken together with food. There is no relevant food interaction for the other NOAC and they may be taken with or without food. Also, concomitant use of proton-pump inhibitors (PPI) and H2-blockers does not constitute a contraindication for any NOAC.

Rate-controlling and anti-arrhythmic drugs interact with P-gp, hence warranting caution for concomitant use of NOACs. For dabigatran and edoxaban it is advised to reduce the NOAC dose when used in combination with verapamil ('orange'). There is a strong effect of dronedarone on dabigatran plasma levels, which constitutes a contraindication for concomitant use. No data are available yet for FXa-inhibitors, but a similar caution may be warranted.

Apart from the pharmacokinetic interactions, it is clear that association of NOACs with other anticoagulants, platelet inhibitors (aspirin, clopidogrel, ticlodipine, prasugrel, ticagrelor, and others), and non-steroidal anti-inflammatory drugs (NSAID) increases the bleeding risk. There is data indicating that the bleeding risk in association with antiplatelet agents increases by at least 60% (similar as in association with VKAs). Therefore, such associations should be carefully balanced against the potential benefit in each clinical situation. Association of NOACs with (dual) antiplatelet drugs is extensively discussed in 'Patient with atrial fibrillation and coronary artery disease' below.

5. Switching between anticoagulant regimens

It is important to safeguard the continuation of anticoagulant therapy while minimising the risk for bleeding when switching between different anticoagulant therapies. This requires insights into the pharmacokinetics and pharmacodynamics of different anticoagulation regimens, interpreted in the context of the individual patient. Practical switching scenarios have been described in the full document [1], for VKA or a parenteral anticoagulant to NOAC and vice versa.

NOACs can immediately be initiated once the INR is lower than 2.0. If the INR is 2.0–2.5, NOACs can be started next day.
NOACs can be started once the intravenous UFH is discontinued.
NOACs can be initiated when the next dose of LMWH would have been foreseen.

Especially for the circumstances where NOAC treatment should be switched to VKA, caution is required: due to the slow onset of action of VKAs, it may take 5–10 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. 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 h 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. three consecutive measurements should have yielded values between 2.0 and 3.0).

Table 5 – Effect on NOAC plasma levels ('area under the curve, AUC') from drug-drug interactions and clinical factors, and recommendations towards NOAC dosing.

	Via	Dabigatran	Apixaban	Edoxaban[a]	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%)[a]	Minor effect (use with caution if CrCl 15/50 ml/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect	+40%[SmPC]	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%)[b]	+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 × 75 mg)	No data yet	+85% (reduce dose by 50%)[a]	No data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140–150% (US: 2 × 75 mg)	+100%[SmPC]	No data yet	Up to +160%
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[SmPC]	No data yet	Up to +153%
Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	-66%	−54%[SmPC]	−35%	Up to −50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	−12–30%	No data yet	No effect	No effect
Other factors					
Age ≥ 80 years	Increased plasma level	See Table 7 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		No data yet	
Age ≥ 75 years	Increased plasma level			No data yet	
Weight ≥ 60 kg	Increased plasma level				
Renal function	Increased plasma level				
Other increased bleeding risk					

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.
[a] No EMA approval yet. Needs update after finalisation of SmPC.
[b] Prespecified dose reduction has been tested in Phase 3 clinical trial (to be published).
BCRP, breast cancer resistance protein; NSAID, non/steroidal anti/inflammatory drugs; H2B, H2-blockers; PPI, proton pump inhibitors; P/gp, P-glycoprotein; GI, gastro-intestinal.

6. Ensuring compliance with new oral anticoagulant intake

New oral anticoagulants have a very predictable anticoagulant effect. Monitoring of the anticoagulant effect is not required to guide therapy, unless in unusual clinical situations (like intercurrent disease). However, the anticoagulant effect of NOACs fades rapidly (12–24 h after the last intake). Therefore, strict therapy compliance by the patient is crucial. Even if appropriate new anticoagulation tests would be used to gauge NOAC plasma levels, they cannot be considered as tools to monitor compliance since their interpretation is highly dependent on the timing of testing with respect to the last intake of the drug, and they do not indicate anything about compliance before the last intake. Physicians should

develop ways to optimise compliance, which is known to be ≤80% for most drugs in daily practice.

6.1. *Practical considerations:*

(1) A once daily (qd) dosing regimen was related to greater adherence vs. bid regimen in cardiovascular patients, and in AF patients (for diabetes and hypertension drugs). It is likely that also for NOACs a qd dosing regime is best from a compliance perspective, but it is unknown whether any regimen is superior in guaranteeing the clinical thromboembolic preventive effects and the safety profile as seen in the clinical trials.
(2) Patient education on the importance of strict adherence is of utmost importance. Many simultaneous approaches should be employed in this regard: leaflets and instructions at initiation of therapy; a patient anticoagulation card; group sessions; and reeducation at every prescription renewal. There is room and potentially a need to develop new tools to enhance compliance with NOACs.
(3) Family members should be involved in this education, so that they too understand the importance of adherence, and help the patient in this regard.
(4) Although INR monitoring is not required, there should be a prespecified follow-up schedule between general practitioner, cardiologist, or electrophysiologist, and the responsibility of each concerning compliance should be clearly communicated. There is emerging interest in nurse-coordinated AF centres that may specifically focus on compliance issues during patient follow-up.
(5) Many technological aids are being explored to enhance compliance: the format of the blisters; medication boxes, smartphone applications, and/or SMS messages that alert the patient about the next intake;… Again, their long-term effects are unknown and one tool may not fit all patients. The prescribing physician, however, should consider individualisation of these aids.
(6) Some patients may prefer INR monitoring to no monitoring. This needs to be discussed with the patient before starting/converting to NOAC therapy. In some patients, there may be a preference for VKA treatment from this perspective.
(7) Some countries have a highly networked pharmacy database, which can help track the number of NOAC prescriptions that individual patients claim. In such countries, pharmacists could be involved in compliance monitoring.
(8) In NOAC patients in whom low compliance is suspected despite proper education and additional tools, conversion to VKAs could be considered.

7. How to deal with dosing errors?

7.1. *Missed dose*

No double dose should be taken to make up for missed individual doses. For NOACs with a bid dosing regimen (i.e. every 12 h), the patient should still take a forgotten dose up till 6 h after the scheduled intake. If that is not possible anymore, the dose should be skipped and the next scheduled dose should be taken. For NOACs with a qd dosing regimen, the patient should still take a forgotten dose up till 12 h after the scheduled intake. If that is not possible anymore, the dose should be skipped and the next scheduled dose should be taken.

7.2. *Double dose*

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

7.3. *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 not take another pill, but to just continue the planned dose regimen, i.e. starting with the next dose at the 12 h interval. For NOACs with a qd dosing regimen, one could advise to take another pill and then continue the planned dose regimen.

7.4. *Overdose*

Depending on the amount of suspected overdose, hospitalisation for monitoring or urgent measures should be advised. For further discussion, see Section 10.

8. Patients with chronic kidney disease

Chronic kidney disease (CKD) constitutes a risk factor for both thrombo-embolic events and bleeding in AF patients. Recent findings suggest that a creatinine clearance of ,60 ml/min may even be an independent predictor of stroke and systemic embolism.

Many patients with mild-tomoderate CKD have been enrolled in the NOAC trials. For FXa inhibitors, pharmacokinetic studies have demonstrated similar plasma area under the curve concentrations for reduced doses in patients with decreased renal function (CrCl 30–50 ml/min) as for the higher dose in patients with normal renal function, and these doses have been prospectively tested in phase 3 trials. In the context of NOAC treatment, CrCl is best assessed by the Cockroft method, as this was used in most NOAC trials. Rivaroxaban is also approved for use in patients with CKD stage IV, i.e. CrCl 15–30 ml/min, with the lower dose regimen, although it should still be used 'with caution' in such patients. However, there are no outcome data for NOACs in patients with advanced chronic kidney disease, and the current ESC Guidelines recommend against their use in such patients (Table 6). Furthermore, there are very little data on patients on dialysis or close to dialysis (glomerular filtration rate ,15 ml/min, CKD stage V), neither from trials nor from clinical experience. In the absence of such experience, **no NOAC is approved for use in dialysis patients.**

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[a]	Rivaroxaban
CrCl ≥60 ml/min CKD Stage I and II	~14 h	No data	~8.6 h	~8.5 h (+44%)
CrCl 30–60 ml/min CKD Stage III	~18 h	No data	~9.4 h	~9 h (+52%)
CrCl 15–30 ml/min CKD Stage IV	~28 h	No data	~16.9 h	~9.5 h (+64%)
CrCl ≤15 ml/min CKD Stage V	No data	No data	No data	No data

CKD, chronic kidney disease; CrCl, creatinine clearance.
Hatching, no available data yet.
[a] No EMA approval yet. Needs update after finalisation of SmPC.

8.1. *Practical suggestions*

(1) Chronic kidney disease should be considered as an additional risk factor for stroke in AF. But CKD also increases bleeding risk, with a relative increase in risk for all oral anticoagulants (VKA and NOACs).
(2) New oral anticoagulants seem to be a reasonable choice for anticoagulant therapy in AF patients with mild or moderate CKD. A similar benefit/risk ratio of NOACs vs. VKAs was seen with a reduced dose rivaroxaban (15 mg qd) in patients with renal impairment (CrCl ,50 ml/min). Apixaban, demonstrated a lower overall rate of major bleeding compared to VKA, and also that the increase in the rate of bleeding by renal dysfunction was significantly less than with VKA. Of note, in the group of patients with a CrCl ,50 ml/min, 24% received a lower dose of apixaban (i.e. 2.5 mg bid) since dose reduction was prespecified according to a combination of renal dysfunction (serum creatinine ≥1.5 mg/dl) plus age (≥80 years) or body weight (≤60 kg) (Table 7).
(3) 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. VKAs depending on kidney function. Therefore, careful balancing of the clinical benefits and risks may justify its choice in stable patients. Also the FXa inhibitors are cleared 25–50% by the kidney (Table 4). Dose reductions have been studied prospectively with apixaban (2.5 mg bid) and rivaroxaban (15 mg qd), and should be considered in patients with CrCl ,50 ml/min along the guidance of Tables 4 and 6.
(4) In the absence of clinical data or experience, NOAC therapy should be avoided in AF patients on haemodialysis. Vitamin K antagonists may be a more suitable alternative for now.
(5) In patients on NOACs, renal function needs to be monitored carefully, at least yearly, to detect changes in renal function and adapt the dose accordingly. If renal function is impaired (≤60 ml/min), 6 monthly checks are required. Renal function monitoring is especially relevant for dabigatran, which is predominantly cleared renally: in elderly patients (.75 years) or otherwise frail patients on dabigatran, renal function should be evaluated at least once every 6 months (see also Table 2 and Fig. 2). Acute illness often transiently affects renal function (infections, acute heart failure…), and therefore should trigger re-evaluation.
(6) Renal function can deteriorate within a few months, and the nature of the kidney disease as well as concomitant conditions that could change the time course of CKD should be considered when deciding on a monitoring scheme.
   (i) **Monitor every year for CKD stage I–II (CrCl ≥60 ml/min)**.
   (ii) **Monitor every 6 months for CKD stage III (CrCl 30–60 ml/min)**.
   (iii) **Monitor every 3 months for CKD stage IV (CrCl ≤30 ml/min)**.

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

Doses of NOACs beyond those recommended expose the patient to an increased risk of bleeding. This may occur when the patient has taken too high a dose or when intercurring events are suspected (like renal insufficiency, especially with dabigatran; administration of drugs that may lead to drug–drug interactions; or other factors: see Section 5) that may have increased plasma concentration of the NOAC beyond therapeutic levels. In terms of management, it is important to distinguish between an overdose with and without bleeding complications. In case of bleeding complications, see Section 10. Rare cases of overdose have been reported without bleeding complications or other adverse reactions in the clinical trials. In the case of recent acute ingestion of an overdose, the use of activated charcoal to reduce absorption may be considered for any NOAC (with a standard dosing scheme for adults of 30–50 g). In case of an overdose suspicion, coagulation tests can help to determine its degree and

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

	Dabigatran	Apixaban	Edoxaban[a]	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. 150 mg bid)	Serum creatinine < 1.5 mg/dl: no adjustment (i.e. 5 mg bid)	Not available	CrCl ≥ 50 ml/min: no adjustment (i.e. 20 mg qd)
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.[b] 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.[SmPC] or with other 'yellow' factor (Table 5): 2.5 mg bid	Not available	15 mg qd when CrCl 15–49 ml/min
Not recommended if	CrCl < 30 ml/min	CrCl < 15 ml/min	Not available	CrCl < 15 ml/min

Orange, reduce dose (from 150 mg BID to 100 mg BID for dabigratran).
Yellow, consider dose reduction if another 'yellow' factor is present (from 20 mg to 15 mg QD for rivaroxaban; from 5 mg BID to 2.5 mg BID for apixaban).
Hatching, no data available yet.
[a] No EMA approval yet. Needs update after finalisation of SmPC.
[b] 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; gd, once daily; SmPC, Summary of product characteristics.

possible bleeding risk (see Section 3 for the interpretation of coagulation tests).

There are currently no specific antidotes for the NOACs, although development for those is ongoing. However, given the relatively short plasma half life of the NOAC drugs, in the absence of bleeding a 'wait-and-see' management can be advocated in most cases.

10. Management of bleeding complications

At this point in time the different NOACs share the fact that specific antidotes and rapid (routine) quantitative measurements of their anticoagulant are missing (see also Section 3), and strategies for reversal of the anticoagulant effects are limited.

10.1. *Non life-threatening bleeding*

In addition to standard supportive measurements (such as mechanical compression, surgical haemostasis, fluid replacement, and other haemodynamic support), in view of the relatively short elimination half lives, time is the most important antidote of the NOACs (see Table 8 and Fig. 3 for a flowchart). After cessation of treatment, restoration of haemostasis is to be expected within 12–24 h after the last taken dose, given plasma half-life of around 12 h for most NOACs. This underscores the importance of inquiring 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 Table 5), and other factors influencing haemostasis (like concomitant use of anti-platelet drugs). Blood volume repletion and restoration of normal platelet count (in case of thrombocytopenia

Table 8 – Possible measures to take in case of bleeding.

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non life-threatening bleeding	Enquire last intake+dosing regimen Estimate normalisation of haemostasis: Normal renal function: 12–24 h CrCl 50–80 ml/min: 24–36 h CrCl 30–50 ml/min: 36–48 h CrCl <30 ml/min ≥ 48 h	Enquire last intake+dosing regimen Normalisation of haemostasis: 12–24 h
	Maintain diuresis Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia $\leq 60 \times 10^9$/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent)	Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia $\leq 60 \times 10^9$/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent)
	Tranexamic acid can be considered as adjutants Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (preliminary evidence: -65% after 4 h) Charcoal haemoperfusion not recommended (no data)	Tranexamic acid can be considered as adjutants Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
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)

RBC, red blood cells; CrCl, creatinine clearance; PCC, prothrombin complex concentrate.

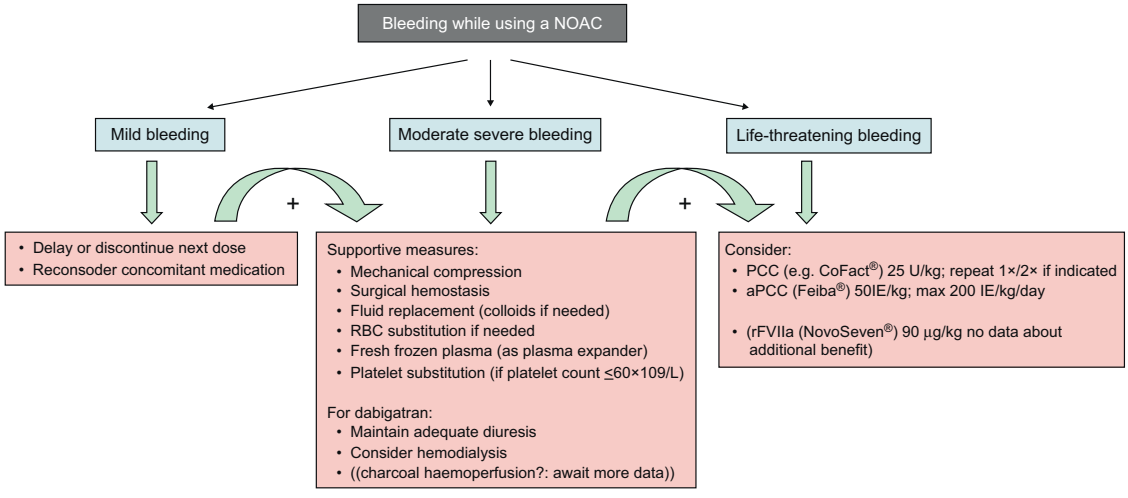

Fig. 3 – Management of bleeding in patients taking NOACs. Possible therapeutic measures in case of minor or severe bleeding in patients on NOAC therapy.

$\leq 60 \times 109$/L or thrombopathy) should be considered. The time frame of drug elimination strongly depends on kidney function in patients taking dabigatran (see also Tables 4 and 6). In case of bleeding in a patient using dabigatran, adequate diuresis must be maintained. Although dabigatran can be dialysed, it should be noted that there is only limited clinical experience in using dialysis in this setting. Moreover, the risks of bleeding at puncture sites for dialysis needs to be balanced vs. the risk of waiting. In contrast to dabigatran, dialysis has not been shown to be an option in patients

treated with any of the FXa inhibitors since due to the high plasma binding of most FXa inhibitors, dialysis is not expected to significantly reduce their plasma levels.

10.2. *Life-threatening bleeding*

In vitro testing using blood samples from volunteers taking rivaroxaban, dabigatran, or apixaban, showed that activated prothrombin complex concentrates (aPCC, i.e. similar to PCC but with activated Factor VIIa; also called FEIBA; brand name Feiba®) corrected more coagulation parameters than PCC alone.

Based on experimental data and given that the efficacy in patients who are actively bleeding has not been firmly established (i.e. that they reduce blood loss and improve outcome), the administration of PCC or aPCC can be considered in a patient with life-threatening bleeding if immediate haemostatic support is required. Based on studies with PCCs in preclinical models and in healthy volunteers, administration could start at a dose of 25 U/kg and can be repeated if clinically indicated. Future studies might provide more information on dosing, and whether dosing should be adapted to the NOAC used. Activated prothrombin complex concentrates (Feiba®, 50 IE/kg, with a maximum of 200 IE/kg/day), could be considered if it is readily available in the hospital.

The place of recombinant activated factor VIIa (NovoSeven®, 90 mg/kg) needs further evaluation. The use of other procoagulants such as antifibrinolytics (e.g. tranexamic acid or aminocaproic acid) or desmopressin (especially in special situations with associated coagulopathy or thrombopathy) can be considered, though there are almost no clinical data of their effectiveness in NOAC-associated bleeding, and their use does not substitute the above mentioned measures. Fresh frozen plasma will not be of help to reverse anticoagulation, but may be indicated to expand plasma volume in patients who require massive transfusion. In the absence of a vitamin K deficiency or a treatment with VKAs, vitamin K administration has no role in the management of a bleeding under NOACs. Similarly, protamine reverses the anticoagulant effects of heparin, but has no role in case of NOAC-associated bleeding.

11. Patients undergoing a planned surgical intervention or ablation

About one-quarter of patients that are in need for anticoagulant therapy require temporary cessation within 2 years. Both patient characteristics (kidney function, age, history of bleeding complications, concomitant medication) and surgical factors should be taken into account while deciding when to discontinue and restart the drug (Table 9). We recommend the development of an institutional guideline and a hospital-wide policy concerning post-operative anticoagulation management in different surgical settings.

For interventions with no clinically important bleeding risk (Table 10), it may be more practical to have the intervention scheduled 18–24 h after the last intake, and then restart 6 h later. For procedures with a minor bleeding risk, it is recommended to discontinue NOACs 24 h before the elective procedure and for procedures that carry a risk for major bleeding to take the last NOAC 48 h before (Table 9). For dabigatran, a more graded pre-intervention termination depending on kidney fiction has been proposed, both for low- and high-risk interventions.

Some coagulation tests (aPTT and PT) may provide a semiquantitative assessment of dabigatran and FXa inhibitors, respectively, but a strategy that includes normalisation of the aPTT or PT prior to elective/urgent interventions has not been validated.

For procedures with immediate and complete haemostasis, the NOAC can be resumed 6–8 h after the intervention. For many surgical interventions, however, resuming full dose anticoagulation within the first 48–72 h after the procedure may carry a bleeding risk that could outweigh the risk of cardio-embolism. One also has to take into account the absence of a specific antidote.

For procedures associated with immobilisation, it is considered appropriate to initiate a reduced venous thromboprophylactic or intermediate dose of low molecular weight heparins (LMWH) 6–8 h after surgery, whereas therapeutic anticoagulation by restarting NOACs is deferred 48–72 h after

Table 9 – Last intake of drug before elective surgical intervention.

	Dabigatran		Apixaban		Edoxaban[a]		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: Perform at trough level (i.e. ≥ 12 h or 24 h after last intake)							
	Low risk	High risk	Low risk	High risk	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[b]	≥ 48 h	≥ 96 h	≥ 24 h	≥ 48 h	No data	No data	≥ 24 h	≥ 48 h
CrCl 15–30 ml/min[b]	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							

Bold values deviate from the common stopping rule of ≥ 24 h low risk, ≥ 48 h high risk.

[a] No EMA approval yet. Needs update after finalisation of SmPC.

[b] Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (15 mg QD).

Low risk = surgery with low risk of bleeding; high risk = surgery with high risk of bleeding. See also Table 10.

CrCl, creatinine clearance.

Table 10 – Classification of elective surgical interventions according to bleeding risk.

Interventions not necessarily requiring discontinuation of anticoagulation
Dental interventions
Extraction of 1–3 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)
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 orthopaedic 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.

the invasive procedure. There are no data on the safety and efficacy of the use of a reduced dose of the NOACs, such as those used for the prevention of VTE after hip/knee replacement.

For AF patients undergoing pulmonary vein isolation, there is some emerging information available on the use of dabigatran. There is no published data on the peri-interventional use of FXa inhibitors undergoing catheter ablation. Too aggressively shortened peri-procedural cessation of NOACs and/or no bridging may be less safe when compared with continued VKA administration and ablation under an INR between 2.0 and 3.0.

12. Patients undergoing an urgent surgical intervention

If an emergency intervention is required, the NOAC should be discontinued. Surgery or intervention should be deferred, if possible, until at least 12 h and ideally 24 h 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 inhibitors) can be considered if there is concern about the pharmacokinetic waning of the anticoagulant effect (e.g. renal insufficiency and/or concomitant conditions).

Nevertheless, such strategy has never been evaluated, and therefore cannot be recommended and should not be used routinely.

13. Patient with atrial fibrillation and coronary artery disease

The combination of AF and coronary heart disease is a common clinical setting. 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 when both ACS and AF converge in a given patient. For the sake of clarity, we have opted to define three clinical scenarios with many different subscenarios, and proposed practical instructions for each: (i) ACS management in an AF patient on NOAC; (ii) management of the patient with a recent ACS (1 year) who develops new-onset AF (Table 11); and (iii) development of AF in a patient with a history of coronary heart disease, but without ACS within the last year (Table 12). Given the complexity of these recommendations, we refer to the full document. The type and level of anticoagulation as well as single vs. dual antiplatelet therapy in combination with NOAC, and its duration, need to

Table 11 – Recommendations concerning new onset AF in patients with a recent (<1 year) ACS.

1. In patients with low or moderate atherothrombotic risk (GRACE risk <1 1 8), VKAs in monotherapy could be considered after 1–3 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 but insignificant increase in the risk of myocardial infarction with dabigatran, but this needs to be weighed against the overall perceived clinical effect (which was not impacted 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 (2.5 mg BID or 5 mg BID) 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.

Table 12 – Recommendations concerning new onset AF in patients with a remote (>1 year) ACS.

1. As 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 although a small increase was noted with dabigatran (but without impacting overall clinical benefit)
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) especially in patients with high atherothrombotic risk and low bleeding risk

ACS, acute coronary syndrome; bid, twice daily; CAD, coronary artery disease.

be highly personalised. We acknowledge that new data, which are highly needed, may change the management options.

14. Cardioversion in a new oral anticoagulant-treated patient

No prospective data are available concerning the safety of cardioversion under NOAC treatment. Observational data from the RE-LY, ROCKET-AF, and ARISTOTLE trials did not show any difference in the number of strokes or systemic embolisms, and that the stroke rate was comparable with that in prior trials with other forms of anticoagulation, with or without TEE guidance. Since there is no coagulation assay available for NOACs that provides information on effective anticoagulation over the past 3 weeks and because patient compliance may be variable, it is mandatory to explicitly ask the patient about adherence over the last weeks and to document the answer in the file. If compliance with NOAC intake can be reliably confirmed, cardioversion seems acceptably safe. However, a prior TEE should be considered if there is doubt about compliance.

15. Patients presenting with acute intracranial bleeding or ischaemic stroke while on new oral anticoagulants

15.1. *The acute phase*

Guidelines for the treatment of intracerebral haemorrhage under oral anticoagulants are limited to strategies for the reversal of VKAs. By analogy to patients being treated with warfarin, the coagulation status of patients under NOAC who have acute or (apparently) on-going life-threatening bleeding such as intracranial haemorrhage should be corrected as rapidly as possible. Measures in this regard were discussed in 'Management of bleeding complications'. For ischaemic stroke, thrombolytic therapy with recombinant tissue plasminogen activator is not recommended in patients under therapy with anticoagulants. As plasma half-life of NOACs range between 8 and 17 h, thrombolytic therapy cannot be given within 48 h after the last administration of NOAC. This is an arbitrary recommendation, which is yet to be tested. We believe that only in exceptional single cases in which reliable coagulation assessment (with specific tests) is within the normal reference range, the use of fibrinolytic agents can be considered. If NOACs have been administered within the last 48 h and/or appropriate coagulation tests are not available or abnormal, mechanical recanalization of occluded vessels maybe considered as an alternative treatment option.

15.2. *Management of the post-acute phase*

A history of a spontaneous intracerebral bleed constitutes a contraindication against anticoagulation, unless the cause of the intracerebral bleed has been reversed. By analogy to the use of VKAs, the 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. However, the same factors that are predictive for embolic stroke are also predictive for haemorrhages. Non-pharmacological prevention strategies such as ablation or occlusion of the atrial appendage should be considered as potential substitutes.

Continuation of NOACs after ischaemic stroke depends on the infarct size. Re-institution of anticoagulation in patients with a transient ischaemic attack (TIA) can be considered 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. If patient compliance and therapeutic effect of coagulation have been assured (i.e. the stroke must have occurred under adequate anticoagulation), alternative causes for ischaemic stroke should be investigated. After a TIA of cardioembolic origin, anticoagulation treatment with NOACs can be started as soon as possible. Bridging with LMWH is not required. Aspirin is not an alternative option.

16. New oral anticoagulants vs. vitamin K antagonists in atrial fibrillation patients with a malignancy

Patients with malignancies are at an increased risk for thromboembolic events. Moreover, cancer therapy may induce bleeding through local wounds (surgery), tissue damage (irradiation), or systemic antiproliferative effects which will reduce platelet count and function (chemotherapy and some forms of irradiation). Antithrombotic therapy in patients with AF and suffering a malignancy needs discussion between cardiologist and oncologist. When anticoagulant therapy needs to be initiated in a patient with malignancy, therapy with VKAs or heparins should be considered over NOACs, because of the clinical experience with these substances

and the possibility of close monitoring. In AF patients stably treated with a NOAC, who develop malignancies for which they need to receive moderately myelosuppressive therapies, continuation of NOACs may be defendable. When a potent myelosuppressive chemotherapy or radiation therapy is planned, temporary dose reduction or cessation of NOAC therapy should be considered, and/ or specific monitoring instituted, including repetitive full-blood counts and regular monitoring of liver and renal function. Gastric protection with PPI or H2-blockers is not contraindicated and should even be considered in all patients treated with anticoagulants.

REFERENCE *

[1] European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Hein Heidbuchel, Peter Verhamme, Marco Alings, Matthias Antz, Werner Hacke, Jonas Oldgren, Peter Sinnaeve, A. John Camm, Paulus Kirchhof. The original text is available free on the ESC website: http://www.escardio.org/communities/EHRA/publications/novel-oral-anticoagulants-for-atrial-fibrillation/Documents/EHRA-NOAC-Practical-Full-EPEuropace-2013.pdf and was originally published in Europace 15 (2013) 625–651.

*All references supporting the recommendations in this document can be found in the original full text.