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EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary†

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New oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with non-valvular atrial fibrillation (AF). Both physicians and patients will have to learn how to use these drugs effectively and safely in specific clinical situations. This text is an executive summary of a practical guide that the European Heart Rhythm Association (EHRA) has assembled to help physicians in the use of the different NOACs. The full text is being published in EP Europace. Practical answers have been formulated for 15 concrete clinical scenarios: (i) practical start-up and follow-up scheme for patients on NOACs; (ii) how to measure the anticoagulant effect of NOACs; (iii) drug–drug interactions and pharmacokinetics of NOACs; (iv) switching between anticoagulant regimens; (v) ensuring compliance of NOAC intake; (vi) how to deal with dosing errors; (vii) patients with chronic kidney disease; (viii) what to do if there is a (suspected) overdose without bleeding, or a clotting test is indicating a risk of bleeding?; (ix) management of bleeding complications; (x) patients undergoing a planned surgical intervention or ablation; (xi) patients undergoing an urgent surgical intervention; (xii) patients with AF and coronary artery disease; (xiii) cardioversion in a NOAC-treated patient; (xiv) patients presenting with acute stroke while on NOACs; (xv) NOACs vs. VKAs in AF patients with a malignancy. Since new information is becoming available at a rapid pace, an EHRA web site with the latest updated information accompanies the guide (www.NOACforAF.eu). It also contains links to the ESC AF Guidelines, a key message pocket booklet, print-ready files for a proposed universal NOAC anticoagulation card, and feedback possibilities.

Keywords Atrial fibrillation • Anticoagulation • Stroke • Bleeding • Pharmacology

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.

Whereas the 2010 ESC Guidelines (and the 2012 Update)[1,2] mainly discuss the indications for anticoagulation in general (e.g. based on the CHA_2DS_2-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.[3] Please note that not

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all drugs discussed in this document may already be EMA approved for the non-valvular AF indication, and/or not 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 (www.NOACforAF.eu, which links to www.escardio.org/COMMUNITIES/EHRA, under 'Publications'). Any item that has been changed from the original printed version will be highlighted in the future. It also contains links to the ESC AF Guidelines, a key message pocket booklet, and print-ready files for a proposed universal NOAC anticoagulation card. Moreover, readers can address their suggestions for change or improvement on the web site.

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

Before prescribing a NOAC to a patient with AF, a risk–benefit analysis should be made concerning anticoagulation 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.[1] 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 pose unfavourable drug–drug interactions (see 'Drug–drug interactions and pharmacokinetics of new oral anticoagulants').

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 (*Figure 1*). It can be downloaded in digital form at 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 *Figure 2*. A checklist for actions during the follow-up contacts is presented in the full document. 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. Nurse-coordinated AF clinics may be very helpful in this regard.[4] Therefore, the card also lists the appropriate timing of laboratory testing, taking the patient profile into consideration. e.g. 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 (see 'Drug–drug interactions and pharmacokinetics of new oral anticoagulants' and 'Patients with chronic kidney disease'; see Table 1 of the ESC AF Guidelines Update[2]).

Minor bleeding is a particular problem in patients treated with any anticoagulant. Most minor bleeding is temporary and is best classified as 'nuisance' in type. It is best dealt with by standard methods to control bleeding, but should not lead readily to discontinuation or dose adjustment of therapy.

2. 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 table with a complete overview of the effect on common coagulation assays by direct thrombin inhibitors (DTI) and FXa inhibitors is present in the full manuscript. 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.[5] 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 normalized ratio (INR) should not be used in patients on NOACs.[6]

3. 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 discussed in tables and figures in the full document. There is 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.[1,7,8] 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 1):

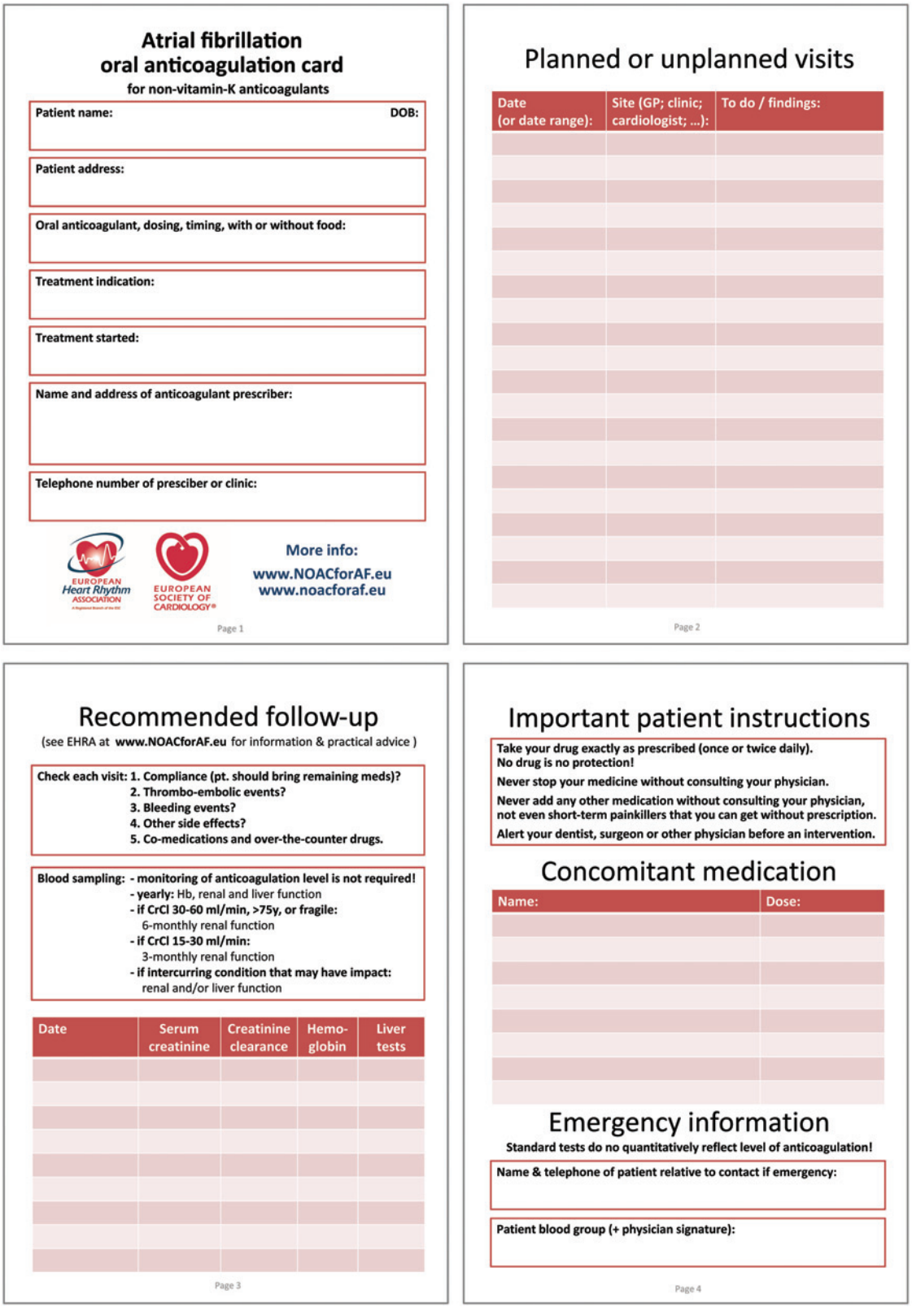

Figure 1 European Heart Rhythm Association proposal for a universal new oral anticoagulation card. A patient information card is crucial, both for the patient (instructions on correct intake; contact information in case of questions) as for health care workers (other care-takers are involved; renal function; follow-up schedule; concomitant medication, etc.). We present a generic and universal card that could serve all patients under new oral anticoagulant therapy.

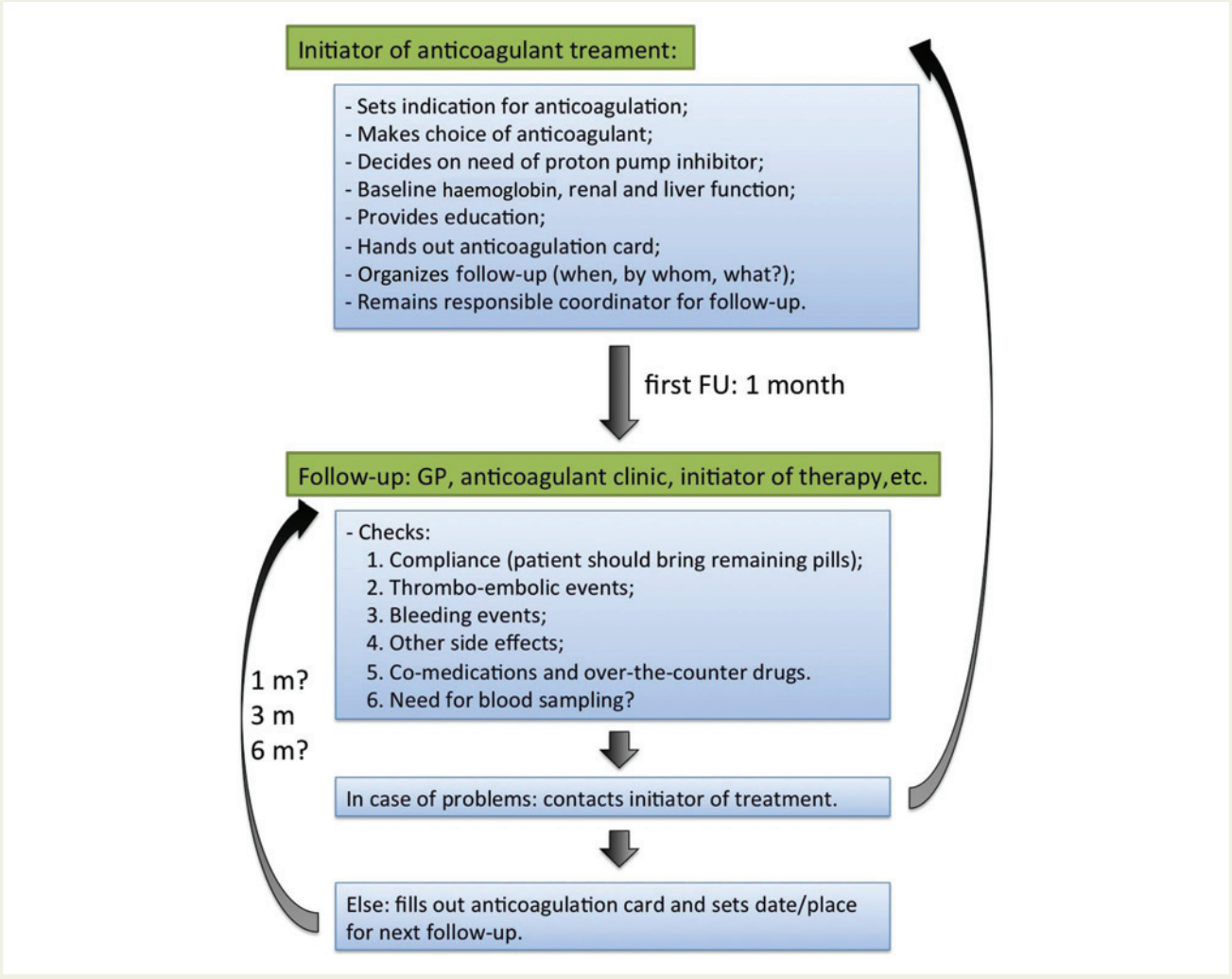

Figure 2 Structured follow-up of patients on new oral anticoagulants. Structured follow-up of patients on new oral anticoagulants is mandatory to ensure safe and effective drug intake. The anticoagulation card, as proposed in *Figure 1*, is intended to document each planned visit, each relevant observation 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.

(i) 'red' interactions preclude the use of a given NOAC in combination (i.e. 'contraindication' or 'discouragement' for use), (ii) 'orange' interactions refer to the recommendation to adapt the NOAC dose, since they result in changes of the plasma levels or effect of NOACs that could potentially have a clinical impact, and (iii) '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.

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.

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).[9–11] 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.

Table 1 **Effect on new oral anticoagulant plasma levels ('area under the curve, AUC') from drug–drug interactions and recommendations towards new oral anticoagulant dosing**

	via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[39]	no data yet	no effect[40]	no effect[41, 42]
Digoxin	P-gp competition	no effect [43]	no data yet	no effect[40]	no effect[42, 44]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180%[45] (reduce dose and take simultaneously)	no data yet	+53% (SR)[40] (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[45]	+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%[40] (Reduce dose by 50%)§	+50%
Amiodarone	P-gp competition	+12-60%[45]	no data yet	no effect[40]	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%[SmPC]	no data yet	up to +160%[42]

fluconazole	moderate CYP3A4 inhibition	no data yet	no data yet	no data yet	+42% (if systemically administered)[42]
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%[42, 46]
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%[41]
Rifampicin; St. John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	-66%[47]	-54%[SmPC]	-35%	up to -50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	-12-30%[45, 48, 49]	no data yet	no effect	no effect[50, 51]
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			[52]	
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 to 110 mg b.i.d. for dabigatran; from 20 to 15 mg q.d. for rivaroxaban; from 5 to 2.5 mg b.i.d. for apixaban); yellow, consider dose reduction if another 'yellow' factor is present; hatching, no data available; recommendation based on pharmacokinetic considerations.
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.
[a]No EMA approval yet. Needs update after finalization of SmPC.
[b]Pre-specified dose reduction has been tested in Phase 3 clinical trial (to be published).

4. Switching between anticoagulant regimens

It is important to safeguard the continuation of anticoagulant therapy while minimizing 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, for VKA or a parenteral anticoagulant to NOAC and vice versa. 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 (i) that the INR be measured just before the next intake of the NOAC during concomitant administration, and (ii) 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).

5. Ensuring compliance with new oral anticoagulant intake

The anticoagulant effect of NOACs fades rapidly 12–24 h after the last intake. Therefore, strict therapy compliance by the patient is crucial for adequate protection. Physicians should develop ways to optimize compliance, which is known to be $\leq$80% for most drugs in daily practice. There is no scientific data yet on the actual compliance of NOACs in non-trial conditions, nor on how it can best be optimized. Nevertheless, all means to optimize compliance should be considered. These include: considerations on choosing a NOAC with once daily or twice daily intake; repeated patient education, as well of their family members; a clearly pre-specified follow-up schedule between general practitioner, cardiologist, or electrophysiologist (see 'Practical start-up and follow-up scheme for patients on new oral anticoagulants'); possibly technological aids like medication boxes or smartphone applications if their effectiveness could be proved; networked pharmacy database (as available in some countries). Finally, in NOAC patients in whom low compliance is suspected despite proper education and additional tools, conversion to VKAs could be considered. Moreover, some patients may themselves prefer INR monitoring to no monitoring.

6. How to deal with dosing errors?

Questions relating to dosing errors are very common in daily practice. Often, the patient calls the hospital, office or even a national poison centre. It is advisable to provide staff workers of these call centres with clear instructions on how to advise patients in these circumstances. To prevent situations as described below, patients on NOACs should be urged to make use of well-labelled weekly pill containers, with separate spaces for each dose. In case of a missed dose, no double dose should be taken to make up for missed individual doses. The forgotten dose may, however, be taken until halfway the dosing interval (e.g. up to 12 h for a once daily dosing). If that is not possible anymore, the dose should be skipped and the next scheduled dose should be taken. In case a double dose has mistakenly been taken, one could opt to forgo the next planned dose. 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. In case of overdose, depending on the amount of suspected overdose, hospitalization for monitoring or urgent measures should be advised (see also 'What to do if there is a (suspected) overdose without bleeding, or a clotting test is indicating a risk of bleeding?').

7. Patients with chronic kidney disease

Chronic kidney disease (CKD) constitutes a risk factor for both thrombo-embolic events and bleeding in AF patients.[12,13] Recent findings suggest that a creatinine clearance of $<$60 mL/min may even be an independent predictor of stroke and systemic embolism.[14,15] Vitamin K antagonist therapy is associated with a significant reduction in the risk of stroke or thrombo-embolism in CKD patients but the risk of bleeding is also significantly increased. Thus, the net clinical effect of VKA treatment requires careful assessment in such patients.[12,16] Many patients with mild-to-moderate CKD have been enrolled in the NOAC trials, with pre-specified dose reductions. In the context of NOAC treatment, CrCl is best assessed by the Cockroft method, as this was used in most NOAC trials. There are no outcome data for NOACs in patients with advanced chronic kidney disease (CrCL $<$ 30 mL/min), and the current ESC Guidelines recommend against their use in such patients.[2] Furthermore, there is 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, not any NOAC is approved for use in dialysis patients.

New oral anticoagulants appear 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, and there are indications that the increase in the rate of bleeding by renal dysfunction was significantly less than with VKA.[13,17–19] There are no comparative studies that the risks from CKD differ among the NOACs. Therefore, careful balancing of the clinical benefits and risks of each drug (and its dose adjustment) may justify its choice. For all drugs, however, a careful follow-up of renal function is required in CKD patients, since all are cleared more or less by the kidney. Renal function monitoring is especially relevant for dabigatran, which is predominantly cleared renally (see also 'Practical start-up and follow-up scheme for patients

Table 2 Possible measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non-life-threatening bleeding	Inquire last intake + dosing regimen Estimate normalization of haemostasis Normal renal function: 12–24 h CrCl 50–80 mL/min: 24–36 h CrCl 30–50 mL/min: 36–48 h CrCl <30 mL/min: ≥48 h Maintain diuresis Local haemostatic measures Fluid replacement(colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (preliminary evidence: −65% after 4h)[53] Charcoal haemoperfusion not recommended (no data)	Inquire last intake + dosing regimen Normalization of haemostasis: 12–24 h Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
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.

on new oral anticoagulants'). Acute illness often transiently affects renal function (infections, acute heart failure, etc.), and therefore should trigger re-evaluation. New oral anticoagulant therapy should be avoided and VKAs may be a more suitable alternative for now in AF patients on haemodialysis.

8. 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. In terms of management, it is important to distinguish between an overdose with and without bleeding complications. In case of bleeding complications, see 'Management of bleeding complications'. 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 the case of an overdose suspicion, coagulation tests can help to determine its degree and possible bleeding risk (see 'How to measure the anti-coagulant effect of new oral anticoagulants?'). There are currently no specific antidotes for the NOACs, although development for those is on-going. 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. If a more aggressive normalization of plasma levels is deemed necessary, or rapid normalization is not expected (e.g. major renal insufficiency) the steps outlined in 'Management of bleeding complications' can be taken.

9. Management of bleeding complications

Given the absence of specific NOAC antidotes, strategies for the reversal of the anticoagulant effects are limited. Reversal of VKAs through the administration of vitamin K has a slow onset (i.e. at least 24 h), but administration of fresh frozen plasma or co-agulation factors more rapidly restores coagulation. In the case of NOACs, however, the plasma abundance of the drug may block newly administered coagulation factors as well. On the other hand, studies have shown that the bleeding profile of NOACs, in particular that of intracranial and other life-threatening bleeding, is more favourable than that of warfarin. Nevertheless, as more patients will start using one of the NOACs, the number of bleeding related events is expected to increase. Currently, recommenda-tions on bleeding management are not so much based on clinical experience, but rather reflect experts' opinions or laboratory end-points. An overview of the possible measures is shown in Table 2, distinguishing non-life-threatening bleeding from life-threatening bleeding, and with slightly different options for dabigatran and

Table 3 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 or 24 h after last intake)							
	Low risk (h)	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 mL/min	≥24	≥48	≥24	≥48	no data	no data	≥24	≥48
CrCl 50–80 mL/min	**≥36**	**≥72**	≥24	≥48	no data	no data	≥24	≥48
CrCl 30–50 mL/min[b]	**≥48**	**≥96**	≥24	≥48	no data	no data	≥24	≥48
CrCl 15–30 mL/min[b]	not indicated	not indicated	**≥36**	**≥48**	no data	no data	**≥36**	**≥48**
CrCl <15 mL/min	no official indication for use							

Low risk, surgery with low risk of bleeding; high risk, surgery with high risk of bleeding. CrCl, creatinine clearance.
[a]No EMA approval yet. Needs update after finalization 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).

FXa inhibitors. Given their relatively short elimination half-lives, time is the most important antidote of the 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 Table 1), and other factors influencing haemostasis (like concomitant use of anti-platelet drugs).

Based on scarce clinical data,[20–22] the administration of PCC or aPCC can be considered in a patient with life-threatening bleeding if immediate haemostatic support is required (Table 2). Awaiting more data on the clinical effectiveness of these strategies, the choice may depend on their availability and the experience of the treatment centre. The place of recombinant-activated factor VIIa needs further evaluation.[23] We recommend consultation among cardiologists, haemostasis experts and emergency physicians to develop a hospital-wide policy concerning bleeding management. Such policy should be communicated well, and be easily accessible (e.g. on an Intranet site or in pocket-sized leaflets).

10. Patients undergoing a planned surgical intervention or ablation

When to stop the new oral anticoagulants?

About one-quarter of patients that are in need for anticoagulant therapy require temporary cessation within 2 years.[24] Both patient characteristics (kidney function, age, history of bleeding complications, concomitant medication) and surgical factors should be taken into account on when to discontinue and restart the drug. Table 3 compiles this information for the different NOAC. Also other societies have formulated advice on temporary cessation of NOAC therapy.[25] Again, we recommend the development of an institutional guideline and a hospital-wide policy concerning post-operative anticoagulation management in different surgical settings that is widely communicated and readily available.

Although common interventions with no clinically important bleeding risk (like some dental procedures or interventions for cataract or glaucoma) can be performed at trough concentration of the NOAC (i.e. 12 or 24 h after the last intake, depending on twice or once daily dosing), it may be more practical to have the intervention scheduled 18–24 h after the last intake, and then restart 6 h later, i.e. with skipping one dose for BID NOAC. For procedures with a minor bleeding risk, it is recommended to discontinue NOACs 24 h before the elective procedure in patients with a normal kidney function, and for procedures that carry a risk for major bleeding to take the last NOAC 48 h before. We have provided a table with classification of surgical interventions according to bleeding risk in the full document. For dabigatran, a more graded pre-intervention termination depending on kidney function has been proposed, both for low- and high-risk interventions, as indicated in Table 3. Although the aPTT and PT may provide a semi-quantitative assessment of dabigatran and FXa inhibitors, respectively (see 'How to measure the anticoagulant effect of new oral anticoagulants?'), a strategy that includes normalization of the aPTT or PT prior to elective/urgent interventions has not been validated.

When to restart the new oral anticoagulants?

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 in case bleeding should occur and/or re-intervention is needed. For procedures associated with immobilization, it is considered appropriate to initiate a reduced venous thromboprophylactic or intermediate dose of low molecular weight heparins (LMWH) 6–8 h after surgery if haemostasis has been achieved, whereas therapeutic anticoagulation by restarting NOACs is deferred 48–72 h 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 atrial fibrillation ablation procedures

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. With the limited available data,[26–29] if a strategy of bridging and restarting of anticoagulation is chosen and appropriately executed, NOACs seem to allow such, whereas a 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, both concerning bleeding and cardioembolic complications.

11. 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.

12. Patient with atrial fibrillation and coronary artery disease

The combination of AF 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.[30] 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; and (iii) development of AF in a patient with a history of coronary heart disease, but without ACS within the last year, without an elective bare metal stent during the last month or a drug-eluting stent over the last 6 months ('stable coronary heart disease'). Given the complexity of these recommendations, we refer to the full document rather than to give an unnuanced summary here. The full document also contains three tables summarizing the recommendations for each of the scenarios. The type and level of anticoagulation as well as single vs. dual antiplatelet therapy in combination with NOAC, and its duration, need to be highly personalized based on atherothrombotic risk, cardioembolic risk, and bleeding risk.[31]

It is highly recommended to formally assess risk using validated tools such as the GRACE,[32] CHA_2DS_2-VASc, and HAS-BLED scores.[1,2] The document also lists key scientific data that form the basis of the guidance. Finally, we acknowledge that new data, which are highly needed, may change the management options.

13. Cardioversion in a new oral anticoagulant-treated patient

Based on the ESC guidelines,[1] in patients with AF of >48 h duration (or AF of unknown duration) undergoing cardioversion, oral anticoagulation should have been given for at least 3 weeks prior to cardioversion, or transoesophageal echocardiography should be performed to rule out left atrial thrombi. After cardioversion, continuous oral anticoagulation is mandatory for another 4 weeks. 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 our without TEE guidance.[33–35] 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. Good prospective registries or even randomized trials are needed on this topic to facilitate patient management in the future.

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

The acute phase

Guidelines for the treatment of intracerebral haemorrhage under oral anticoagulants are limited to strategies for the reversal of VKAs.[36] Data concerning NOACs are missing yet. 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'. The efficacy and safety of such strategies for ICH needs to be further evaluated in clinical studies.[37]

For ischaemic stroke, according to current guidelines and official labelling, 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 (corresponding to four plasma half-lives). This is an arbitrary recommendation, which has yet to be tested. In the case of uncertainty concerning last NOAC administration, a

prolonged aPTT (for dabigatran) or PT (for FXa inhibitors) indicates that the patient is anticoagulated and thrombolysis should not be administered. We believe that only in exceptional single cases in which reliable coagulation assessment (with specific tests, see 'How to measure the anticoagulant effect of new oral anticoagulants?') 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. Again, no prospective data exist in this regard.

Management of the post-acute phase

According to the labelling of VKAs and also of the NOACs, 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 (age, hypertension, previous stroke, and others) are also predictive for haemorrhages. Non-pharmacological prevention strategies such as ablation or occlusion of the atrial appendage should be considered as potential substitutes.[1,2]

Continuation of NOACs after ischaemic stroke depends on the infarct size. Clinical study data regarding re-institution of anticoagulation are missing. Some advocate as a rule of thumb the 1-3-6-12 day rule, with re-institution of anticoagulation in patients with a transient ischaemic attack (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. 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 no alternative option: in AF patients considered not suitable for VKA thrombo-embolic preventive treatment, the FXa inhibitor apixaban was shown to be superior to aspirin in stroke prevention.[7]

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

Patients with malignancies are at an increased risk for thrombo-embolic events. Many forms of cancer interact directly or indirectly with the coagulation system. 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, some forms of irradiation).[38] There is very little controlled data for antithrombotic therapy in AF patients with malignancy. Active malignancy usually was an exclusion criterion in NOAC trials. Antithrombotic therapy in patients with AF and suffering a malignancy needs discussion between cardiologist and oncologist, taking into consideration the impact of the cancer on morbidity and mortality, the specific oncologic therapy used, and the anticipated effects of tumour and therapy on both thrombo-embolic risk and bleeding risk. 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, the possibility of close monitoring (for VKAs and unfractionated heparin, UFH), and reversal options (for VKAs and UFH). 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 (including platelets), regular monitoring of liver and renal function, and careful clinical examination for bleeding signs. Gastric protection with PPI or H2-blockers is not contraindicated and should even be considered in all patients treated with anticoagulants.

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