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EHRA PRACTICAL GUIDE

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

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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 clinical practice. Many unresolved questions on how to optimally use these drugs in specific clinical situations remain. The European Heart Rhythm Association set out to co-ordinate a unified way of informing physicians on the use of the different NOACs. A writing group listed 15 topics of concrete clinical scenarios and formulated as practical answers as possible based on available evidence. The 15 topics are: (1) Practical start-up and follow-up scheme for patients on NOACs; (2) How to measure the anticoagulant effect of NOACs; (3) Drug–drug interactions and pharmacokinetics of NOACs; (4) Switching between anticoagulant regimens; (5) Ensuring compliance of NOAC intake; (6) How to deal with dosing errors; (7) Patients with chronic kidney disease; (8) What to do if there is a (suspected) overdose without bleeding, or a clotting test is indicating a risk of bleeding? (9) Management of bleeding complications; (10) Patients undergoing a planned surgical intervention or ablation; (11) Patients undergoing an urgent surgical intervention; (12) Patients with AF and coronary artery disease; (13) Cardioversion in a NOAC-treated patient; (14) Patients presenting with acute stroke while on NOACs; (15) 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 this text (www.NOACforAF.eu).

Keywords Atrial fibrillation • Anticoagulation • Stroke • Bleeding • Pharmacology

Introduction

New oral anticoagulants (NOACs) have emerged as an alternative for vitamin K antagonists (VKAs) for thromboembolic prevention in patients with non-valvular atrial fibrillation (AF). This will have an impact on many practical considerations in the daily management of these patients. 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

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deal with NOAC in specific clinical situations. Moreover, despite the different AF anticoagulation trials, there are still many under--explored aspects of NOAC that are relevant already today when these drugs are used by cardiologists, neurologists, geriatricians, and general practitioners. Each of the new NOACs entering the market will be accompanied by tools for its proper use in many clinical situations (Summary of Product Characteristics or SmPC; patient card; information leaflets for patients and physicians), but there is a risk that multiple, and often slightly different, physician education tools could lead to more confusion than clarity. Based on these premises, the European Heart Rhythm Association (EHRA) set out to coordinate a unified way of informing physicians on the use of NOACs. This document thus supplements the AF guidelines as a practical guidance tool for safe, effective use of NOAC when prescribed.

A writing group listed 15 topics of concrete clinical scenarios, and formulated as practical answers as possible based on available knowledge. The writing group was assisted by medical experts of the companies that bring NOACs to the market: they assured that the latest information on the different NOAC was evaluated, and provided feedback on the alignment of the text with the approved SmPC. Nevertheless, the responsibility of this document resides entirely with the EHRA writing group, also because in some instances we opted to make recommendations beyond the information available in SmPC in order to provide practice advice to physicians in the field.

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. Please note that not all drugs discussed in this document may already be European medicines agency (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.

We hope that this collaborative effort has yielded the practical tool that EHRA envisioned. The authors realize that there will be gaps, unaddressed questions, and many areas of uncertainty/debate. Therefore, readers can address their suggestions for change or improvement on the web site. This whole endeavour should be one for and by the medical community.

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

1.1 Start of therapy

Before prescribing a NOAC to a patient with AF, it should have been decided that anticoagulation is merited and that the use of a novel agent is appropriate. Thus, a risk/benefit, analysis relating to anticoagulation is in favour of the treatment, and the choice of anticoagulant has been made on the basis of approved indications as provided by regulatory authorities, professional societies and local formulary committees, and on the preference of the patient after discussion of the different options.[1] The general indications for anticoagulation are fully explained in professional guidelines and the specific indications for NOACs are outlined in relevant SmPC and local agreements/regulations. *Table 1* lists the NOACs approved or under evaluation for stroke prevention in AF patients. It should be appreciated that in many countries not all NOACs share precisely the same indication and that local factors, especially with regard to the cost of therapy may influence their use. Concerning the choice of a given NOAC, it is also important to consider co-medications taken by the patient, some of which may be contraindicated or pose unfavourable drug–drug interactions (see Section 4). Alternatively, some co-medications such as proton pump inhibitors (PPI) may be considered to reduce the risk for gastro-intestinal bleeding.

Users of VKAs have routinely been advised to carry information about their anticoagulant therapy to alert any (para)medical participant in their care. It should be equally important that those treated with NOACs carry details of this therapy. Each manufacturer provides proprietary information cards, but it is suggested that a uniform card should be completed and carried by each patient. *Figure 1* shows a proposal for such a card, which can be downloaded in digital form at www.NOACforAF.eu.

It is critically important to educate the patient about the importance of daily intake of NOACs at each visit, and to convince them that a NOAC should not be discontinued because of the rapid decline of protective anticoagulation that will occur. Similarly,

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[3]	ARISTOTLE[4] AVERROES[4]	ENGAGE-AF[5]	ROCKET-AF[6]

[a]No EMA approval yet. Needs update after finalization 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.

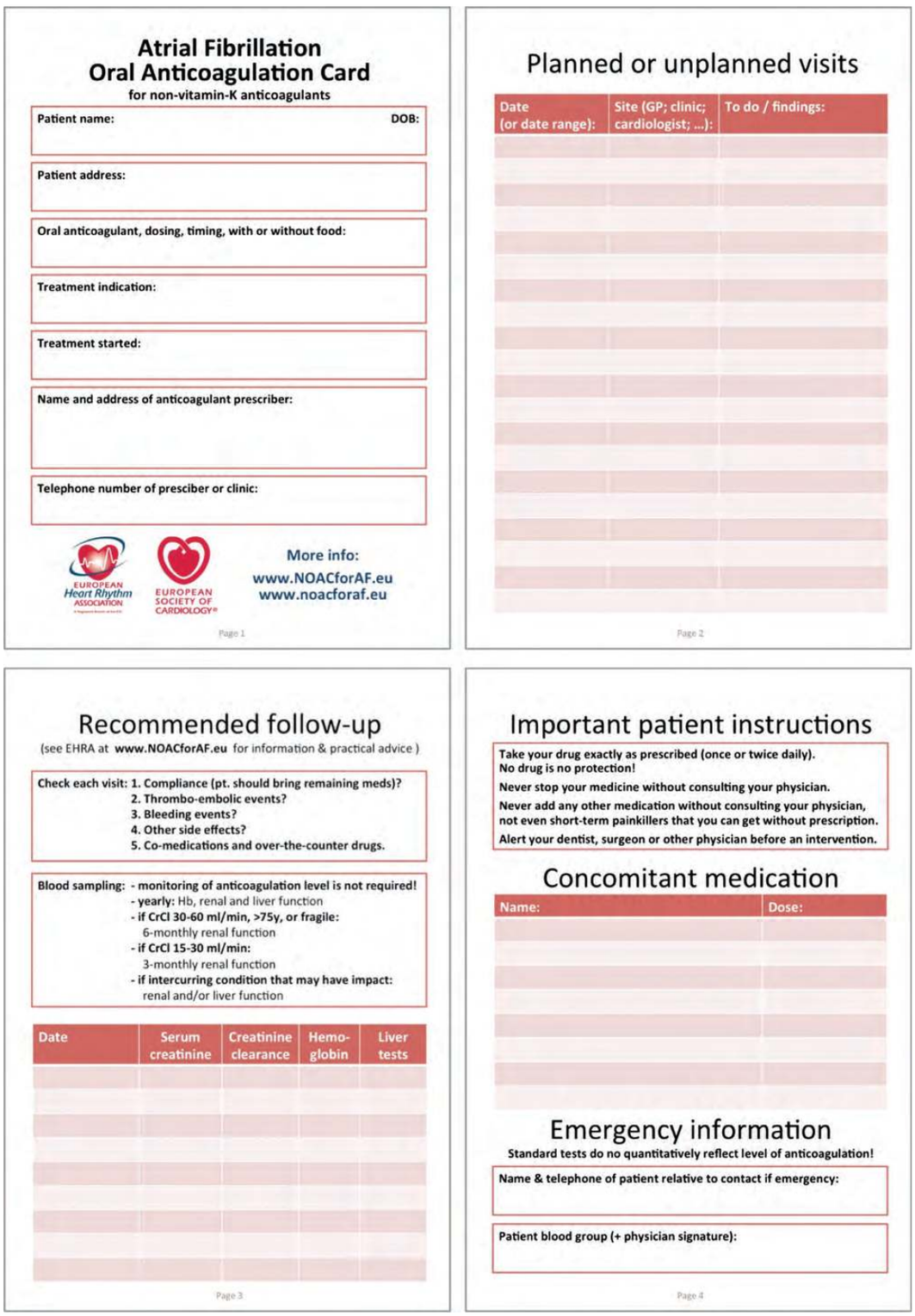

Figure 1 European Heart Rhythm Association proposal for a universal NOAC anticoagulation card. A patient information card is crucial, both for the patient (instructions on correct intake; contact information in case of questions) as for health care workers (other care-takers are involved; renal function;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

forgetting to take the medication or leaving it behind when travelling is dangerous. This should be carefully explained to the patient who should be made aware of the importance of strict adherence to the prescribed NOAC regimen.

1.2 How to organize follow-up?

The follow-up of AF patients who are taking anticoagulant therapy should be carefully specified and communicated among the different caretakers of the patient. All anticoagulants have some drug–drug interactions and they may cause serious bleeding. Therapy prescription 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 with experience in this field and/or by appropriate secondary care physicians (*Figure 2*). Nurse-coordinated AF clinics may be very helpful in this regard.[7,8]

Regular review has to systematically document (1) therapy adherence (ideally with inspection of the prescribed medication in blister packs or bottles, in addition to appropriate questioning); (2) any event that might signal thromboembolism in either the cerebral, systemic or pulmonary circulations; (3) any adverse effects, but particularly (4) bleeding events (occult bleeding may be revealed by falling haemoglobin levels, see below); (5) co-medications, prescribed or over-the-counter; and (6) blood sampling for haemoglobin, renal (and hepatic) function. *Table 2* lists the appropriate timing of these evaluations, taking the patient profile into consideration. For example, 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 Sections 4 and 8; see *Table 3* of the ESC AF Guidelines Update[2]). Although the RE-LY protocol did not specify dose reduction in patients with chronic kidney disease and a CrCl of 30–50 ml/min (unless e.g.

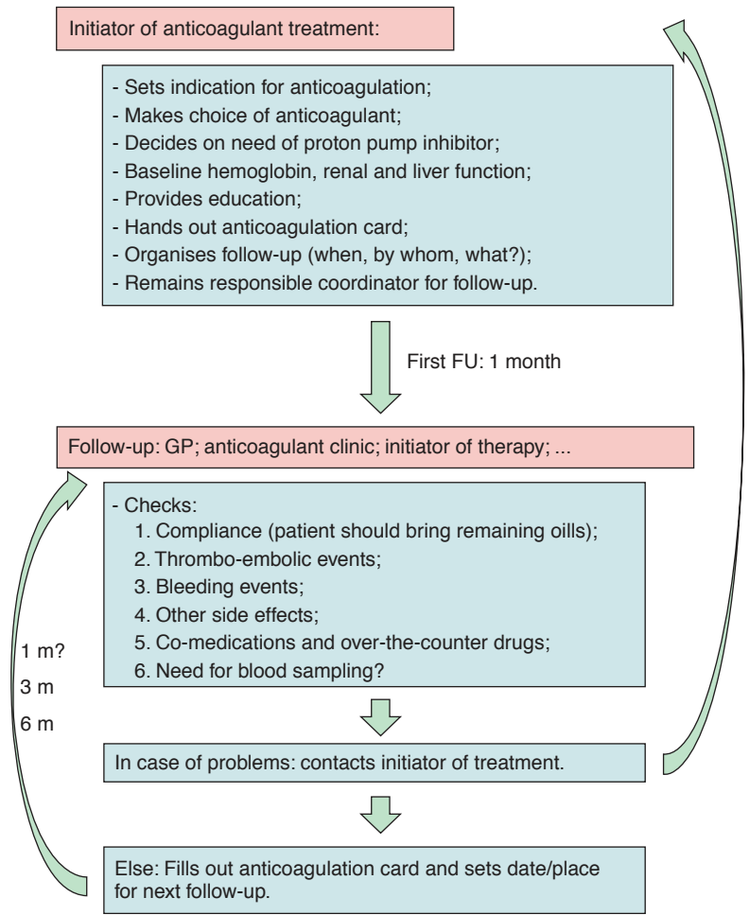

Figure 2 Structured follow-up of patients on NOACs. It is mandatory to ensure safe and effective drug intake. The anticoagulation card, as proposed in *Figure 1*, is intended to document each planned visit, each relevant observation or examination, and any medication change, so that every person following 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.

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 or 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[9]	16–24 h after ingestion
PT	Cannot be used	Cannot be used	Prolonged but no known relation with bleeding risk[5,9]	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: >2x ULN suggests excess bleeding risk	Cannot be used	Prolonged but no known relation with bleeding risk[9]	Cannot be used
dTT	At trough: >200 ng/ml or >65 s: excess bleeding risk	Cannot be used	Cannot be used[10]	Cannot be used
Anti-FXa chromogenic assays	Not applicable	No data yet	Quantitative;[10] 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

[a]No EMA approval yet. Needs update after finalization of SmPC.
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 normalized ratio; ULN, upper limit of normal.

HAS-BLED ≥3; see Section 8 and *Table 7*), its higher renal clearance makes it more vulnerable to acute regression of kidney function.

Minor bleeding is a particular problem in patients treated with any anticoagulant. It is best dealt with by standard methods to control bleeding, but should not lead readily to discontinuation or dose adjustment of therapy. Minor bleeding is not necessarily predictive of major bleeding risk. Most minor bleeding is temporary and is best classified as 'nuisance' in type. Obviously when such bleeding occurs frequently the patient's quality of life might be degraded and the specific therapy or dose of medication might

require review, but this should be undertaken very carefully to avoid depriving the patient of the very valuable thromboprophylactic effect of the 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 for the current registered indications. However, the quantitative assessment of the drug exposure and the anticoagulant effect may be needed in emergency situations, such as a serious bleeding and thrombotic events, need for urgent surgery, or in special clinical situations such as patients who present with renal or hepatic insufficiency, in case of potential drug–drug interactions or of suspected overdosing.

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 maximum effect of the NOAC on the clotting test will occur at its maximal plasma concentration, which is approximately 3 h after intake for each of these drugs. A coagulation assay obtained on a blood sample taken 3 h after the ingestion of the NOAC (at peak level) will demonstrate a much larger impact on the coagulation test than when performed at trough concentration, i.e. 12 or 24 h after ingestion of the same dose. Even a sample taken 6 h after drug intake will yield different results. Moreover, depending on the clinical profile of the patient, an estimation of the elimination half-life should be done: especially with dabigatran, this is dependent on the kidney function (see Section 8). The time delay between intake and blood sampling should therefore be carefully recorded when biological monitoring is performed.

The activated partial thromboplastin time (aPTT) may provide a qualitative assessment of the presence of dabigatran and the prothrombin time (PT) for rivaroxaban (and likely other factor Xa inhibitors), but these respective tests are not sensitive for the quantitative assessment of the NOAC. Quantitative tests for direct thrombin inhibitors (DTIs) and FXa inhibitors do exist, but they may not (yet) be routinely available in most hospitals. Point of care tests should not be used to assess the international normalized ratio (INR) in patients on NOACs.[11] An overview of the interpretation of all the coagulation tests for different NOACs can be found in *Table 3* and will be discussed in more detail below.

2.1 Direct thrombin inhibitor (dabigatran)

For dabigatran, the *aPTT* may provide a qualitative assessment of dabigatran level and activity. The relation between dabigatran and the aPTT is curvilinear (*Figure 3*).[12] Nevertheless, the sensitivity of the different aPTT reagents varies greatly. In patients receiving chronic therapy with dabigatran 150 mg twice daily (bid), the median peak aPTT was approximately two-fold that of control. Twelve hours after the last dose, the median aPTT was 1.5-fold that of control, with less than 10% of patients exhibiting two-fold increases. Therefore, 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.[12]

Dabigatran has little effect on the *PT and INR* at clinically relevant plasma concentrations, resulting in a very flat response curve. The INR is therefore unsuitable for the quantitative assessment of the anticoagulant activity of dabigatran.[12]

The *ecarin clotting time* (ECT) assay provides a direct measure of the activity of DTIs, but may not be readily available. When dabigatran is used, with twice daily dosing, ≥3 times elevated ECT at trough is associated with a higher risk of bleeding.[13]

The results of a diluted thrombin time (dTT) test can more accurately predict the coagulation state. However, thrombin time results depend on the coagulometer and the thrombin lot used. A dTT has been developed, with appropriate calibrators for interpretation in the context of dabigatran use (Hemoclot®). The dTT displays a direct linear relationship with dabigatran concentration. It is prolonged already at low concentrations of dabigatran. It is suitable for the quantitative assessment of dabigatran concentrations. A normal dTT measurement indicates no clinically relevant anticoagulant effect of dabigatran. When dabigatran is used with twice daily dosing, a dTT measured at trough (≥12 h after the previous dose) with the Hemoclot® of >200 ng/mL dabigatran plasma concentration (i.e. dTT approximately >65 s), is associated with an increased risk of bleeding.[13] It is important to note that there are no data on a cut-off dTT below which elective or urgent surgery is 'safe', and therefore its use in this respect cannot be recommended at this time (see also Sections 11 and 12).

2.2 Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)

The different Factor Xa-inhibitors affect the PT and the aPTT to a varying extent. The *aPTT* cannot be used for any meaningful evaluation of FXa inhibitory effect because of the weak

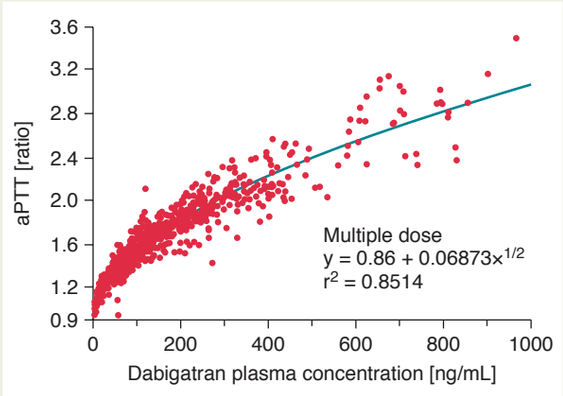

Figure 3 Curvilinear relation between aPTT and dabigatran plasma levels. From van Ryn *et al.*,[12] with permission.

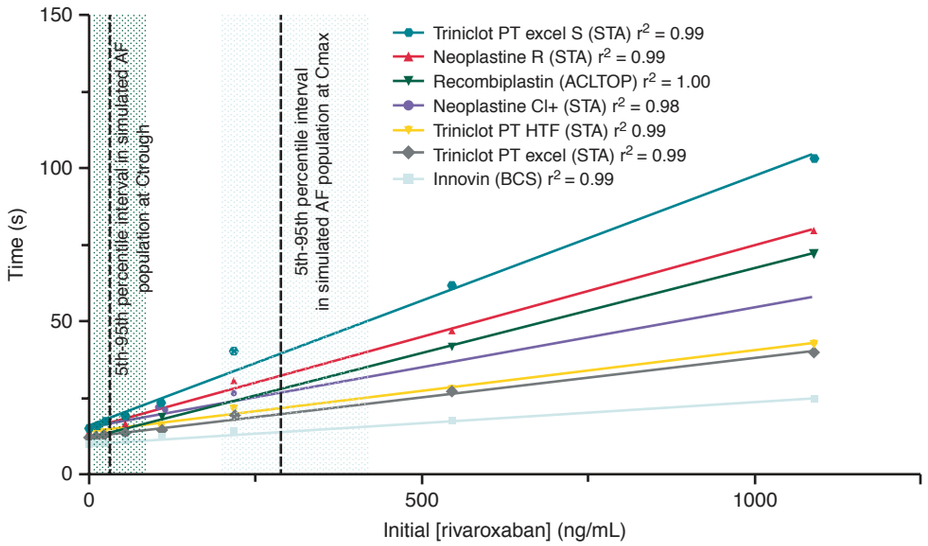

Figure 4 Relation between PT and FXa inhibitor (rivaroxaban) plasma levels. But the sensitivity is dependent on the reagent used. The figure shows data for rivaroxaban. The slopes will vary for other FXa inhibitors and reagents. Moreover, as in *Figure 3*, there is a high variation of measured values at different concentrations. It is clear that only qualitative information can be gained, without precise measurement of the anticoagulant effect. From Douxils *et al.*[15] with permission.

prolongation, variability of assays, and paradoxical response at low concentrations.[14]

Factor Xa-inhibitors demonstrate a concentration-dependent prolongation of the PT. Nevertheless the effect on the PT depends both on the assay and on the FXa inhibitor. For rivaroxaban, the PT may provide some quantitative information, even though the sensitivity of the different PT reagents varies greatly (*Figure 4*). If Neoplastin Plus or Neoplastin is used as thromboplastin reagent, the PT is influenced in a dose-dependent manner with a close correlation to plasma concentrations.[16] Neoplastin Plus is also more sensitive than Neoplastin.[14] Assay-specific calibrators and calibration curves can be made (*Figure 4*). There are currently no such data available for edoxaban and apixaban. Importantly, the INR (and certainly a point-of-care determined INR) is completely unreliable for the evaluation of FXa inhibitory activity.

Anti-FXa 'chromogenic assays' have been developed to assess plasma concentrations of the FXa-inhibitors using validated calibrators and are commercially available. Low and high plasma levels can be measured with acceptable inter-laboratory precision. However, there are currently no data that associate a coagulation parameter or a drug level at trough or at peak with bleeding risk or risk for thrombo-embolism.

2.3 Impact of new oral anticoagulants on coagulation system assessment

The NOACs interfere with routine coagulation tests, but also with thrombophilia tests or the measurement of coagulation factors. Abnormal coagulation tests should be interpreted with caution if the time window between blood sampling and NOAC intake is unknown. Therefore, a time window of at least 24 h is recommended between the last intake of a NOAC and blood sampling to assess coagulation parameters and this time window may be even longer for lupus anticoagulant measurements ($\geq$48 h).

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

Treatment with VKAs requires careful consideration of multifold food and drug interactions. Despite high expectations of less interactions with the NOAC drugs, physicians will have to consider pharmacokinetic effects of accompanying drugs and of comorbidities when prescribing NOACs. This section wants to provide a simple guide to deal with such situations. However, every patient may require more specific consideration, especially when a combination of interfering factors is present. Moreover, the knowledge base on interactions (with effect on plasma levels and/or on clinical effects of NOAC drugs) is expanding, so that new information may modify existing recommendations. Check the web site accompanying this text for the most up-to-date information (www.NOACforAF.eu).

The uptake, metabolization and elimination of the different NOACs are graphically depicted in *Figure 5* and summarized in *Table 4*. We believe that anyone involved in the treatment of patients with NOACs should have this information at hand. An important interaction mechanism for all NOACs except rivaroxaban consists of significant re-secretion over a P-glycoprotein (P-gp) transporter after absorption in the gut. Moreover, the P-gp transporter may also be involved in renal clearance (also for

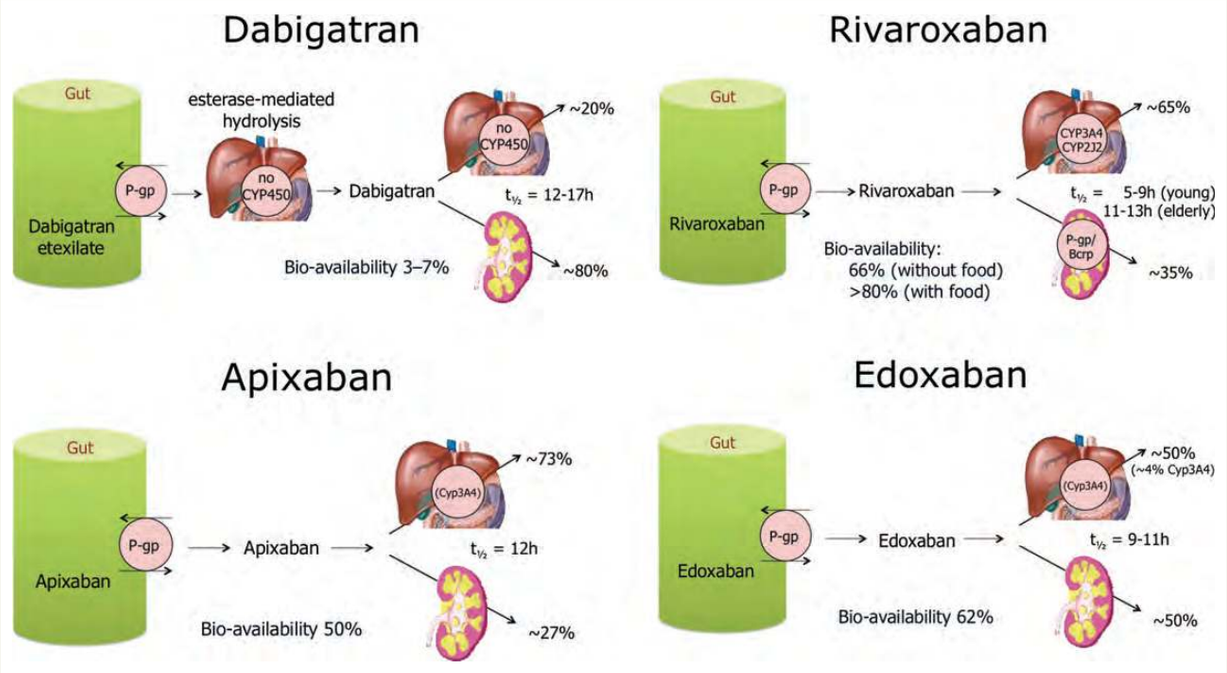

Figure 5 Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolisation and excretion. The brackets around (Cyp3A4) in the apixaban graph indicate a minor contribution of this pathway to hepatic clearance, the majority of the drug being excreted as unchanged parent. See also *Table 4* for the size of the interactions based on these schemes.

Table 4 Absorption and metabolism of the different NOACs

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Bio-availability	3–7%	50%	62%[17]	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%[18]	50%/50%[9]	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination; minor CYP3A4 contribution)[19]	Minimal (<4% of elimination)	Yes (elimination)
Absorption with food	No effect	No effect	6–22% more[20]	+39% more[21]
Intake with food recommended?	No	No	No official recommendation yet	Mandatory
Absorption with H2B/PPI	−12–30%[22–24]	No effect	No effect	No effect[21,25]
Asian ethnicity	+25%[24]	No effect	No effect[20]	No effect
GI tolerability	Dyspepsia 5–10%	No problem	No problem	No problem
Elimination half-life	12–17 h[23]	12 h	9–11 h[9]	5–9 h (young) 11–13 h (elderly)

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

rivaroxaban)[26]: competitive inhibition of this pathway therefore will result in increased plasma levels. Many drugs used in AF patients are P-gp substrates (e.g. verapamil, dronedarone, amiodarone, quinidine). CYP3A4 type cytochrome P450-dependent elimination is involved in rivaroxaban and apixaban hepatic clearance.[27] Strong CYP3A4 inhibition or induction may affect rivaroxaban plasma concentrations and effect, and should be evaluated in context (see below). Most of the hepatic clearance of apixaban is as unchanged molecule, with only a minority being metabolized (in part via CYP3A4), which makes CYP3A4 interactions of less importance for this drug.[19] Nevertheless, its SmPC indicates that apixaban should be used with caution if co-administered with strong inducers of both CYP3A4 and P-gp, and is contra-indicated in combination with strong inhibitors of both CYP3A4 and P-gp. It seems that for edoxaban, CYP3A4 is only weakly involved, but caution is still warranted until more definitive interaction data are available. The bio-availability of dabigatran is markedly lower than that of the other drugs (*Table 4*).[22] This means that slight fluctuations in absorption or elimination may have a greater impact on the plasma levels than with other drugs.

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.[1,4,28] 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, precluding the use of a given NOAC in combination (i.e. 'contraindication' or 'discouragement' for use); (2) 'orange' interactions, with 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 (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.

3.1 Food intake and antacids

Intake with food does not affect dabigatran absorption, which therefore can be taken irrespective of meals. Since food intake has an impact on the absorption and bioavailability of rivaroxaban (area under the curve plasma concentrations increase by 39%), the official recommendation is to take rivaroxaban with food (resulting in almost complete absorption and a very high bioavailability of almost 100%). There is no relevant food interaction for edoxaban,[20] nor for apixaban which may be taken with or without food. Absorption of dabigatran in the gastro-intestinal tract is dependent on an acid milieu, which is provided by the formulation of the drug. Concomitant use of PPIs and H2-blockers leads to a small reduced bioavailability but without effect on clinical efficacy.[22,23] Therefore, antacid intake does not constitute a contra-indication for dabigatran use.

3.2 Rate and rhythm control drugs

Rate-controlling and anti-arrhythmic drugs interact with P-gp, hence warranting caution for concomitant use of NOACs. The P-gp effects of verapamil are dependent on the formulation: when an immediate release preparation is taken within 2 h of dabigatran intake (mainly if before), plasma levels of dabigatran may increase up to 180%. Separating both drugs' intake $\geq$2 h removes the interaction (but is hard to guarantee safely in clinical practice). With a slow-release verapamil preparation, there may be a 60% increase in dabigatran dose. Observational data from the RE-LY trial showed an average 23% increase in dabigatran levels in patients taking (all sorts) of verapamil.[24] A similar interaction has been noted for edoxaban.[5] Therefore, for both drugs it is advised to reduce the NOAC dose when used in combination with verapamil ('orange'). Diltiazem has a lower inhibitory potency of P-gp, resulting in non-relevant interactions, although there is a 40% increase in plasma concentrations of apixaban ('yellow'; *Table 5*).[24] 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. Although amiodarone increases the dabigatran plasma levels slightly, there is no need for dose reduction of dabigatran when only amiodarone is interacting, although other factors should be evaluated ('yellow').

3.3 Other drugs

Table 5 lists the potential interaction mechanisms for other drugs, and their clinical relevance. Since some drugs are both inhibitors of CYP3A4 and of P-gp, they may have an effect on plasma levels although either the P-gp or CYP3A4 effect by itself is minimal. In general, although the NOACs are substrates of CYP enzymes or P-gp/BCRP (breast cancer resistance protein), they do not inhibit those. Therefore, they can be co-administered with substrates of CYP3A4 (e.g. midazolam), P-gp (e.g. digoxin), or both (e.g. atorvastatin) without concern of changing the plasma levels of these drugs.

3.4 Pharmacodynamic interactions

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 increases the bleeding risk. There are data indicating that the bleeding risk in association with antiplatelet agents increases by at least 60% (similar as in association with VKAs).[36–38] Therefore, such associations should be carefully balanced against the potential benefit in each clinical situation. Association of NOACs with dual antiplatelet drugs requires active measures to reduce time on triple therapy (see Section 13).

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.

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%[29]	No data yet	No effect[30]	No effect[27,31]
Digoxin	P-gp competition	No effect[32]	No data yet	No effect[30]	No effect[27,33]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12–180%[24] (reduce dose and take simultaneously)	No data yet	+53% (SR)[30] (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[24]	+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%[30] (reduce dose by 50%)[b]	+50%
Amiodarone	P-gp competition	+12–60%[24]	No data yet	No effect[30]	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%[27]
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[27]
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%[26,27]
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%[27]
Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	−66%[34]	−54%[SmPC]	−35%	Up to −50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	−12–30%[22–24]	No data yet	No effect	No effect[21,25]
Other factors					
Age ≥80 years	Increased plasma level	No data yet			
Age ≥75 years	Increased plasma level	No data yet			
Weight ≤60 kg	Increased plasma level				
Renal function	Increased plasma level	See Table 7			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

Red, contraindicated/not recommended.
Orange, reduce dose (from 150 mg bid to 110 mg bid for dabigatran; from 20 mg to 15 mg qd for rivaroxaban; from 5 mg bid to 2.5 mg bid for apixaban).
Yellow, consider dose reduction if another 'yellow' factor is present.
Hatching, no data available; recommendation based on pharmacokinetic considerations.
[a]No EMA approval yet. Needs update after finalization 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.

4.1 Vitamin K antagonist to new oral anticoagulant

The NOAC can immediately be initiated once the INR is lower than 2.0. If the INR is 2.0–2.5, NOACs can be started immediately or (better) the next day. For INR >2.5, the actual INR value and the half-life of the VKA need to be taken into account to estimate the time when the INR value will likely drop to below this threshold value: acenocoumarol $t_{\frac{1}{2}}$ 8–14 h, warfarin $t_{\frac{1}{2}}$ 36–42 h, phenprocoumon $t_{\frac{1}{2}}$ 6 days (120–200 h). At that time, a new INR measurement can be scheduled.

4.2 Parenteral anticoagulant to new oral anticoagulant

Intravenous unfractionated heparin (UFH): NOACs can be started once the intravenous UFH (half-life ±2 h) is discontinued. Care should be taken in patients with chronic kidney disease where the elimination of heparin may take longer.

Low molecular weight heparin (LMWH): NOACs can be initiated when the next dose of LMWH would have been foreseen.

4.3 New oral anticoagulant to vitamin K antagonist

Owing 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, similarly as when LMWHs are continued during VKA initiation. A loading dose is not recommended for acenocoumarol and warfarin, but is appropriate with phenprocoumon.

As 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).

4.4 New oral anticoagulant to parenteral anticoagulants

The parenteral anticoagulant (UFH, LMWH) can be initiated when the next dose of the NOAC is due.

4.5 New oral anticoagulant to new oral anticoagulant

The alternative NOAC can be initiated when the next dose is due, except in situations where higher-than therapeutic plasma concentrations are expected (e.g. in a patient with impaired renal function). In such situations, a longer interval may be foreseen, as discussed in *Tables 6* and *9*.

4.6 Aspirin or clopidogrel to new oral anticoagulant

The NOAC can be started immediately and aspirin or clopidogrel stopped, unless combination therapy is deemed necessary despite the increased bleeding risk of the association (see also Section 13).

5. 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 in 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 optimize compliance, which is known to be ≤80% for most drugs in daily practice. There are 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.

Practical considerations

(1) A once daily (qd) dosing regimen was related to greater adherence vs. bid regimen in cardiovascular patients,[39] and in AF patients (for diabetes and hypertension drugs).[40] 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; re-education 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.[7]

(5) Many technological aids are being explored to enhance compliance: the format of the blisters; medication boxes (conventional or with electronic verification of intake); smartphone applications, and/or SMS messages that alert the patient about the next intake; . . . Again, their long-term effects are unknown and one tool may not fit all patients. The prescribing physician, however, should consider individualization 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 (preferably with long half-life like phenprocoumon?) could be considered.

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 timing.

6.1 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.

6.2 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.

6.3 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.

6.4 Overdose

Depending on the amount of suspected overdose, hospitalization for monitoring or urgent measures should be advised. For further discussion, see Section 9.

7. Patients with chronic kidney disease

Chronic kidney disease (CKD) constitutes a risk factor for both thrombo-embolic events and bleeding in AF patients.[41,42] Recent findings suggest that a creatinine clearance of <60 ml/min may even be an independent predictor of stroke and systemic embolism.[43,44] Vitamin K antagonist therapy is associated with a significant reduction in the risk of stroke or thromboembolism 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.[41,45] Many patients with mild-to-moderate 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,[16] 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. The FDA (but not EMA) has approved a low dose of dabigatran (75 mg bid) for patients with severe renal insufficiency (CrCl 15–30 ml/min) based on pharmacokinetic simulations. However, 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 (*Table 7*).[2]

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, not any NOAC is approved for use in dialysis patients.

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).[46] 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.[42] 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*).[42]

(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.[3,47] Therefore, careful balancing of the clinical benefits and risks may justify its choice in stable patients. xAlso the FXa inhibitors are cleared for 25–50% by the kidney (*Table 4*). Dose reductions have been studied prospectively with apixaban (2.5 mg bid)[4] and rivaroxaban (15 mg qd),[46]

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[48]	No data	~8.6 h[49]	~8.5 h[50] (+44%)
CrCl 30–60 ml/min CKD Stage III	~18 h[48]	No data	~9.4 h[49]	~9 h (+52%)
CrCl 15–30 ml/min CKD Stage IV	~28 h[48]	No data	~16.9 h[49]	~9.5 h (+64%)
CrCl ≤15 ml/min CKD Stage V	No data	No data	No data	No data

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

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%[9]	35%
Bio-availability	3–7%	50%	62%[17]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	14%	37%[9]	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)[2] 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; qd, once daily; SmPC, summary of product characteristics.

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. Even the benefit of VKAs in haemodialysis patients is not unequivocally proven, however. Vitamin K deficiency secondary to malnutrition, frequent antibiotic use, and abnormal cholesterol metabolism may lead to fluctuations in responsiveness to VKAs. Therefore, a careful individualised risk/benefit for anticoagulation is warranted.

(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 *Figure 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)

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. This may occur when the patient has (intentionally) taken a too high 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 4) 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. Interestingly, as result of limited absorption, a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of ≥50 mg rivaroxaban.[51] There are no data in this respect concerning the other FXa inhibitors.

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 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. 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 Section 10 can be taken.

9. 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. Reversal of the effects 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 coagulation factors more rapidly restores coagulation. In case of NOACs, however, the plasma abundance of the drug may block newly administered coagulation factors as well. On the other hand, restoration of coagulation does not necessarily equal good clinical outcome, and 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, recommendations on bleeding management are not so much based on clinical experience, but rather reflect experts' opinions or laboratory endpoints.

9.1 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 *Figure 6* 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.[52] 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 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 $\leq 60 \times 10^9$/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.[12,53,54] Moreover, the risks of bleeding at puncture sites for dialysis needs to be balanced vs. the risk of waiting. In an open-label study in which a single 50 mg dose of dabigatran was administered to six patients with end-stage chronic kidney disease on maintenance haemodialysis, the mean fraction of drug removed by dialysis was 62% at 2 h and 68% at 4 h.[48] Whether enhanced removal of dabigatran from plasma is possible via haemoperfusion over a charcoal filter is under evaluation.[12] At this moment, the latter cannot be recommended in patients.

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.

Table 8 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 4 h)[48] 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.

9.2 Life-threatening bleeding

In mice, expansion of dabigatran-induced haematoma was prevented by administration of concentrates of coagulation factors II (VII), IX, and X (prothrombin complex concentrate, PCC, also called PPSB; some brand names are Cofact®, Confidex®, Octaplex®, and Beriplex®) in one study,[55] but not in another one.[56] In rabbits, Beriplex® inhibited dabigatran-induced bleeding in a rapid, dose-dependent manner.[57,58] The effect of an overdose of rivaroxaban could be reversed in a rabbit model by recombinant activated factor VII (rFVIIa) and PCC as assessed by laboratory anticoagulation parameters (aPTT and thrombelastographic clotting time), but did not reverse rivaroxaban induced-bleeding.[59] In healthy volunteers, administration of 50 U/kg of PCC completely reversed rivaroxaban-induced prolongation of the PT, but had no effect on dabigatran-induced prolongation of coagulation tests, in particular of thrombin time and ECTs.[60] Bleeding time was not evaluated in this study. Finally, *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.[61,62]

Based on these (scarce) 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),[63] the administration of PCC or aPCC can be considered in a patient with life-threatening bleeding if immediate haemostatic support is required. Awaiting more data on the clinical effectiveness of these strategies, the choice may depend on their availability and the experience of the treatment centre. 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 μg/kg) needs further evaluation.[53]

The use of other pro-coagulants 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.

We recommend consultation among cardiologists, haemostatis 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

10.1 When to stop the new oral anticoagulants?

Surgical interventions or invasive procedures that carry a bleeding risk require the temporary discontinuation of the NOAC. Trials have shown that about one quarter of patients that are in need for anticoagulant therapy require temporary cessation within 2 years.[64] 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, as indicated in *Table 9*. Bridging was proposed in AF patients with higher thrombo-embolic risk treated with VKAs,[1] but is not necessary in NOAC-treated patients since the predictable waning of the anticoagulation effect allows properly timed short-term cessation and reinitiation of NOAC therapy before and after surgery.[64] Also other societies have formulated advice on temporary cessation of NOAC therapy.[65]

Again, we recommend the development of an institutional guideline and a hospital-wide policy concerning peri-operative anticoagulation management in different surgical settings that is widely communicated and readily available.

When the intervention does carry 'no clinically important bleeding risk' and/or when adequate local haemostasis is possible, like some dental procedures or interventions for cataract or glaucoma, the procedure can be performed at trough concentration of the NOAC (i.e. 12 or 24 h after the last intake, depending on bid or qd dosing) but should not be performed at peak concentration. Nevertheless, 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. In any such cases, the patient can only leave the clinic when the bleeding has completely stopped, and be instructed about the normal postprocedural course and the measures to be taken in case of bleeding, i.e. to contact the physician or dentist in case of bleeding that does not stop spontaneously. The physician or dentist (or an informed colleague) has to be accessible in such case. For dental procedures, the patient could rinse the mouth gently with 10 ml of tranexamic acid 5%, four times a day for 5 days.

For procedures 'with a minor bleeding risk' (of which some have been listed in *Table 10*), it is recommended to discontinue NOACs 24 h before the elective procedure in patients with a normal kidney function (*Table 9*). In case of procedures that carry a 'risk for major bleeding',[66] it is recommended to take the last NOAC 48 h before.

In a patient taking rivaroxaban but with a CrCl of 15–30 ml/min, we recommend consideration of earlier interruption than 24 h, both for interventions with low and high risk for bleeding, i.e. $\geq$36 h respectively $\geq$48 h. When the SmPC of edoxaban will be finalized, specific advice for this NOAC will be formulated.

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 9*.

Procedures such as spinal anaesthesia, epidural anaesthesia, and lumbar puncture may require complete haemostatic function, and

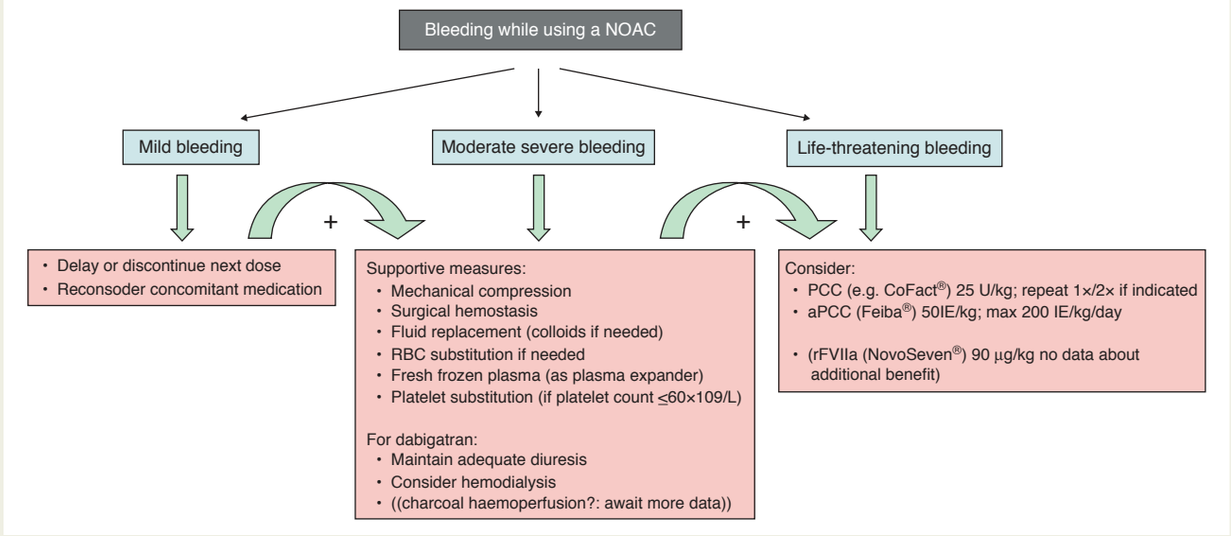

Figure 6 Management of bleeding in patients taking NOACs. Possible therapeutic measures in case of minor or severe bleeding in patients on NOAC therapy. Based on van Ryn *et al.*[12]

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.

fall under the 'high risk of bleeding' category. This writing group does not recommend the use of NOACs in the presence of neuraxial anaesthesia.

Although the aPTT and PT may provide a semi-quantitative assessment of dabigatran and FXa inhibitors, respectively (see Section 3), a strategy that includes normalization of the aPTT or PT prior to elective/urgent interventions has not been validated.

10.2 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. The same applies after atraumatic spinal/epidural anaesthesia or clean lumbar puncture (i.e. non-bloody tap).

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 LMWHs 6–8 h after surgery if haemostasis has been achieved, whereas therapeutic anticoagulation by restarting NOACs is deferred 48 to 72 h after the invasive procedure. Maximal anticoagulation effect of the NOACs will be achieved within 2 h of ingestion. 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.

10.3 Special considerations concerning atrial fibrillation ablation procedures

For atrial fibrillation patients undergoing pulmonary vein isolation, there is some emerging information available on the use of dabigatran. There are no published data on the peri-interventional use of FXa inhibitors undergoing catheter ablation. One multicentre,

Table 10 Classification of elective surgical interventions according to bleeding risk

Interventions not necessarily requiring discontinuation of anticoagulation
Dental interventions
Extraction of 1 to 3 teeth
Paradontal surgery
Incision of abscess
Implant positioning
Ophthalmology
Cataract or glaucoma intervention
Endoscopy without surgery
Superficial surgery (e.g. abscess incision; small dermatologic excisions; . . .)
Interventions with low bleeding risk
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single transseptal puncture)
Angiography
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
Interventions with high bleeding risk
Complex left-sided ablation (pulmonary vein isolation; VT ablation)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy

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

observational study in 290 patients demonstrated that a strategy of (by the manufacturer discouraged) uninterrupted administration of dabigatran 150 mg bid except for the dose in the morning of the procedure (irrespective also of renal function), ACT-guided heparinisation during the procedure, and dabigatran reinitiation 0–3 h after sheath removal, numerically increased the risk of both bleeding and thromboembolic complications compared with uninterrupted VKA therapy (INR 2.0–3.5).[67] Two other studies with a similar protocol and 150 mg bid, respectively, 110 mg bid (in Japanese patients), but resumption in the evening of the ablation, did, however, not show any difference in bleeding or thrombo-embolic complications.[68,69] Moreover, another study that discontinued dabigatran earlier (36 h if normal kidney function), administered enoxaparin 0.5 mg/kg immediately after ablation and after 12 h, and reinitiated dabigatran 22 h after the ablation, did also not find any bleeding or thromboembolic event in 123 patients.[70] Also another large case-control study showed that when dabigatran was stopped ≥24 h before ablation and resumed 4h after it, this strategy was as safe and effective as uninterrupted warfarin.[71] Therefore, with the available data, if a strategy of bridging and restarting of anticoagulation is chosen and appropriately executed, NOACs seem to allow such, whereas a too aggressively shortened periprocedural 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. Recent data from RE-LY have shown that urgent surgery was associated with much higher rates of bleeding than elective procedures, but the bleeding rate in dabigatran patients was not higher (and even tended to be lower) than in VKA-treated patients (although it is not known in how many patients actions had been undertaken to optimize coagulation).[64] Evaluation of common coagulation tests (aPTT for DTI; sensitive PT for FXa inhibitors) or of specific coagulation test (dTT for DTI; chromogenic assays for FXa inhitibors) can be considered if there is concern about the pharmacokinetic waning of the anticoagulant effect (e.g. renal insufficiency and/or concomitant conditions as in *Table 4*; see also Section 3). Nevertheless, such strategy has never been evaluated, and therefore cannot be recommended and should not be used routinely. If surgery cannot be delayed, the risk of bleeding will be increased and should be weighed against the urgency of the intervention.

12. Patient with atrial fibrillation and coronary artery disease

The combination of atrial fibrillation and coronary heart disease not only is a common clinical setting, it is also a complex situation on how to deal with anticoagulation and antiplatelet therapy, and it is associated with significantly higher mortality rates.[72] Unfortunately, there are not sufficient data available to optimally guide clinical practice in such settings. Moreover, new antiplatelet agents have entered the market for acute coronary syndromes (ACSs), 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. For background information and key scientific data that form the basis of the guidance spelled out here, see below.

12.1 *Key 'scientific' data on the use of NOAC in ACS plus AF*

- Atrial fibrillation complicating an ST-elevation (STE) or non-ST-elevation (NSTE) ACS and vice versa is relatively frequent, and is associated with significantly higher mortality rates.[72–74] AF patients with ACS receive less evidence-based therapies or procedures, and antithrombotic cocktails vary considerably. Thrombotic vs. bleeding risk in observational or post hoc studies is heavily influenced by comorbidities, perception, local/regional practices, and other confounding factors.
- Measures to reduce the bleeding risk in patients with ACS should be retained: low doses of aspirin (75–100 mg), especially when combined with a P2Y12 inhibitor; bare-metal stents (minimizing the duration of triple therapy); and a radial approach for interventional procedures (reducing at least the risk of access site bleeding).
- VKA treatment is protective after an ACS.[75] Warfarin plus aspirin (ASA) reduces the risk of recurrent ischaemic events after an ACS, compared to ASA alone. In patients at low-to-intermediate bleeding risk, the benefit of combination of warfarin and ASA appears to exceed the risk. In WARIS-2, well-controlled warfarin with an INR between 2.8 and 4.2 alone also reduced the risk of recurrent events, and was associated with a lower bleeding risk than VKAs + ASA (with an INR between 2 and 2.5).[76] Low intensity VKA (or poor INR control) does not appear to be protective.[77–79]
- Registry data indicate a high risk of major bleeding with triple therapy.[80,81] To date, only one trial, WOEST, randomized patients requiring chronic anticoagulation and undergoing percutaneous coronary intervention (PCI) to triple therapy (i.e aspirin, clopidogrel and VKA) or dual therapy (clopidgrel plus VKA) (presented at ESC Meeting 2012, unpublished).[82] Almost 70% received OAC because of AF. WOEST demonstrated that triple therapy doubles the risk of bleeding complications compared with a single antiplatelet agent (clopidogrel) plus VKA. Importantly, clopidogrel plus VKA was associated with a significantly lower mortality rate, the mechanism of which remains elusive. Of note, no data are available on how single antiplatelet therapy with ASA + VKA would have performed. A recent nationwide Danish registry studied antithrombotic combinations in myocardial infarction patients with AF.[83] Both triple therapy and VKA plus a single antiplatelet (SAPT) agent significantly increased the risk of bleeding in these patients, compared to dual antiplatelet therapy or VKA in monotherapy; the excess risk was especially high during the first three months, but persisted throughout one year. There was a slightly higher bleeding risk with clopidogrel + OAC than with ASA + OAC, as also prior data had indicated.[80] As

in WOEST, triple therapy carried a significantly higher risk of bleeding than VKA plus SAPT, without any benefit in terms of ischaemic events (death, myocardial infarction or stroke). These (partly unpublished) data indicate that triple therapy should be kept as short as possible or might even be unnecessary, and that long-term single antiplatelet and VKA treatment might be sufficient for many patients. Whether that single antiplatelet should be ASA or clopidogrel remains unclear.

- Triple therapy with dual antiplatelet therapy (DAPT) and NOACs at least doubles the risk of major bleeding after an ACS.[37,38,83]
- In a post hoc substudy of the ReLy trial (with dabigatran) association of single and dual antiplatelet drug increased bleeding risk by about 60% and 130% respectively.[36] As there are no comparative studies, it is unknown whether SAPT/DAPT plus VKA is safer in post-ACS patients than SAPT/DAPT + NOAC or vice versa. There was no interaction with (dual) antiplatelet therapy on both efficacy and bleeding in the AF trials with NOAC except for the higher dose of dabigatran for which the thromboembolic benefit compared to warfarin was attenuated in combination with antiplatelets (hazard ratio = 0.80 compared to 0.52, *P* for interaction = 0.058).[36] Therefore, it might be assumed that the respective advantages of the NOAC over VKA are maintained in dual or triple therapy. In addition, there was also no interaction between SAPT vs. DAPT in the ACS trials with the NOACs apixaban and rivaroxaban.
- In addition, several new antiplatelets and anticoagulants have recently been shown to be beneficial when separately evaluated for either ACS or AF.[84,85] However, there are no clinical studies on combinations of these new antiplatelets and VKAs or NOACs, nor are there trials assessing these agents in patients with both (recent) ACS and AF.
- Dabigatran has not been evaluated in a phase III study of patients with recent ACS. In a meta-analysis of dabigatran trials, there was a significantly higher rate of myocardial infarctions with dabigatran vs. VKA (odds ratio 1.33, 95% confidence interval 1.03–1.71, $P = 0.03$), although the absolute excess was very low (about 3 per 1000 patients).[86] However, the net clinical benefit of dabigatran over VKA was maintained in AF patients with a previous myocardial infarction (MI), and the relative effects of dabigatran vs. VKA on myocardial ischaemic events were consistent in patients with or without a previous MI or coronary artery disease (CAD).[87] No excess of MI was observed in the AF trials assessing the new FXa inhibitors.
- After ACS, DAPT on top of apixaban at a dose proven to be protective in AF significantly increases major and fatal bleeding risk including intracranial haemorrhage (ICH), without clear evidence of reduction in ischaemic events including stroke.[38]
- Low-dose rivaroxaban on top of DAPT significantly improves ischaemic outcome after ACS, but is also associated with increased major and intracranial bleeding risk.[37] It is unknown whether this rivaroxaban dose reduces the stroke risk associated with AF. The risk of stroke was not reduced with low-dose rivaroxaban on top of DAPT in mainly non-AF ACS patients. However, low-dose rivaroxaban is currently not available (or labelled as such) and kept out of the equation of this document. A study in stable AF patients undergoing PCI is on its way.
- A PCI seems safe in VKA-treated patients, without bridging and without additional periprocedural heparin.[88] It is unknown if this applies also to NOACs, since all clinical studies have suggested interruption of NOAC therapy at PCI. The increased risk of catheter thrombosis with fondaparinux in OASIS-5/6,[89,90] could indicate that periprocedural solitary FXa inhibition with oral FXa inhibitors might be insufficient as well.

12.2 Scenario 1: Acute coronary syndrome management in atrial fibrillation patients on new oral anticoagulants

In contrast with VKAs, NOACs have a relatively short half-life. This implies that it is important to know the last intake of these drugs. Whereas guidelines recommend to maintain VKA patients on their treatment, also during percutaneous interventions like for an ACS, NOACs should preferably be temporarily discontinued upon presentation with ACS, as has been recommended during the phase 3 AF trials. Temporary discontinuation of the short-acting NOACs allows safe initiation of the newer P2Y12 inhibitors like ticagrelor and prasugrel which have shown superiority over clopidogrel in ACS situations, but for whom the bleeding risk in association with NOACs is not known. In the absence of contraindications, all ACS patients should receive low-dose aspirin immediately at admission (150–300 mg loading dose) as well as a P2Y12 inhibitor (*Table 11*). As clopidogrel takes considerable time to achieve its maximal antiplatelet effect in unstable patients, routine clopidogrel without aspirin cannot be recommended if an invasive management is planned. In frail patients at high bleeding risk, aspirin only might be a safer initial therapy awaiting invasive management, when indicated.

Risk scores for ischaemic and bleeding events, as recommended by the ESC NSTE-ACS guidelines,[91] may guide in choosing between diverse therapeutic options to optimize the balance between bleeding vs. thrombotic risk. It is important to stress that combining antiplatelet with anticoagulant agents significantly increases the risk of major bleeding, with single and even more with dual antiplatelet agents. Reducing the time exposed to dual therapy, and for some patients also to triple therapy, needs to drive the physician's choice between the myriad of possible combinations both in the acute phase and for long-term therapy (see below). A combination chosen at the time of discharge might not necessarily be required to be continued indefinitely: a prespecified planned downgrade schedule of antithrombotic agents will reduce the longer-term risk of bleeding while protecting against coronary events.

12.2.1 Acute management

12.2.1.1 ST-elevation myocardial infarction

In case of an ST-elevation myocardial infarction, primary PCI via a radial approach is strongly recommended over fibrinolysis. It is recommended to use additional parenteral anticoagulation, regardless of the timing of the last dose of NOAC. Given its short-lasting action and lower bleeding risk, bivalirudin during the procedure, and discontinued immediately after the primary PCI, might be preferred over UFH or enoxaparin. Unless for bail-out situations, glycoprotein IIb/IIIa inhibitors should generally be avoided.

Table 11 Recommendations concerning management of AF patients on NOACs who present with an acute coronary syndrome

1. Temporarily discontinue NOAC on presentation
2. Immediately initiate DAPT on presentation unless in frail patients with a high bleeding risk (only aspirin; delay DAPT until complete waning of the anticoagulative effect of NOAC). Unless for patients allergic to aspirin, monotherapy with clopidogrel is not recommended in the acute setting
3. Low dose of aspirin (150–300 mg loading; 75–100 mg/d later), preferably combined with an ADP receptor inhibitor (ticagrelor or prasugrel preferred over clopidogrel)
4. After waning of the anticoagulative effect of NOAC, parenteral anticoagulation should be initiated. Fondaparinux is preferred in NSTE-ACS because of its lower bleeding risk
5. In case of an STEMI, primary PCI is strongly recommended over fibrinolysis
   (a) If fibrinolysis is the only available reperfusion therapy: avoid UFH or enoxaparin until the NOAC effect has disappeared
6. In case of NSTE-ACS:
   (a) If not urgent, delay coronary angiography until complete waning of NOAC effect
   (b) Periprocedural anticoagulation per local practice (preferably UFH or bivalirudin)
7. In case of PCI:
   (a) A radial approach is preferred as it reduces at least the risk of access site bleeding
   (b) If possible and indicated, a balloon angioplasty without stenting significantly reduces the need for (prolonged) triple therapy
   (c) Bare-metal stents minimize the duration of dual or triple therapy and are generally preferred
   (d) Use additional parenteral anticoagulation, regardless of the timing of the last dose of NOAC
   (e) Because of its short half-time and reduced bleeding risk, periprocedural bivalirudin is preferred. Discontinue immediately after PCI
   (f) Avoid glycoprotein IIb/IIIa inhibitors unless for bail-out situations.
8. In patients requiring (extensive) revascularization, bypass surgery might be preferred to avoid prolonged triple therapy
9. When restarting NOAC consider dose reduction according to bleeding and atherothrombotic risk and aim at shortest necessary duration of dual or triple therapy
10. The newer platelet inhibitors prasugrel and ticagrelor have not been evaluated with OAC or NOAC. It may be prudent to await further data before combining these platelet inhibitors and NOAC

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

If fibrinolysis is the only available reperfusion therapy, it may be considered if the patient presents with dTT, ECT, aPTT (for DTI), or PT (for FXa inhibitors) not exceeding the upper limit of normal. Additional UFH or enoxaparin should be avoided until the NOAC effect has disappeared (12 h or longer after last intake; see Section 11).

12.2.1.2 Non-ST-elevation myocardial infarction (NSTE-ACS)

After discontinuing the NOAC and waning of its effect (12 h or longer after last intake; see Section 11), fondaparinux (preferred), UFH, or enoxaparin can be initiated. Upstream use of glycoprotein IIb/IIIa inhibitors should be avoided in this setting.

12.2.1.3 Percutaneous coronary intervention in non-ST-elevation-acute coronary syndromes

To reduce the risk of access site bleeding, a radial approach is preferred. If possible, bare-metal stents (BMSs) are preferred above drug-eluting stents (DES) to shorten exposure to dual or triple therapy. Sole balloon angioplasty, or bypass surgery, might also be valid options to reduce the need for long-term dual or triple therapy.

If a coronary angiography is not urgent, the NOAC should be discontinued before patients are taken to the cath lab and the NOAC effect should have disappeared (24 h or longer after last intake; see Section 11). Periprocedural anticoagulation should be used per local practice. Unfractionated heparin (70 IU/kg) or bivalirudin rather than enoxaparin is preferred. Unfractionated heparin should be administered to target ACT or aPTT levels per standard clinical practice. Bivalirudin might be a safer alternative for high-risk patients.

In more urgent situations, assessment of the NOAC effect may be considered (see Section 3) to guide the antithrombotic periprocedural management. However, because of uncertainty about the interpretation of routine coagulation tests in the setting of NOAC use and the fact that their results depends on the timing of the last dose (and the patient's renal function), such an approach is probably of limited value in daily practice and it cannot be recommended at this time.

12.2.1.4 Resumption of anticoagulation

In stabilized patients (i.e. no recurrent ischaemia or need for other invasive treatment), anticoagulation can be restarted after parenteral anticoagulation is safely stopped. It is reasonable to restart the same NOAC in patients who had an indication for a NOAC over VKA. There are insufficient data to recommend switching to one particular NOAC over others because of a recent ACS. As at least one antiplatelet agent is required, choosing a lower dose of NOAC should be considered and might be a safer option (see below).

12.2.2 Chronic setting (from discharge to 1 year after acute coronary syndrome)

Combining single or dual antiplatelet therapy with chronic anticoagulation (NOAC as well as VKA) significantly increases bleeding risk, regardless of any of the large variety of possible combinations. There is no ideal combination fitting every patient. The type and level of anticoagulation as well as single vs. dual antiplatelet therapy and its duration need to be highly personalized, based on atherothrombotic risk, cardioembolic risk, and bleeding risk.[92] It is highly recommended to formally assess risk using validated tools such as the GRACE,[93] CHA_2DS_2-VASc, and HAS-BLED scores.[1,2]

ACS guidelines recommend dual antiplatelet therapy during 1 year after the acute event.[91,94] However, in a cohort study (i.e. prone to confounding factors) on 11 480 patients with AF and admitted with MI or for PCI, dual antiplatelet therapy on top of VKA dramatically increases the risk of bleeding compared with a single

antiplatelet agent plus VKA, without reducing the risk of ischaemic events.[81] Taken together with results from the WOEST trial randomizing patients requiring chronic anticoagulation and undergoing PCI to triple therapy (i.e. aspirin, clopidogrel, and VKA) or to dual therapy (clopidogrel plus VKA), clopidogrel plus VKA appears to be the most sensible combination early after PCI in AF patients. The period of additional antiplatelet therapy should be kept as short as possible (i.e. unless the residual ischaemic risk is considered to be very high), e.g. 1 month for a bare metal stent to 3 (or even 6) months for DES (depending on the type of stent) after PCI. After that monotherapy with VKA/NOAC could be considered in some patients with low-to-intermediate atherothrombotic risk and moderate-to-high bleeding risk. If antiplatelet therapy is deemed to be necessary throughout 1 year after the acute event, a lower dose of NOAC might be a safer option, especially in those with a HAS-BLED score of $\geq$3. There might even be a preference for VKAs, with an INR target around 2–2.5, especially in the (very) elderly and patients with impaired renal function. For patients requiring ticagrelor or prasugrel, even more caution is necessary when adding either VKAs or NOACs. Before new data become available, it may be prudent to avoid NOACs in such patients.

For the therapy beyond the first year, we refer to Scenario 3 below.

12.3. Scenario 2: Management of the patient with a recent acute coronary syndrome (<1 year) who develops new-onset atrial fibrillation

Acute coronary syndrome guidelines recommend dual antiplatelet therapy for up to 1 year after the acute event. If AF develops during this time window, and there is an indication for thromboembolic prevention with anticoagulation, the question on starting/adding VKAs or NOACs emerges. In patients with low atherothrombotic risk, VKAs in monotherapy could be considered after 1–3 months (or 6 months in case of recent DES), especially when their bleeding risk is elevated (HAS-BLED $\geq$3). A protective atherothrombotic effect of NOACs in monotherapy (i.e. without antiplatelet agents) needs to be proven. In contrast, in patients with a high GRACE risk score (e.g. >118, corresponding to >8% post-discharge mortality rate at 6 months), additional clopidogrel might be warranted in the first 6–12 months after the acute event. Temporary dual antiplatelet therapy without additional anticoagulation might also be a safe and effective alternative for patients with a low CHA_2DS_2-VASc (i.e. $\leq$1), especially in those with a high residual risk for recurrent ACS (i.e. GRACE risk score >118) (*Table 12*).

If a NOAC would be indicated, a FXa inhibitor could be preferred in view of the small albeit insignificant increase in the risk of MI with dabigatran. Nevertheless, the net clinical benefit of dabigatran over VKAs was also maintained in patients with prior MI.[87] There are no direct comparative data between DTI and FXa inhibitors in this setting. A low dose of rivaroxaban (2.5 mg BID or 5 mg BID) decreases ischaemic events in ACS patients on DAPT (albeit with an increase in bleeding), but its protective effect against AF-related stroke by this dose remains to be determined.[37] Therefore, such policy certainly cannot be defended in AF patients with higher thromboembolic risk, awaiting dedicated studies addressing this combination.

12.4 Scenario 3: A stable coronary artery disease patient (acute coronary syndrome $\geq$1 year ago; elective bare-metal stent $\geq$1 month; drug-eluting stent $\geq$6 months) develops atrial fibrillation

Stable CAD patients developing AF should receive anticoagulation, depending on their CHA_2DS_2-VASc score. Since VKAs alone are superior to aspirin post-ACS, and VKAs + ASA may not be more protective but associated with excess bleeding (see above), anticoagulation with VKAs without additional antiplatelet agents is considered sufficient for most AF patients with stable CAD (*Table 13*).[91]

Are the NOACs safe and effective alternatives in such patients? About 15–20% of patients in the three Phase 3 NOAC AF trials had a prior MI. No interaction in terms of outcome or safety was observed between patients with or without a prior MI, although it is unclear in how many patients antiplatelet therapy was maintained and for how long. It is likely that the advantages of NOACs (in monotherapy) over VKAs are preserved in CAD patients with AF. Even for dabigatran, which is associated with a modest but non-significant higher risk of MI, the net clinical benefit was maintained.[87] Moreover, other myocardial ischaemic events were not increased. Since direct comparative data are lacking, there is no strong argument for choosing one NOAC over another in this setting. Nevertheless, in patients on dabigatran

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

1. In patients with low or moderate atherothrombotic risk (GRACE risk <118), VKAs in monotherapy could be considered after 1–3 months (or 6 months in case of DES), especially when the bleeding risk is elevated (HAS-BLED $\geq$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 CHA_2DS_2-VASc score (i.e. $\leq$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 13 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.

with low bleeding risk and high atherothrombotic risk, one might consider adding low-dose aspirin in patients, accepting that this will increase the bleeding risk by approximately 60%.[36]

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 be given for at least 3 weeks prior to cardioversion, or transoesophageal echocardiography (TEE) 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 trial in a large cohort of patients have shown a comparatively low stroke rate related to cardioversion in patients treated with dabigatran and VKAs. The stroke rate was comparable to that in prior trials with other forms of anticoagulation, with our without TEE guidance. However, more dabigatran patients underwent prior TEE and there was a slight, but not statistically significant higher left atrial thrombus prevalence in dabigatran patients.[95] So far, data for the use of oral FXa inhibitors undergoing cardioversion is only published in abstract form. Analysis of data from the ARISTOTLE trial showed that patients undergoing cardioversions under apixaban ($n = 286$) or warfarin ($n = 291$) had no thromboembolic events within the first 90 days.[96] Likewise, there was no difference in the ROCKET-AF trial in the number of strokes or systemic embolisms ($n = 3$ in the warfarin group and $n = 3$ in the rivaroxaban group) over a median follow up of 2.1 years in patients who underwent electrical cardioversion ($n = 143$), pharmacological cardioversion ($n = 142$), or catheter ablation of atrial fibrillation ($n = 79$).[97]

As there is no coagulation assay available for any NOAC 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. We urge for the creation of good prospective registries or even randomized trials on this topic, which is important to facilitate patient management in the future.

14. Patients presenting with acute stroke while on new oral anticoagulants

14.1 The acute phase

14.1.1 Patients with acute haemorrhagic stroke

Patients undergoing treatment with VKAs constitute 12–14% of patients with ICH.[98] Guidelines for the treatment of intracerebral haemorrhage under oral anticoagulants are limited to strategies for reversal of VKAs.[99] 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) ongoing life-threatening bleeding such as ICH, should be corrected as rapidly as possible. As there is no specific antidote for NOACs at this moment, the first treatment strategy is discontinuation of the drug and supportive therapy. The limited data on the use of specific procoagulants such as PCC, aPCC, and aFVII for severe bleeding associated with NOACs are discussed in Section 10. The efficacy and safety of this strategy applied for ICH needs to be further evaluated in clinical studies.[55] In essence, the situation is not different to the one of VKA-treated patients with spontaneous brain haemorrhage. In VKA-treated patients, vitamin K itself is considered an antidote, but works too slowly to influence the brain haemorrhage expansion. Therefore, PCC or fresh frozen plasma is recommended instead. In Re-Ly, patients with intracranial bleeds on warfarin (the majority of whom were treated with vitamin K) had the same poor prognosis as patients on dabigatran (without an antidote).[100]

In situations without evidence for ongoing bleeding, an expectant management can be applied, given the short half-life of NOACs. If rapid normalization is not expected, the steps outlined in Sections 9 and 10 can be taken.

14.1.2 Patients with acute ischaemic stroke

According to current guidelines and official labelling, thrombolytic therapy with recombinant tissue plasminogen activator (rtPA), which is approved within a 4.5 h time window from onset of stroke symptoms, is not recommended in patients under therapy with anticoagulants. As plasma half-life of NOACs ranges 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 case of uncertainty concerning last NOAC administration, a prolonged aPTT (for dabigatran) or PT (for Fxa inhibitors) indicates that the patient is anticoagulated (see Section 3) and thrombolysis should not be administered. Until there are reliable and sensitive rapid (point-of-care) tests for the individual NOAC, we would discourage the use of thrombolytics in situations with uncertainty about the anticoagulaton

status. Therefore, we believe that only in exceptional single cases in which reliable coagulation assessment (with specific tests, see Section 3) 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 appropriate coagulation tests are not available or abnormal, mechanical recanalization of occluded vessels may be considered as an alternative treatment option. So far, no prospective data exist in this regard.

14.2 Management of the post-acute phase

14.2.1 Haemorrhagic stroke

As mentioned above, trial-based guidelines regarding NOACs in intracerebral haemorrhage are missing. By analogy to the use of VKAs, 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. For patients with low cardioembolic risk and high bleeding risk, the indication for oral anticoagulation should be reconsidered. This is the theory. In practice, however, the same factors that are predictive for embolic stroke (age, hypertension, previous stroke, and others) are also predictive for haemorrhages. We should not forget that 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. This is especially true after an intracerebral bleeding in a patient with amyloid angiopathy.

It will always be a very difficult individual decision making whether to reconstitute anticoagulation of any type in patients who have experienced an anticoagulation related intracerebral haemorrhage. This is also true for extracerebral, intracranial haemorrhages such as subdural or epidural haemorrhages, both spontaneous or traumatic. Non-pharmacological prevention strategies such as ablation or occlusion of the atrial appendage should be considered as potential (and likely only partial) substitutes for the contra-indicated resumption of long-term anticoagulation.[1,2]

14.2.2 Ischaemic stroke

Continuation of NOACs after ischaemic stroke depends on the infarct size. If the infarct size is not expected to relevantly increase the risk of early secondary intracerebral bleeding, administration of NOACs should be continued by analogy to VKAs. 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.

14.2.3 Patients with transient ischaemic attack of cardioembolic origin

In this case, anticoagulation treatment with NOACs can be started as soon as possible. Regarding the fast onset of action, bridging with LMWH is generally not required. Aspirin is no alternative option: in AF patients considered not suitable for VKA thromboembolic preventive treatment, the FXa inhibitor apixaban was shown to be superior to aspirin in stroke prevention.[4]

14.2.4 Patients with ischaemic stroke of cardioembolic origin

Guidelines for initiation of anticoagulation after ischaemic stroke do not yet consider NOACs. By analogy to recommendations for VKAs, initiation of anticoagulation after ischaemic stroke depends on infarct size and risk of new embolic stokes. If NOACs are used instead of VKAs, quicker onset of action should be considered and bridging with heparins is not required. Aspirin has no place in secondary stroke prevention.[1,2]

14.2.5 Patients with atrial fibrillation and significant carotid stenosis

In these patients carotid endarterectomy and not stenting is recommended to avoid triple therapy which is associated with considerably increased bleeding, as discussed in Section 13.

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

Many cancers occur in elderly patients, similar to atrial fibrillation. Unlike for prevention of venous thromboembolism, there are very little controlled data for antithrombotic therapy in AF patients with malignancy. Active malignancy usually was an exclusion criterion in NOAC trials (also in the VTE trials), and although there were a few patients with cancer in the phase 3 AF trials, the absence of type and stage of cancer information precluded any subgroup analysis. 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 thromboembolic risk and bleeding risk.

15.1 Patients with malignancies are at increased risk for thromboembolic events

Many forms of cancer interact directly or indirectly with the coagulation system. Some tumours directly secrete prothrombotic factors, while others induce inflammatory reactions either through humoral or direct interaction with the immune system. The increased risk for thromboembolism justifies consideration of established anticoagulant therapy.

15.2 Cancer therapy inflicts bleeding risks

Every form of cancer therapy, be it surgery, irradiation, or chemotherapy, may induce a bleeding through local wounds (surgery), tissue damage (irradiation), or systemic antiproliferative effects which will reduce platelet count and function (chemotherapy, some forms of irradiation).[101] Moreover, many malignancies are associated with increased risk of mucosal bleeding, e.g. bronchial

carcinoma, urogenital cancers, gastro-intestinal cancers, head, and neck cancers. The main bleeding risk induced by most chemotherapy is mediated by the myelosuppressive effect of the therapy, which is monitored by platelet counts. Marked myelosuppressive effects are usually defined as leucopoenia $<1000 \times 10^9$/L and platelet counts $<50 \times 10^9$/L. Some chemotherapy may directly interact with platelet function or the coagulation cascade. These may need to be avoided. Furthermore, myelosuppression reduces red blood cells and thereby reduces the safety margin in case of a bleeding event. The degree of myelosuppression varies markedly between therapies, from mild to prolonged periods of almost complete aplasia. Oncologists can best estimate the coagulation side effects of a specific planned therapy. Nevertheless, much is still unknown about drug–drug interactions between NOACs and specific chemotherapeutic agents, urging some caution.

15.3 Practical suggestions

(1) Patients with malignancies and AF require multidisciplinary care by cardiologists and oncologists including a careful planning of antithrombotic therapy.
(2) 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, and reversal options.
(3) The presence of a malignancy in patients with AF increases stroke risk. Established anticoagulant therapy should therefore be continued, including NOAC therapy, whenever possible.
(4) Based on data in patients with venous embolism, NOAC therapy at AF dosing regimens will also prevent venous embolism. Hence, no additional anticoagulant therapy is needed (such as low molecular heparins) in case a NOAC is used.
(5) In many patients with malignancies who receive moderately myelosuppressive therapies, continuation of NOACs may be defendable.
(6) In patients with malignancy and NOAC therapy who have to undergo tumour surgery, the same principles apply as in other patients undergoing elective surgery (see Section 12).
(7) Patients undergoing radiation therapy or chemotherapy without a marked myelosuppressive effect should preferably continue NOAC, provided that the dose is adapted to anticipated therapy-induced changes in organ function (especially liver and renal function).
(8) When a myelosuppressive chemotherapy or radiation therapy is planned, an interdisciplinary team involving a cardiologist and the cancer team should consider temporary dose reduction or cessation of NOAC therapy. Specific monitoring modalities should be considered including
    (a) Repetitive full blood counts including platelets.
    (b) Careful clinical examination for bleeding signs.
    (c) Regular monitoring of liver and renal function.
(9) As mentioned in Section 2, gastric protection with PPI or H2 blockers should be considered in all patients treated with anticoagulants.
(10) Patients with malignancies on NOACs should be instructed to carefully monitor signs for bleeding (petechiae, haemoptysis, black stools) and be instructed to contact their therapy centre should those signs develop.

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