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EHRA PRACTICAL GUIDE

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

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The current manuscript is an update of the original Practical Guide, published in June 2013[Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, *et al*. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013;15:625–51; Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, *et al*. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J* 2013;34:2094–106]. Non-vitamin K antagonist 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 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 coordinate a unified way of informing physicians on the use of the different NOACs. A writing group defined what needs to be considered as 'non-valvular AF' and listed 15 topics of concrete clinical scenarios for which practical answers were formulated, based on available evidence. The 15 topics are (i) practical start-up and follow-up scheme for patients on NOACs; (ii) how to measure the anticoagulant effect of

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NOACs; (iii) drug–drug interactions and pharmacokinetics of NOACs; (iv) switching between anticoagulant regimens; (v) ensuring adherence of NOAC intake; (vi) how to deal with dosing errors; (vii) patients with chronic kidney disease; (viii) what to do if there is a (suspected) overdose without bleeding, or a clotting test is indicating a risk of bleeding?; (xi) management of bleeding complications; (x) patients undergoing a planned surgical intervention or ablation; (xi) patients undergoing an urgent surgical intervention; (xii) patients with AF and coronary artery disease; (xiii) cardioversion in a NOAC-treated patient; (xiv) patients presenting with acute stroke while on NOACs; and (xv) NOACs vs. VKAs in AF patients with a malignancy. Additional information and downloads of the text and anticoagulation cards in >16 languages can be found on an European Heart Rhythm Association web site (www.NOACforAF.eu).

Keywords Atrial fibrillation • Anticoagulation • Stroke • Bleeding • Pharmacology • Non-VKA oral anticoagulants • NOAC

Introduction

Non-vitamin K antagonist (VKA) oral anticoagulants (NOACs)[1,2] have emerged as an alternative to VKAs for thrombo-embolic prevention in patients with non-valvular atrial fibrillation (AF). Some authors refer to these drugs as 'direct oral anticoagulants' (DOACs),[3] but since the term NOAC has been used for many years and is widely recognized, we prefer to continue to use NOAC. Non-vitamin K antagonist oral anticoagulants have an improved efficacy/safety ratio, predictable effect without need for routine monitoring, and fewer food and drug interactions compared with VKAs. However, the proper use of NOACs requires different approaches to many practical aspects compared with VKAs. Whereas the ESC Guidelines[4,5] mainly discuss the indications for anticoagulation in general (e.g. based on the CHA_2DS_2-VASc score) and of NOACs in particular, they offer less guidance on how to deal with NOACs in specific clinical situations. Moreover, there are still under-explored aspects of NOAC use that is relevant when these drugs are used by cardiologists, neurologists, geriatricians, and general practitioners. Each of the NOACs available on the market is accompanied by the instructions for its proper use in many clinical situations [summary of product characteristics (SmPCs); patient card; information leaflets for patients and physicians], but multiple, and often slightly different, physician education tools sometimes create confusion rather 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. A first Practical Guide was published in 2013 to supplement the AF guidelines as a guidance for safe, effective use of NOAC when prescribed.[6,7] This text is a first update to the original Guide.

A writing group formulated practical answers to 15 clinical scenarios, based on available and updated knowledge. The writing group was assisted by medical experts from the companies that bring NOACs to the market: they provided assurance that the latest information on the different NOACs was evaluated, and provided feedback on the alignment of the text with the approved SmPCs. However, the responsibility of this document resides entirely with the EHRA writing group. In some instances, the authors opted to make recommendations that do not fully align with all SmPC, with the goal to provide more uniform and simple practical advice (e.g. on the start of NOAC after cessation of VKA; on advice after a missed or forgotten dose). An EHRA website, www.NOACforAF.eu, accompanies the Practical Guide. Whereas this updated text integrates all changes, an Executive Summary in the European Heart Journal will outline the items that have been changed from the original version.

The Practical Guide is summarized in a Key Message booklet which can be obtained through EHRA and ESC. Please tune in to the www.NOACforAF.eu website for related information. The website also provides EHRA members with a downloadable slide kit on the Practical Guide.

We hope that this collaborative effort has yielded the practical tool that EHRA envisioned and that it has become even better with this revision. 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 website. This whole endeavour should be one for and by the medical community.

Definition of 'non-valvular atrial fibrillation' and eligibility for non-vitamin K antagonist oral anticoagulants

Non-valvular AF refers to AF that occurs in the absence of mechanical prosthetic heart valves and in the absence of moderate to severe mitral stenosis (usually of rheumatic origin) (*Table 1*). Both types of patients were excluded from all NOAC trials. Atrial fibrillation in patients with other valvular problems is defined as 'non-valvular' and such patients were included in the trials. Atrial fibrillation in patients with biological valves or after valve repair constitute a grey area, and were included in some trials on 'non-valvular AF'. They may be suitable NOAC candidates, as will be discussed below. There are no data on patients after percutaneous aortic valve interventions [percutaneous transluminal aortic valvuloplasty (PTAV) or transcatheter aortic valve implantation (TAVI)]. Since oral anticoagulation is not required in these patients in the absence of AF, they seem to to be eligible for NOAC therapy in case of AF. Nevertheless, PTAV or TAVI requires mandatory single or even dual antiplatelet therapy (DAPT).[9] The addition of an anticoagulant increases bleeding risk. There is no prospective data in such patients under NOAC therapy, nor is the best combination strategy known (in analogy for acute coronary syndome patients, described in 'Patient with atrial fibrillation and coronary artery disease' section). For the same reasons, hypertrophic cardiomyopathy AF patients seem to be eligible for

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Table 1 Valvular indications and contraindications for NOAC therapy in AF patients

	Eligible	Contra-indicated
Mechanical prosthetic valve		✓
Moderate to severe mitral stenosis (usually of rheumatic origin)		✓
Mild to moderate other native valvular disease	✓	
Severe aortic stenosis	✓ Limited data. Most will undergo intervention	
Bioprosthetic valve[a]	✓ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	✓ (except for the first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk)	
Hypertrophic cardiomyopathy	✓ (but no prospective data)	

PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
[a]American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.[8]

NOAC therapy, although there is also little or no published experience with NOACs in this condition.[9]

Post hoc analysis from the ARISTOTLE trial has shown that 26.4% of the study population had at least moderate valvular disease (including aortic stenosis and regurgitation, moderate mitral regurgitation, but excluding more than mild mitral stenosis) or a history of valve surgery (5.2%)[10]: these patients had a higher risk of thrombo-embolism and bleeding, but the relative benefit of apixaban over warfarin was preserved, both for efficacy and bleeding. Propensity-matched RE-LY data indicated that patients with valvular disase had a higher risk of major bleeding (but not stroke), irrespective of anticoagulant treatment, and confirmed similar relative benefits of dabigatran vs. warfarin in both those and those without valvular disease.[11] A similar analysis from ROCKET-AF (rivaroxaban) showed similar efficacy findings of NOAC vs. VKA, although bleeding rates with rivaroxaban were higher than with VKA in patients with valvular disease, and the rate of systemic embolism (not stroke) was marginally higher with rivaroxaban.[12] ENGAGE-AF included patients with bioprosthetic heart valves and/or valve repair, but no data on these patients are available yet. The RE-LY trial also excluded patients with severe (haemodynamically relevant) aortic stenosis and the clinical experience with such patients is limited in other trials. However, most of these patients will undergo valve surgery or a percutaneous intervention (PTAV or TAVI).

Therefore, it seems reasonable to treat AF patients with moderate to severe valvular disease (including aortic valve disease, but excluding more than mild mitral stenosis) with NOACs, although the benefits of thrombo-embolic and bleeding risks have to be weighed. The same may apply to patients with bioprosthetic heart valves or after valve repair (conditions that by itself do not require oral anticoagulation) although no prospective data are available except for the few hundred patients in ARISTOTLE (both types, but without information on how many patients with bioprosthesis)[10] and ROCKET-AF (only valvuloplasty).[12] Please note that American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.[8] However, in light of the RE-ALIGN findings, a study in patients with a mechanical prosthetic valve (79% implanted within a week before randomization), it is not recommended to use NOACs during the first three, respectively, 6 months post-operatively since the study showed inferiority of dabigatran compared with warfarin.[13] The early post-operative phase might have contributed to these findings. No information in this regard is available on any of the factor Xa-inhibitors.

Mechanical prosthetic heart valves constitute a strict contraindication for the use of any NOAC until further data become available.

1. Practical start-up and follow-up scheme for patients on non-vitamin K antagonist oral anticoagulants

Choice of anticoagulant therapy and its initiation

Indication for anticoagulation and choice between vitamin K antagonist and non-vitamin K antagonist oral anticoagulant

Before prescribing an NOAC to a patient with AF, it should have been decided that anticoagulation is merited based on a risk/benefit analysis. The choice of anticoagulant (VKA or NOAC; type of NOAC) has to be made on the basis of approved indications by regulatory authorities and guidelines by professional societies. The kidney function [expressed by a Cockcroft–Gault estimate of glomerular filtration rate (GFR)] is required, since NOACs have exclusions based on GFR (see 'Patients with chronic kidney disease' section and *Table 8*). Also product characteristics (as explained in the SmPCs), patient-related

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clinical factors, and patient preference after discussion of the different options need to be taken into account.[4,14–16]

European guidelines have expressed a preference for NOACs over VKA in stroke prevention for AF patients, based on their overall clinical benefit.[5] Asians are especially vulnerable to VKA, with higher major bleeding and intracranial haemorrhage (ICH) rates than in non-Asians despite lower international normalized ratios (INRs). In contrast, NOACs are associated with a significantly higher relative risk reduction for bleeding and ICH in Asians, while maintaining their efficacy profile. Therefore, NOACs are considered to be preferentially indicated in Asians.[17]

In some countries, an NOAC will only be indicated if INR control under VKA has been shown to be suboptimal (i.e. after a failed 'trial of VKA'). There is evidence that clinical scores like SAMe-TT_2R_2 may be able to predict poor INR control. SAMe-TT_2R_2 calculates a maximum of eight points for Sex; Age (<60 years); Medical history (at least two of the following: hypertension, diabetes, coronary artery disease (CAD)/myocardial infarction (MI), peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease); Treatment (interacting drugs, e.g. amiodarone for rhythm control) (all one point); and Tobacco use within 2 years (two points) and Race (non-Caucasian; two points).[18] SAMe-TT_2R_2 has a significant, although moderate, ability to identify patients with a poor anticoagulation control under VKA, i.e. time-in-therapeutic range of <65%,[19–21] and was even statistically associated with outcomes on VKA.[19–23] A practical algorithm for implementing SAMe-TT_2R_2 in decision-making on NOACs vs. VKA has been proposed, which could be used to prevent exposing patients to a 'trial of VKA' (when the score is >2), whereas patients with a score of 0–2 could be treated with VKA and only switched over if poor adherence and/or TTR < 65%.[21,23,24] Further prospective studies are required to validate such strategies. Also the UK National Institute for Health and Care Excellence suggested this as an area for further research in its 2014 AF Guidelines (https://www.nice.org.uk/guidance/cg180).

Choosing the type and dose of non-vitamin K antagonist oral anticoagulant

Table 2 lists the NOACs approved for stroke prevention in AF patients. Non-vitamin K antagonist oral anticoagulants do not have precisely the same indications and availability in every country. Local factors, such as formulary committees and especially cost of therapy, may influence NOAC availability. Concerning the choice of a given NOAC and its dosing, 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 'Drug–drug interactions and pharmacokinetics of non-vitamin K antagonist anticoagulants' section). Also patient age, weight, renal function (see 'Patients with chronic kidney disease' section), and other co-morbidities influence the choice, and are discussed in many of the sections below. In some patients, proton pump inhibitors (PPIs) may be considered to reduce the risk for gastrointestinal bleeding, especially in those with a history of such bleeding or ulcer.

A non-vitamin K antagonist oral anticoagulant anticoagulation card

Users of VKAs have routinely been advised to carry information about their anticoagulant therapy to alert any healthcare provider about their care. It is equally important that those treated with NOACs carry details of this therapy. Each manufacturer provides proprietary information cards, but we recommend a uniform card to be completed by physicians and carried by patients. *Figure 1* shows a proposal for such a card, which will be updated for download in digital form in 16 languages at www.NOACforAF.eu. In case a new translation is required, please use the feedback form on the website to start-up the translation process.

It is critically important to educate the patient at each visit about the modalities of intake [once daily (OD) or twice a day (BID); with food in case of rivaroxaban], the importance of strict adherence to the prescribed dosing regimen, and to convince patients that an NOAC should not be discontinued (because of the rapid decline of protective anticoagulation that will occur). Similarly, patients should be educated on how not to forget taking medication, or leaving it behind when travelling. Education sessions can be facilitated using checklists.[15,16,30]

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

Table 2 Non-VKA oral anticoagulant drugs, approved for prevention of systemic embolism or stroke in patients with non-valvular AF

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Dose	150 mg BID 110 mg BID[a,b] (75 mg BID)[b]	5 mg BID 2.5 mg BID[a]	60 mg OD[c] 30 mg OD[a]	20 mg OD 15 mg OD[a]
Phase III clinical trial	RE-LY[25]	ARISTOTLE[26] AVERROES[27]	ENGAGE-AF[28]	ROCKET-AF[29]

BID, twice a day; OD, once daily.
[a]See further tables and text for discussion on dose reduction considerations.
[b]110 mg BID not approved by FDA. 75 mg BID approved in USA only, if CrCl 15–30 mL/min or if CrCl 30–49 mL/min and other 'orange' factor as in *Table 6* (e.g. verapamil).
[c]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients with high creatinine clearance after a careful evaluation of the individual thrombo-embolic and bleeding risk'.

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Atrial Fibrillation Oral Anticoagulation Card

for non-vitamin K antagonist anticoagulants (NOACs)

Patient name: **DOB:**

Patient address:

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

Treatment indication and start date:

? Concomitant antiplatelet(s): type, indication, start & stop dates:

Name and address of physician, coordinating NOAC treatment:

Telephone number of coordinating physician or clinic:

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Planned or unplanned visits

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

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Recommended follow-up

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

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

Blood sampling:
- **monitoring of anticoagulation level is not required!**
- **yearly:** Hb, renal and liver function
- **if >75-80 y (especially if dabigatran or edoxaban), or frail:** 6-monthly renal function
- **if CrCl ≤ 60 ml/min:** recheck interval in months = CrCl / 10
- **if intercurrent condition that may have impact:** renal and/or liver function

Date	Serum creatinine	Creatinine clearance	Hemo-globin	Liver tests

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Important patient instructions

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

Never stop your medicine without consulting your physician.

Never add any other medication without consulting your physician, not even short-term painkillers that you can get without prescription.

Alert your dentist, surgeon or other physician before an intervention.

Concomitant medication

Name:	Dose:

Emergency information

Standard tests do not quantitatively reflect level of anticoagulation!

Name & telephone of patient relative to contact:

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Figure 1 European Heart Rhythm Association 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 healthcare workers (other caretakers are involved; renal function; follow-up schedule; concomitant medication, etc.). This generic and universal card can serve all patients under NOAC therapy.

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interactions and they may cause serious bleeding. Therapy prescription with this class of drugs requires vigilance, also because the target patient population may be fragile and NOACs are drugs with potentially severe complications. Patients should return on a regular basis for on-going review of their treatment, preferably after 1 month initially, and later 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.[31,32] As clinical experience with NOACs grows,[33] follow-up intervals may become longer based on individual (patient-specific) or local (centre-specific) factors. Each caregiver, including nurses and pharmacists, should indicate with a short input on the patient NOAC card whether any relevant findings were present, and when and where the next follow-up is due.

Regular review has to systematically document (i) therapy adherence (ideally with inspection of the NOAC card, prescribed medication in blister packs, dosette packs or bottles, in addition to appropriate questioning); (ii) any event that might signal thrombo-embolism in either the cerebral, systemic or pulmonary circulations; (iii) any adverse effects, but particularly (iv) bleeding events (occult bleeding may be revealed by falling haemoglobin levels, see below); (v) new co-medications, prescriptions, or over-the-counter; and (vi) blood sampling for haemoglobin, renal (and hepatic) function. *Table 3* lists the appropriate timing of these evaluations, taking the patient profile into consideration. For example, renal function should be assessed more frequently in compromised patients such as the elderly (>75–80 years), frail (defined as ≥3 of the following criteria: unintentional weight loss, self-reported exhaustion, weakness assessed by handgrip test, slow walking speed/gait apraxia, low physical activity),[34,35] or in those where an intercurrent condition may affect renal function, since all NOACs require dose reductions depending on renal function (see 'Drug–drug interactions and pharmacokinetics of non-vitamin K antagonist anticoagulants' and 'Patients with chronic kidney disease' sections; see *Table 4* of the ESC AF Guidelines Update[5]). An online frailty calculator can be

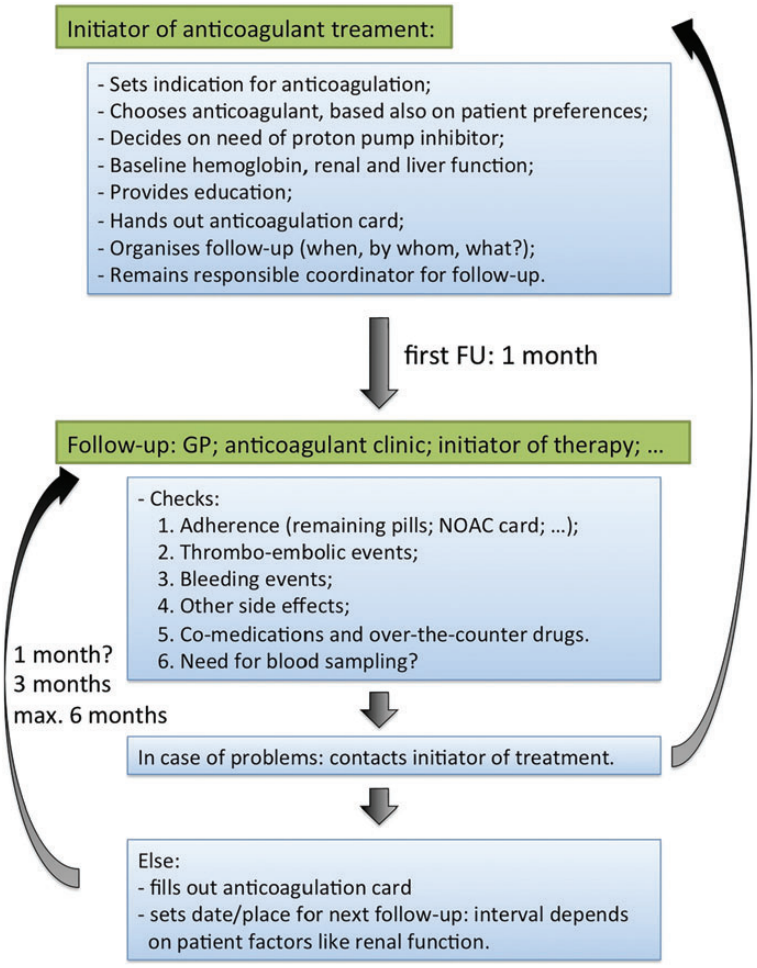

Figure 2 Initiation and structured follow-up of patients on NOACs. It is mandatory to ensure safe and effective drug intake. The anticoagulation card, as proposed in *Figure 1*, is intended to document each planned visit, each relevant observation or examination, and any medication change, so that every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

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Table 3 Checklist during follow-up contacts of AF patients on anticoagulation[a]

	Interval	Comments
1. Adherence	Each visit	Instruct patient to bring NOAC card and remaining medication: make note and assess average adherence Re-educate on importance of strict intake schedule Inform about adherence aids (special boxes, smartphone applications, etc.)
2. Thromboembolism	Each visit	Systemic circulation (TIA, stroke, and peripheral) Pulmonary circulation
3. Bleeding	Each visit	'Nuisance' bleeding: preventive measures possible? (PPI, haemorrhoidectomy, etc.). 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, especially aspirin and NSAID (see 'Drug–drug interactions and pharmacokinetics of non-vitamin K antagonist anticoagulants' section) Careful interval history: also temporary use can be risky!
6. Blood sampling	Yearly 6-monthly x-monthly On indication	Haemoglobin, renal and liver function $\geq$75–80 years (especially if on dabigatran or edoxaban), or frail[b] If renal function $\leq$60 mL/min: recheck interval = CrCl/10 If intercurrent condition that may impact renal or hepatic function

TIA, transient ischaemic attack; PPI, proton pump inhibitor; CrCl, creatinine clearance (preferably measured by the Cockcroft method).
[a]For frequency of visits: see *Figure 2*.
[b]Frailty is defined as three or more criteria of unintentional weight loss, self-reported exhaustion, weakness assessed by handgrip test, slow walking speed, or low physical activity.[34]
On online frailty calculator can be found at http://www.biomedcentral.com/1471-2318/10/57 under Additional Files.

found at http://www.biomedcentral.com/1471-2318/10/57 under additional files. Although the RE-LY protocol did not specify dose reduction in patients with chronic kidney disease (CKD) (see 'Patients with chronic kidney disease' section and *Table 8*), the high renal clearance of dabigatran makes its plasma level more vulnerable to acute impairment of kidney function. Its European label also requires a dose adaptation to 110 mg BID in those $\geq$80 years, or its consideration between 75 and 80 years (see *Table 6*). Edoxaban, which is also cleared 50% renally, specifies a dose reduction if CrCl is $\leq$50 mL/min. The laboratory values can be entered in a dedicated table on the patient NOAC card, allowing serial overview. It may also be useful to add the patient's baseline (non-anticoagulated) readings for relevant generic coagulation assays [such as activated partial thromboplastin time (aPTT) and prothrombin time (PT)] since this information may be important in the case of such a test being used to check the presence or absence of an NOAC effect in an emergency (see 'How to measure the anticoagulant effect of non-vitamin K antagonist oral anticoagulants?' section).

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 readily lead to discontinuation or dose adjustment. Minor bleeding is not necessarily predictive of major bleeding risk. Most minor bleeding are temporary and are best classified as 'nuisance' in type. In some instances, e.g. epistaxis, causal therapy like cauterization of the intranasal arteries, can be initiated. 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 thromboprophylactic effect of the therapy. In many patients who report nuisance bleeds or minor adverse effects, switching to another drug can be attempted.

2. How to measure the anticoagulant effect of non-vitamin K antagonist oral anticoagulants?

Non-VKA 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, assessment of drug exposure and 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, potential drug–drug interactions or suspected overdosing.

When interpreting a coagulation assay in a patient treated with a NOAC, much more than with VKA coagulation monitoring, it is paramount to know 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 ~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. Moreover, depending on the clinical profile of the patient, an estimation of the elimination

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Table 4 Interpretation of coagulation assays in patients treated with different NOACs and range of values at trough (P5–P95) in patients with normal function and the standard dose, as measured in clinical trials

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Plasma peak level	2 h after ingestion	1–4 h after ingestion	1–2 h after ingestion	2–4 h after ingestion
Plasma trough level	12 h after ingestion	12 h after ingestion	24 h after ingestion[36]	24 h after ingestion
PT	Cannot be used	Can be prolonged but no known relation with bleeding risk[37]	Prolonged but variable and no known relation with bleeding risk[36,38] Range at trough: NA	Prolonged but no known relation with bleeding risk Range at trough: 12–26 s with Neoplastin Plus as reagent; local calibration required
INR	Cannot be used	Cannot be used	Cannot be used	Cannot be used
aPTT	Range (P10–P90) at trough D150: 40.3–76.4 s Range (P10–P90) at trough D110: 37.5–60.9 s At trough: >2× ULN may be associated with excess bleeding risk[39]	Cannot be used	Prolonged but no known relation with bleeding risk[36]	Cannot be used
dTT	No data from RE-LY trial on range of values At trough: >200 ng/mL ≥65 s: may be associated with excess bleeding risk[39,40]	Cannot be used	Cannot be used[41]	Cannot be used
Anti-FXa chromogenic assays	Not applicable	Quantitative; no data on threshold values for bleeding or thrombosis Range at trough: 1.4–4.8 IU/mL	Quantitative[41]; no data on threshold values for bleeding or thrombosis Range at trough: 0.05–3.57 IU/mL[a]	Quantitative; no data on threshold values for bleeding or thrombosis Range at trough: 6–239 μg/L
ECT	Range (P10–P90) at trough D150: 44.3–103 Range (P10–P90) at trough D110: 40.4–84.6 At trough: ≥3× ULN: excess bleeding risk[39]	Not affected[37]	Not affected	Not affected
ACT	Rather flat dose response. No investigation on its use. Limited utility	No data. Cannot be used	No data. Cannot be used	Minor effect. Cannot be used

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; ECT, ecarin clotting time; INR, international normalized ratio; ACT: activated clotting time; ULN, upper limit of normal.
[a](P2.5–P97.5) for edoxaban.

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half-life should be done, which may be longer in the elderly and patients with reduced kidney function (see 'Patients with chronic kidney disease' section). The time delay between intake and blood sampling should therefore be carefully recorded when biological monitoring is performed.

The aPTT may provide a qualitative assessment of the presence of dabigatran and the PT for rivaroxaban. Because the sensitivity of the different assays varies greatly, it is recommended to check the sensitivity of the aPTT and PT in your institution for dabigatran and rivaroxaban, respectively.[42,43] Most PT assays are not sensitive for apixaban, whereas little information is available for edoxaban.

Quantitative tests for direct thrombin inhibitors (DTIs) and FXa inhibitors do exist: check their availability in your institution. Point of care tests should not be used to assess the INR in patients on NOACs.[44] An overview of the interpretation of all the coagulation tests for different NOACs can be found in *Table 4* and will be discussed in more detail below.

There are currently no data on cut-off values of any coagulation test below which elective or urgent surgery is possible without excess bleeding risk. No studies have investigated whether measurement of drug levels and dose adjustment based on laboratory coagulation pararmeters reduces the risk for bleeding or is associated with thrombo-embolic complications during chronic treatment.

Direct thrombin inhibitor (dabigatran)

For dabigatran, the **aPTT** may provide a qualitative assessment of dabigatran level and activity. The relationship between dabigatran and the aPTT is curvilinear.[39] In patients receiving chronic therapy with dabigatran 150 mg 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 $<$10% of patients exhibiting two-fold values. 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.[39] Conversely, a normal aPTT in dabigatran-treated patients has been used in emergency situations to exclude any relevant remaining anticoagulant effect and even to guide decisions on urgent interventions.[45] Although these reports are encouraging, such a strategy has not been systematically tested. It is important to be mindful that the sensitivity of the various aPTT reagents is different.

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.[39]

The ecarin clotting time (**ECT**) assay provides a direct measure of the activity of DTIs, but is not readily available. Calibrated tests for dabigatran are also available as ecarin chromogenic assay; these provide a linear correlation with dabigatran concentrations and are now commercially available. They may allow faster ECT measurements. When the ECT is prolonged at trough (greater than three-fold elevation over baseline) with BID dosing of dabigatran, this may be associated with a higher risk of bleeding.[40] An ECT close to the baseline (determined in the individual laboratory) indicates no clinically relevant anticoagulant effect of dabigatran.

Dabigatran increases the **activated clotting time** (**ACT**) in a curvilinear fashion, consistent with the effects on aPTT.[39] The ACT has not been investigated to gauge dabigatran anticoagulant activity in clinical practice. Data in ablation patients indicated that longer cessation of dabigatran before the procedure was assocated with the need for a higher dose of heparin to reach target levels, reflecting the effect of dabigatran on the ACT.[46]

The thrombin time (**TT**) is very sensitive to the presence of dabigatran and a normal TT excludes even low levels of dabigatran. The TT is not suited for the quantitative assessment of dabigatran plasma concentrations in the range expected with clinical use. Diluted thrombin time (**dTT**) tests (such as Hemoclot®, Technoview®, or Hemosil®) are available that can more accurately predict dabigatran anticoagulation. These dTT tests display a direct linear relationship with dabigatran concentration and are suitable for the quantitative assessment of dabigatran concentrations. A normal dTT measurement indicates no clinically relevant anticoagulant effect of dabigatran. When dabigatran is dosed BID, a dTT measured at trough ($\geq$12 h after the previous dose) indicating a dabigatran plasma concentration of $>$200 ng/mL (i.e. dTT $\sim>$65 s) may be associated with an increased risk of bleeding and warrants caution especially in patients with bleeding risk factors.[40] There are no data on cut-off values below which elective or urgent surgery is without excess bleeding risk, and therefore its use in this respect cannot be currently recommended (see also 'Patients undergoing a planned surgical intervention or ablation' and 'Patients requiring an urgent surgical intervention').

Factor Xa inhibitors (rivaroxaban, apixaban, and 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 prolongation, variability of assays, and paradoxical response at low concentrations.[47]

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. Furthermore, PT is not specific and can be influenced by many other factors (e.g. hepatic impairment, cancer vitamin K deficiency).[47] For edoxaban and apixaban, the PT cannot be used for assessing their anticoagulant effects. For rivaroxaban, the PT may provide some quantitative information, even though the sensitivity of the different PT reagents varies importantly.[42] 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.[48] Neoplastin Plus is more sensitive than Neoplastin.[47] Many laboratories in the EU use Innovin as reagent, in which case the PT is very insensitive for FXa effect. Hence, even a normal PT does not rule out an FXa anticoagulant effect.

Importantly, conversion of PT to **INR** does not correct for the variation and even increases the variability. The INR (including a point-of-care determined INR) is completely unreliable for the evaluation of FXa inhibitory activity. The prolongation of the PT/INR by NOACs can be misleading during the transition of an NOAC to a VKA. Therefore, switching needs to be executed diligently, as discussed in 'Non-vitamin K antagonist oral anticoagulant to vitamin K antagonist' section.

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There is a small dose-dependent effect of rivaroxaban or apixaban on the **ACT**.[49,50] The ACT cannot be used to gauge FXa antocoagulant activity.

Anti-FXa 'chromogenic assays' are available to measure plasma concentrations of the FXa inhibitors using validated calibrators. Low and high plasma levels can be measured with acceptable inter-laboratory precision. Ranges of values, as measured in the clinical trials at trough, are given in *Table 4* for each FXa inhitibor. A calibrated quantitative anti-FXa assay may be useful in situations where knowledge of exposure is required to inform clinical decisions, like in overdose and emergency surgery. We advise you to inquire with your haematology laboratory whether the test is available.

Impact of non-vitamin K antagonist anticoagulants on coagulation system assessment

The **ACT** test is used as a point-of-care test in settings where high heparin doses are administered and where aPTT is too sensitive (e.g. bypass surgery, ablations, etc.). It is a test on whole blood, based on contact activation. FXa inhibitors only have a modest impact on ACT, at plasma concentrations above therapeutic levels, although only limited data are available.[49] It seems reasonable to use the same target ACT levels for heparine titration in NOAC-treated patients. However, since ACT is a non-standardized test, ACT target levels require centre validation.

The NOACs also interfere with **thrombophilia tests or the measurement of coagulation factors**. Therefore, a time window of at least 24 h is recommended between the last intake of an NOAC and blood sampling to confidently assess coagulation parameters. This time window may be even longer for lupus anticoagulant measurements (≥48 h).

3. Drug–drug interactions and pharmacokinetics of non-vitamin K antagonist anticoagulants

Treatment with VKAs requires careful consideration of multiple food and drug interactions. Despite high expectations of less interactions with the NOAC drugs, physicians will have to consider pharmacokinetic (PK) effects of accompanying drugs and of comorbidities when prescribing NOACs. This section aims 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 based 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.

The uptake, metabolism, and elimination of the different NOACs are graphically depicted in *Figure 3* and summarized in *Table 5*. 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 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[66]: competitive inhibition of this pathway therefore will result in increased plasma levels. Many drugs used in AF patients are P-gp inhibitors (e.g. verapamil, dronedarone, amiodarone, and quinidine).

CYP3A4-type cytochrome P450-dependent elimination is involved in rivaroxaban and apixaban hepatic clearance.[67] Strong

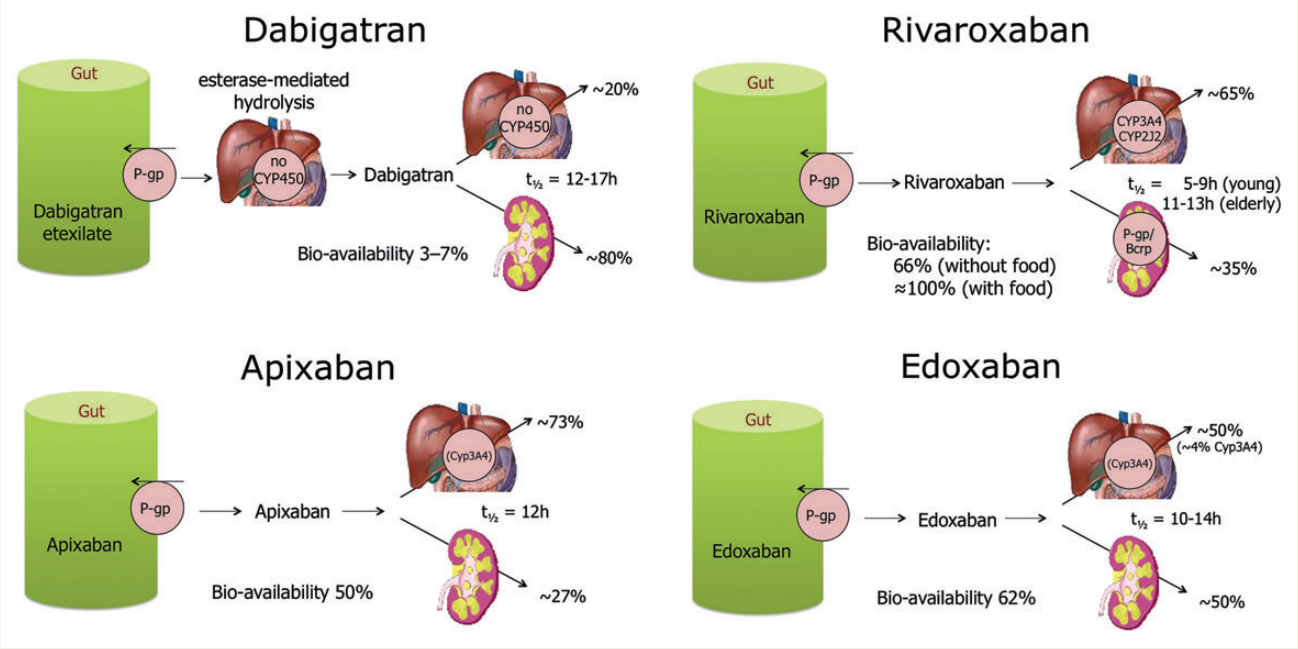

Figure 3 Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabilization and excretion. See also *Table 5* for the size of the interactions based on these schemes.

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Table 5 Absorption and metabolism of the different NOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	3 to 7%	50%	62%[51]	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 'Patients with chronic kidney disease' section)[a]	20%/80%	73%/27%[52–55]	50%/50%[36,51,56]	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination, moderate contribution)[57]	Minimal (<4% of elimination)	Yes (elimination, moderate contribution)
Absorption with food	No effect	No effect	6–22% more; minimal effect on exposure[58]	+39% more[59]
Intake with food recommended?	No	No	No	Mandatory
Absorption with H2B/PPI	−12 to 30% (not clinically relevant)[60–62]	No effect[63]	No effect	No effect[59,64]
Asian ethnicity	+25%[62]	No effect	No effect[58]	No effect
GI tolerability	Dyspepsia 5 to 10%	No problem	No problem	No problem
Elimination half-life	12 to 17 h[61]	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)

H2B, H2-blocker; PPI, proton pump inhibitor; GI, Gastrointestinal.
[a]For clarity, data are presented as single values, which are the mid-point of ranges as determined in different studies.

CYP3A4 inhibition or induction may affect plasma concentrations and effect, and should be evaluated in context (see *Table 6* and colour coding, discussed below). Non-renal clearance of apixaban is diverse (metabolism, biliary excretion, and direct excretion into the intestine), with at most a minor contribution of CYP3A4, which makes CYP3A4 interactions of less importance for this drug.[57] The apixaban SmPC indicates that it is not recommended in combination with strong inhibitors of both CYP3A4 and P-gp. Conversely, strong inducers of P-gp and CYP3A4 (such as rifampicin, carbamazepine, etc.) will strongly reduce the NOAC plasma levels, and therefore such combination should also be used with caution. For edoxaban, CYP3A4 is only very weakly involved (<4%): no dose adjustment is required for co-administration with even strong CYP3A4 inhibitors. The bioavailability of dabigatran is markedly lower than that of the other drugs (*Table 5*).[60] This means that slight fluctuations in absorption 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.[4,27,28,84,85] Data from RE-LY[86] and ENGAGE-AF[87] have shown a relationship between dose, patient characteristics, plasma concentration, and outcomes, with similar data on file for the other NOACs. A *post hoc* analysis of RE-LY data has shown that similar dose adjustments for dabigatran as per the EU label (i.e. 110 mg BID if age ≥80 years or concomitant use of verapamil) would have further improved its overall net clinical benefit over the randomized use of 110 or 150 mg BID as per the design of the RE-LY trial.[88] Therefore, physicians should make informed decisions when selecting the appropriate dose for their patients. The proposed dosing algorithms for the different NOACs have been evaluated and shown to be well-choosen, preserving efficacy and safety. Therefore, physicians should take care only to reduce dose along these algorithms or with good rationale. Not all clinical settings are covered by these algorithms. 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 6*): (i) 'red' interactions, precluding the use of a given NOAC in combination (i.e. 'contraindication' or 'discouragement' for use); (ii) '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 (iii) 'yellow' interactions, with the recommendation to keep the original dose, unless two or more concomitant 'yellow' interactions are present. Two or more 'yellow' interactions need expert evaluation, and may lead to the decision of not prescribing the drug ('red') or of adapting its dose ('orange'). Unfortunately, for many potential interactions with drugs that are often used in AF patients no detailed information is available yet. These have been shaded in the table. It is prudent to abstain from using NOACs in such circumstances until more information is available.

Food intake, antacids, and nasogastric tube administration

Rivaroxaban should be taken with food [the area under the curve (AUC) plasma concentrations increase by 39% to a very high

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Table 6 Effect on NOAC plasma levels (AUC) from drug–drug interactions and clinical factors, and recommendations towards NOAC dose adaptation

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs:					
Amiodarone	moderate P-gp competition	+12-60%[58]	No PK data[$]	+40%[63, 64, 244]	Minor effect[$] (use with caution if CrCl <50 ml/min)
Digoxin	P-gp competition	No effect[245]	No data yet	No effect	No effect[246, 247]
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[58]	+40%[60]	No data yet	Minor effect[#] (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp competition and CYP3A4 inhibition	+70-100% (US: 2 x 75 mg if CrCl 30-50 ml/min)	No PK or PD data: caution	+85% (Reduce NOAC dose by 50%)	Moderate effect[#] but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%[248 & SMPC]	No data yet	+77%[240, 249, 250] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180%[58] (reduce NOAC dose and take simultaneously)	No PK data	+53% (SR)[64, 249] (No dose reduction required by label)	Minor effect[***] (use with caution if CrCl 15-50 ml/min)
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[251]	No data yet	No effect	No effect[252]
Antibiotics					
Clarithromycin; Erythromycin	moderate P-gp competition and CYP3A4 inhibition	+15-20%	No data yet	+90%[64] (reduce NOAC dose by 50%)	+30-54%[42, 247]
Rifampicin***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[253]	minus 54%[238]	avoid if possible: minus 35%, but with compensatory increase of active metabolites[243]	Up to minus 50%
Antiviral drugs					
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%[247]

Continued

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Table 6 ***Continued***

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[247]
Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 x 75 mg if CrCl 30-50 ml/min)	+100%[60]	+87-95%[64] (reduce NOAC dose by 50%)	Up to +160%[247]
Immunosuppressive					
Cyclosporin; Tacrolimus	P-gp competition	Not recommended	No data yet	+73%	Extent of increase unknown
Antiphlogistics					
Naproxen	P-gp competition	No data yet	+55%[254]	No effect (but pharmacodynamically increased bleeding time)	No data yet
Antacids					
H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12-30%[45, 53, 58]	No effect[55]	No effect	No effect[241, 242]
Others					
Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[253]	minus 54%[SmPC]	minus 35%	Up to minus 50%
Other factors:					
Age ≥ 80 years	Increased plasma level		#	%	
Age ≥75 years	Increased plasma level			%	
Weight ≤ 60 kg	Increased plasma level		#		
Renal function	Increased plasma level	See Table 8			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history of GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

Red: contra-indicated/not recommended. **Orange**: reduce dose (from 150 to 110 mg BID for dabigatran; from 20 to 15 mg OD for rivaroxaban; from 5 to 2.5 mg BID for apixaban). **Yellow**: consider dose reduction if 2 or more 'yellow' factors are present. Hatching: no clinical or PK data available.
%: age had no significant effect after adjusting for weight and renal function.
BCRP, breast cancer resistance protein; NSAID, non-steroidal anti-inflammatory drugs; H2B, H2-blockers; PPI, proton pump inhibitor; P-gp, P-glycoprotein; GI, Gastrointestinal.
***Some interactions lead to *reduced* NOAC plasma levels in contrast to most interactions that lead to increased NOAC plasma levels. This may also constitute a contraindication for simultaneous use, and such cases are coloured **brown**. The label for edoxaban mentions that co-administration is possible in these cases, despite a decreased plasma level, which are deemed not clinically relevant (**blue**). Since not tested prospectively, however, such concomitant use should be used with caution, and avoided when possible.
$Based on *in vitro* investigations, comparing the IC_{50} for P-gp inhibition to maximal plasma levels at therapeutic dose, and/or on interaction analysis of efficacy and safety endpoints in the Phase III clinical trials.[82,83] No direct PK interaction data available.
#The SmPC specifies dose reduction from 5 to 2.5 mg BID if two of three criteria are fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL.

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bioavailability of almost 100%], while there is no interaction for the other NOACs. The concomitant use of PPIs and H2-blockers leads to a small reduced bioavailability of dabigatran, but without effect on clinical efficacy.[60,61] There is also no relevant antacid interaction for the other NOACs.[58,63] There is no PK data on fish oil supplements for any of the NOAC, but interaction is unlikely.

Data have shown similar bioavailability for apixaban and rivaroxaban when administered in crushed form, e.g. via a nasogastric tube.[89] Also an oral solution of apixaban is being developed, which has shown comparable exposure.[90] Dabigatran capsules should not be opened. No information is available on the possibility for crushing edoxaban tablets.

Rate and rhythm control drugs

Rate-controlling and antiarrhythmic drugs interact with P-gp, hence warranting caution for concomitant use of NOACs. The P-gp effects of **verapamil** on dabigatran levels 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 in clinical practice). With a slow-release verapamil preparation, there may be a 60% increase in dabigatran dose. Pharmacokinetic data from the RE-LY trial showed an average 23% increase in dabigatran levels in patients taking (all sorts) of verapamil.[62] It is advised to reduce the dabigatran dose when used in combination with verapamil ('orange').

A similar interaction has been noted for edoxaban.[38] However, after analysis of Phase III data, this interaction was considered as not clinically relavant. No dose reduction is recommended in the label, but caution might be warranted in combination with other factors ('yellow'). There are no specific interaction PK data for apixaban or rivaroxaban with verapamil. *In vitro* investigations (comparing the IC_{50} for P-gp inhibition with maximal plasma levels at therapeutic dose), and/or interaction analyses of efficacy and safety endpoints in Phase III clinical trials, indicate that the interaction potential of verapamil is considered 'clinically not relevant' for apixaban or rivaroxaban but one has to be aware that direct interaction PK data are not available. Therefore, the potential of relevance, especially when in combination with other 'yellow' factors, cannot unequivocally be judged. **Diltiazem** has a lower inhibitory potency of P-gp, resulting in non-relevant interactions,[62] although there is a 40% increase in plasma concentrations of apixaban ('yellow'; *Table 6*).[74]

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'). As for verapamil, *in vitro* data and analysis of Phase III interaction data indicate a minor effect of amiodarone on apixaban, rivaroxaban, or edoxaban plasma levels.[28,68,82,83] Of note, there was a significant interaction on the efficacy of the low-dose edoxaban regimen in its Phase III trial.[28,68] Again, direct PK data are lacking except for edoxaban, which show around 40% in AUC increase in patients with normal renal function.[69] Therefore, we would consider amiodarone a 'yellow' factor for all drugs, to be interpreted in combination with other 'yellow' factors.

There is a strong effect of **dronedarone** on dabigatran plasma levels, which constitutes a contraindication for concomitant use. The interaction potential is considered moderate for edoxaban ('orange') and the ENGAGE-AF protocol prespecified a dose reduction of edoxaban in patients taking dronedarone, as confirmed in its labelling.[28] There are no interaction PK data available for rivaroxaban and apixaban but effects on their plasma levels can be anticipated based on P-gp and CYP3A4 interactions, calling for caution (i.e. 'yellow'). It may be best to avoid such combination, especially in situations where other 'yellow' factors are present.

Other drugs

Table 6 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/breast cancer resistance protein (BCRP), 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.

Pharmacodynamic interactions

Apart from the PK 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).[91–93] 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 'Patient with atrial fibrillation and coronary artery disease' section).

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 PKs and pharmacodynamics of different anticoagulation regimens, interpreted in the context of the individual patient.

Vitamin K antagonist to non-vitamin K antagonist oral anticoagulant

The NOAC can immediately be initiated once the INR is $<$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 $t_{1/2}$ 8–14 h, warfarin $t_{1/2}$ 36–42 h, phenprocoumon $t_{1/2}$ 6 days (120–200 h). At that time, a new INR measurement can be scheduled. The proposed scheme (also shown in *Figure 4*, top panel) tries to unify different specifications in the SmPCs, which state that NOAC can be started when INR is $\leq$3 for rivaroxaban, $\leq$2.5 for edoxaban, and $\leq$2 for apixaban and dabigatran.

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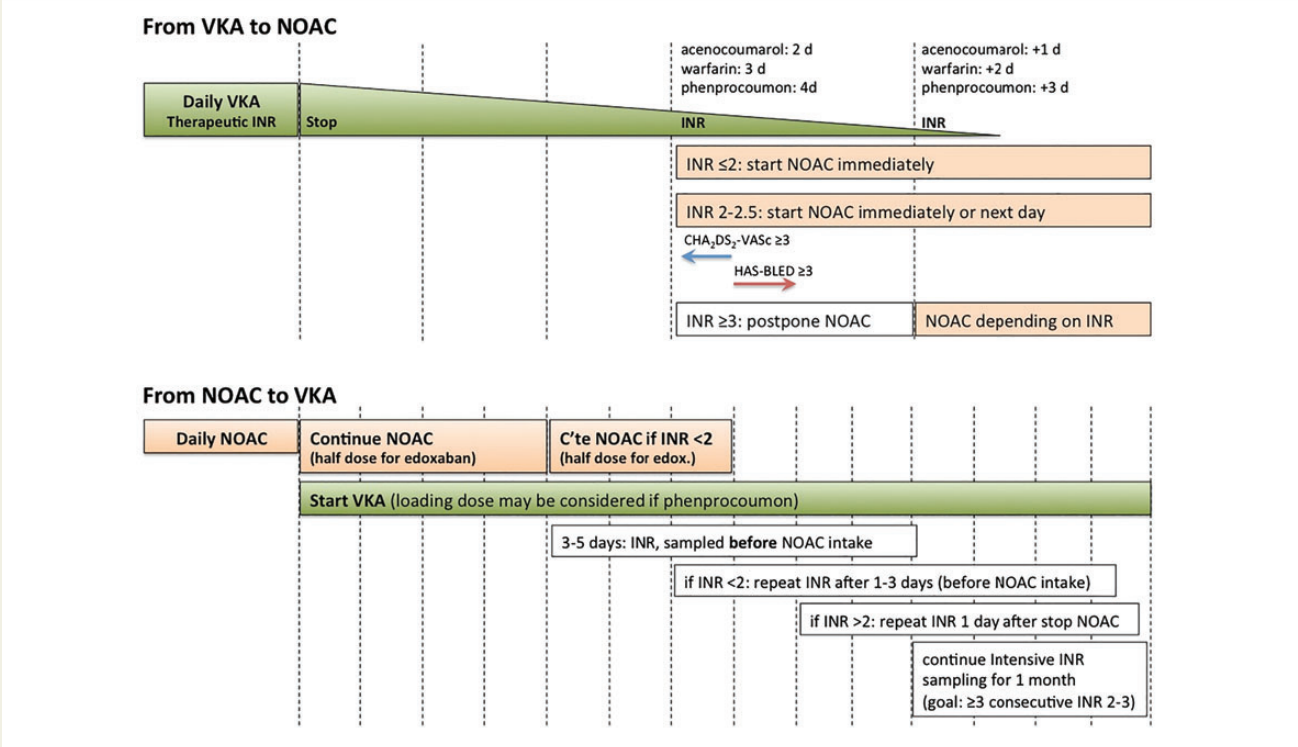

Figure 4 Switching between VKAs and non-VKA oral anticoagulants and vice versa.

Parenteral anticoagulant to non-vitamin K antagonist oral anticoagulant

Intravenous unfractionated heparin (UFH): NOACs can be started once intravenous UFH (half-life ± 2 h) is discontinued. Care should be taken in patients with CKD 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.

Non-vitamin K antagonist 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 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 (*Figure 4*, lower panel). 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 (i) that the INR be measured just before the next intake of the NOAC during concomitant administration, and (ii) be re-tested 24 h after the last dose of the NOAC (i.e. sole VKA therapy) to assure adequate anticoagulation. It is also recommended to closely monitor INR within the first month until stable values have been attained (i.e. three consecutive measurements should have yielded values between 2.0 and 3.0). At the end of the ENGAGE-AF trial, patients on edoxaban transitioning to VKA received up to 14 days of a half dose of the NOAC until INR was within range, in combination with the above intensive INR testing strategy.[94]

Incorrect transitioning has shown to be associated with increased stroke rates,[29,95–97] while switching according to the scheme mentioned above has been proved safe.[28,94] Whether the half-dose bridging regimen also applies to other NOACs is unknown.

Non-vitamin K antagonist oral anticoagulant to parenteral anticoagulants

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

Non-vitamin K antagonist oral anticoagulant to non-vitamin K antagonist 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*.

Aspirin or clopidogrel to non-vitamin K antagonist oral anticoagulant

The NOAC can be started immediately and aspirin or clopidogrel stopped, unless combination therapy is deemed necessary despite

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the increased bleeding risk of the association (see also 'Patient with atrial fibrillation and coronary artery disease' section).

5. Ensuring adherence to prescribed oral anticoagulant intake

The anticoagulant effect of NOACs fades rapidly 12–24 h after the last intake. Therefore, strict adherence to medication intake is crucial. Even if appropriate new anticoagulation tests would be used to gauge NOAC plasma levels, they cannot be considered as tools to monitor adherence since their interpretation is highly dependent on the timing of testing in respect to the last intake of the drug. In contrast to INR measurements in VKA-treated patients, NOAC plasma determination does not indicate anything about adherence before the last intake. The absence of a need for routine plasma level monitoring means that NOAC patients are less likely to be seen as frequently during follow-up compared with VKA patients. Physicians should develop ways to optimize adherence, since this is known to be $\leq$80% for most drugs in daily practice.[98,99] Such low adherence rate would severely diminish the benefit of treatment. There are limited data yet on the actual adherence to NOAC therapy, nor studies on how it can best be optimized. Some of these concerns have been alleviated by recent 'real world' data showing reduced ischaemic stroke and mortality rates in patients treated with dabigatran compared with warfarin, mimicking the RE-LY findings and therefore suggesting adequate adherence.[33,100] Initial real world data do suggest variable adherence to NOAC intake (mainly studied for dabigatran, the first available NOAC).[101,102] Interestingly, patients with higher morbidity, including patients with a higher risk of stroke or bleeding, exhibited better adherence to dabigatran.[101] There is also evidence for significantly lower discontinuation rates in NOAC patients than in VKA patients ('persistence').[103] There are no data on the actual adherence to correct medication intake in those who continued.[104–106] Only a single study so far has started to reliably assess adherence to NOAC (the AEGEAN study with apixaban; NCT01884350), using electronic devices to measure pill intake. All means possible to optimize adherence should be considered.

Practical considerations

(i) **Patient education** on the relevance of strict adherence is of utmost importance.[15,16,30,107] 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. Several organizations also offer online patient support websites, including EHRA (http://www.afibmatters.org/), the AF Association in the UK (http://www.atrialfibrillation.org.uk/), Anticoagulation Europe (http://www.anticoagulationeurope.org/), and AFNET (http://www.kompetenznetz-vorhofflimmern.de/de/vorhofflimmern/patienteninformation-vorhofflimmern).

(ii) **Family members** should be involved in this education, so that they can understand the importance of adherence, and help the patient in this regard.

(iii) There should be a **prespecified follow-up** schedule for the NOAC patient, known to and shared by general practitioners, pharmacists, nurses, anticoagulation clinics, and other professionals providing care. Each of those actors has responsibility to reinforce adherence. Each one's efforts should be clear to the others, e.g. by filling out a line on the NOAC Anticoagulation Card as mentioned under 'Practical start-up and follow-up scheme for patients on non-vitamin K antagonist oral anticoagulants' section. Nurse-coordinated AF centres may be helpful in coordinating patient follow-up and checking on adherence.[31]

(iv) 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 adherence monitoring, and this information should be used to cross-check appropriate prescription and dosing.

(v) Many **technological aids** are being explored to enhance adherence: the format of the blisters; medication boxes (conventional or with electronic verification of intake); smartphone applications with reminders and/or SMS messages to alert the patient about the next intake some even requiring confirmation that the dose has been taken. Again, the long-term effects of such tools are unknown and one tool may not suit all patients. The prescribing physician, however, should consider individualization of these aids.

(vi) An OD **dosing regimen** was related to greater adherence vs. BID regimens in cardiovascular patients,[108] and in AF patients (for diabetes and hypertension drugs).[99] It is likely that also for NOACs an OD dosing regimen is best from a total pill count perspective, but it is unknown whether any regimen is superior in guaranteeing the clinical thrombo-embolic preventive effects and safety profile as seen in the clinical trials. There is modelling data suggesting that there is potentially a larger decrease in anticoagulant activity occuring when a single pill is omitted from an OD dosing regimen compared with when a single or even two pills are omitted from a BID regimen.[109] The clinical relevance of these fluctuations is unkown and until proven clinically it is essential to ensure that drugs are taken acccording to the prescibed regimen to obtain the results observed in the clinical trials. FDA-compiled registry data with dabigatran have confirmed the risk/benefit profile of dabigatran compared with VKA as seen in RE-LY.[33] Similar registry data will be important for all NOACs since they may shed light on the performance of all NOACs in daily life, where adherence may be less optimal than in the trials.

(vii) Some **patients may explicitly prefer INR** monitoring to no monitoring or NOAC over VKA therapy. Patient education needs to discuss these preferences before starting/converting to NOAC therapy and management decisions have to take these preferences into account to optimize health outcomes.[15,107]

(viii) In NOAC patients in whom low adherence 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

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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. Of note, dabigatran cannot be taken out of its original package until immediately before intake.

Missed dose

A forgotten dose may be taken until 50% of the dosing interval has passed. Hence, for NOACs with a BID dosing regimen (i.e. every 12 h), the patient can take a forgotten dose up until 6 h after the scheduled intake. For patients with a high stroke risk and low bleeding risk, this can be extended up till the next scheduled dose.

For NOACs with an OD dosing regimen, the patient can take a forgotten dose up until 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.

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 an OD dosing regimen, the patient should continue the normal dosing regimen, i.e. without skipping the next daily dose.

Uncertainty about dose intake

Sometimes, the patient is not sure about whether a dose has been taken or not.

For NOACs with a BID dosing regimen, one could advise to 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 an OD dosing regimen, when bleeding risk is low (HAS-BLED $\leq$2) or thrombotic risk is high (CHA_2DS_2-VASc $\geq$3), one could advise to take another pill and then continue the planned dose regimen. In case bleeding risk is high (HAS-BLED $\geq$3) or thrombotic risk is low (CHA_2DS_2-VASc $\leq$2), one could advise to wait until the next scheduled dose.

Overdose

Depending on the amount of suspected overdose, hospitalization for monitoring or urgent measures should be advised. For further discussion, see 'What to do if there is a (suspected) overdose without bleeding, or a clotting test is indicating a risk of bleeding?' section.

7. Patients with chronic kidney disease

Chronic kidney disease constitutes a risk factor for both thromboembolic events and bleeding in AF patients[110] and the importance of CKD for arrhythmia management in general is increasingly recognized.[111] This has been confirmed in the NOAC trials[85,112,113] and a nationwide registry.[110,114] Recent findings suggest that a creatinine clearance of <60 mL/min may even be an independent predictor of stroke and systemic embolism.[115,116] Some data suggest that oral anticoagulation conveys a greater relative benefit in patients with mild to moderate CKD compared with normal renal function.[117,118] The picture is less clear in patients with end-stage kidney disease and dialysis: both stroke and bleeding risks seem elevated, and we have very little data informing on the benefit of oral anticoagulants in this setting. Some have suggested that VKAs may be harmful,[119] although others have concluded that VKA therapy has positive net clinical benefit.[114] Prospective data are not available in end-stage CKD patients, either with VKA, or with NOAC. Registry data have shown a higher risk of hospitalization or death from bleeding in dialysis patients started on NOAC (although contraindicated) compared with VKA.[120] Thus, the net clinical effect of (the type of) oral anticoagulation requires careful assessment in patients with severe impairment of kidney function (GFR < 30 mL/min).[110,121]

All NOACs are partially eliminated via the kidney. Assessment of kidney function therefore is important to estimate their clearance from the body (*Table 7*). In the context of NOAC treatment, CrCl is best estimated by the Cockcroft–Gault method, as this was used in most NOAC trials. The formula includes age, body weight, and gender to estimate CrCl from serum creatinine

Table 7 Estimated drug half lives and effect on AUC NOAC plasma concentrations in different stages of CKD compared to healthy controls

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
CrCl >80 mL/min	12–17 h[61]	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)
CrCl 50–80 mL/min CKD Stages I and II	~17 h[122] (+50%)	~14.6 h[123] (+16%)	~8.6 h[124] (+32%)[SmPC]	~8.7 h[125] (+44%)[126]
CrCl 30–50 mL/min CKD Stage III	~19 h[122] (+320%)	~17.6 h (+29%)	~9.4 h[124] (+74%)[SmPC]	~9.0 h (+52%)[126]
CrCl 15–30 mL/min CKD Stage IV	~28 h[122] (+530%)	~17.3 h (+44%)	~16.9 h[124] (72%)[SmPC]	~9.5 h (+64%)[126]
CrCl ≤ 15 mL/min CKD Stage V; off-dialysis	No data	– (+36%)	– (+93%)[SmPC]	– (+70%)[127]

CKD, chronic kidney disease; CrCl, creatinine clearance.

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(CrCl = (140 − age) × weight (in kg) × [0.85 if female]/72 × serum creatinine (in mg/dL)). We encourage every physician to have a web- or App-based calculator available during clinical work. Websites include http://nephron.com/cgi-bin/CGSI.cgi, http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation, http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault, and many others. Popular Apps are NephroCalc, MedMath, MedCalc, Calculate by QxMD, and Archimedes. For monitoring of kidney function over time, the estimated GFR as calculated by e.g. the MDRD or CKD-EPI formulas can provide a rough estimate of kidney function.[111]

Many patients with mild-to-moderate CKD (i.e. CrCl 30–89 mL/min) have been enrolled in the NOAC trials. In patients with a CrCl of 30–49 mL/min, dabigatran 150 mg BID can be prescribed according to the SmPC but the ESC Guidelines recommend to use the 110 mg BID dose.[5] For the three FXa inhibitors, PK studies or modelling have demonstrated similar plasma concentrations for reduced doses in patients with decreased renal function (CrCl 30–50 mL/min; for rivaroxaban) and/or concomitant patient factors such as weight and age (for apixaban and edoxaban) as for the standard dose in patients with normal renal function. These dose reduction schemes have been prospectively tested in the Phase III trials and have shown similar outcomes.[28,85,112] Intriguingly, data analysis from the ARISTOTLE trial suggests that the bleeding benefit of NOACs compared with VKA becomes significantly more prominent at lower CrCl, while the stroke reduction benefit is maintained.[112] *Post hoc* analyses of the ENGAGE-AF TIMI 48 trial also indicate a preserved bleeding benefit for edoxaban compared with VKA in patients with CrCl 30–50 mL/min (as described in its SmPC). If confirmed with prospective data, and if extended to patients with even lower CrCl, such data could lead to a clear benefit of NOAC therapy over VKA in patients with CKD. This requires further studies, especially testing the appropriateness of dose reduction schemes in such patients. Non-vitamin K antagonist oral anticoagulant companies should provide physicians with clear insights into the relationships between renal function, plasma levels, and clinical outcomes, and adapt dose reduction schemes if appropriate.

Rivaroxaban, apixaban, and edoxaban are also approved in Europe for the use in patients with CKD Stage IV, i.e. CrCl 15–30 mL/min, with the reduced dose regimen. However, there are no effectiveness and safety outcome data for NOACs in patients with advanced CKD (CrCL < 30 mL/min), and the current ESC Guidelines recommend against their use in such patients (*Table 8*).[5]

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 PK simulations. Although the FDA did not formally approve the use of apixaban in patients with CrCl ≤ 15 mL/min (CKD Stage V), it suggests the standard dose regimen if apixaban is used in haemodialysis patients (i.e. 5 mg BID, reduced to

Table 8 Approved European labels for NOACs and their dosing in CKD

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fraction renally excreted of absorbed dose	80%	27%[52–55]	50%[36]	35%
Bioavailability	3–7%	50%	62%[51]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	12–29%[52–55]	37%[36]	33%
Approved for CrCl ≥ . . .	≥30 mL/min	≥15 mL/min	≥15 mL/min	≥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)[a]	CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)[b]	CrCl ≥ 50 mL/min: no adjustment (i.e. 20 mg OD)
Dosing if CKD	When CrCl 30–49 mL/min, 150 mg BID is possible (SmPC) but 110 mg BID should be considered (as per ESC guidelines)[5] Note: 75 mg BID approved in US only[c]: if CrCl 15–30 mL/min if CrCl 30–49 mL/min and other orange factor *Table 6* (e.g. verapamil)	CrCl 15–29 mL/min: 2.5 mg BID If two-out-of-three: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg: 2.5 mg BID	30 mg OD when CrCl 15–49 mL/min	15 mg OD when CrCl 15–49 mL/min
Not recommended if	CrCl < 30 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min

Red: contra-indicated/not recommended. **Orange**: reduce dose as per label. **Yellow**: consider dose reduction if two or more 'yellow' factors are present (see also *Table 6*).
CKD, chronic kidney disease; CrCl, creatinine clearance; BID, twice a day; OD, once daily; SmPC, summary of product characteristics.
[a]The SmPC specifies dose reduction from 5 to 2.5 mg BID if two of three criteria are fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine >1.5 mg/dL.
[b]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients with high CrCl after a careful evaluation of the individual thrombo-embolic and bleeding risk' because of a trend towards reduced benefit compared to VKA.
[c]No EMA indication. FDA recommendation based on PKs. Carefully weigh risks and benefits of this approach. Note that 75 mg capsules are not available on the European market for AF indication.

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2.5 mg BID if ≥80 years or ≤60 kg), again based on PK modelling data. However, given the complete absence of any trial data and clinical experience in this patient cohort, we recommend to refrain from NOAC use in end-stage renal disease patients with CrCl < 15 mL/min. Clinical trials are needed in order to better define the risk/benefit profile.

Practical suggestions:

(i) Chronic kidney disease should be considered as a *risk factor* for stroke in AF. Chronic kidney disease also increases bleeding risk, with a relative increase in risk for all oral anticoagulants (VKA and NOACs).

(ii) Non-vitamin K antagonist 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 reduced doses according to prespecified dose reduction algorithms in trials with rivaroxaban, apixaban, and edoxaban. These dose reduction schemes, sometimes including other patient factors such as weight, age, or concomitant medications, should be implemented in practice (see also *Tables 6* and *8*). ESC Guidelines recommend the 110 mg dose of dabigatran in patients with CrCl 30–49 mL/min.[5]

(iii) There are *no comparative studies* that the risks from CKD differ among the NOACs. In light of the potential impact of further kidney function fluctuations and deterioriation, dabigatran, which is primarily cleared renally, may not be the NOAC of first choice in patients with known moderate CKD, especially when CrCl approaches 30 mL/min. Although there was no significant interaction in RE-LY between the relative risk/benefit of dabigatran vs. VKAs depending on kidney function,[25,128] later analysis showed that the major bleeding risk with each of these dabigatran doses is significantly related to CrCl (interaction *P* values were 0.027 and 0.13 for 110 mg BID respectively 150 mg BID dose when based on Cockcroft–Gault formula, and 0.002 respectively 0.011 when based on the CKD-EPI formula): while bleeding is significantly lower than with VKA at normal renal function, this advantage is lost at lower CrCl.[113] Prospective randomized data with the 75 mg dose are lacking (only available in the USA based on PK modelling), although preliminary data indicate exposure in agreement with modelled plasma levels in CKD Stage IV patients, i.e. comparable with plasma levels with the higher doses in patients with CrCl > 30 mL/min.[129] Another Phase IV PK study with dabigatran in AF patients with CKD Stage IV is enrolling (NCT01896297). If confirmed, this may open opportunities for reduced dosing schemes of dabigatran in such patients. Again, dose reduction as outlined above along the guidance of *Tables 5* and *7* may optimize the benefit/risk balance in individual patients but needs further study and refinement.

(iv) In the absence of clinical data or experience, NOAC therapy should be avoided in AF patients on *haemodialysis or preterminal CKD* (CrCl ≤ 15 mL/min, Stage V). Vitamin K antagonists may be a more suitable alternative for now although even the benefit of VKAs in such patients is not unequivocally proven. Vitamin K deficiency secondary to malnutrition, frequent antibiotic use, and abnormal cholesterol metabolism may lead to fluctuations in responsiveness to VKAs. Therefore, a careful individualized risk/benefit for anticoagulation is warranted. We call for active research in this area in which more efficient and safer treatment options are needed.

(v) 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 (i.e. CrCl ≤ 60 mL/min, one could specify a recheck interval in number of 'months = CrCl/10'. In elderly (≥75–80 years) or otherwise frail patients, renal function should be evaluated at least once every 6 months (see also *Table 3* and *Figure 2*), especially if on dabigatran or edoxaban which depend more on renal clearance. Acute illness often transiently affects renal function (infections, acute heart failure, etc.), and therefore should also trigger re-evaluation. This guidance is also present on the updated NOAC Card (*Figure 1*).

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 an excessive dose or when intercurrent events are suspected (such as acute renal failure, especially with dabigatran; administration of drugs that may lead to drug–drug interactions; or other factors: see 'Drug–drug interactions and pharmacokinetics of non-vitamin K antagonist anticoagulants' section) 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 'Management of bleeding complications' section. 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 seen at supratherapeutic doses of ≥50 mg rivaroxaban.[130] There are no data in this respect concerning the other FXa inhibitors or dabigatran.

In the case of recent acute ingestion of an overdose (especially when ≤2 h ago), 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) although clinical data on its effectiveness are lacking.[40,131,132]

In case of an overdose suspicion, coagulation tests can help to determine its degree and possible bleeding risk (see 'How to measure the anticoagulant effect of NOACs?' section for the interpretation of coagulation tests). Given the relatively short plasma half-life of the NOAC drugs, a 'wait-and-see' management can be advocated in most cases without active bleeding. If a more aggressive normalization of plasma levels is deemed necessary, or rapid normalization is not expected (e.g. major renal insufficiency) the steps outlined in 'Management of bleeding complications' section can be taken, including the use of non-specific reversal agents.

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Three different types of specific NOAC reversal agents are under active development (see 'Management of bleeding complications' section).

9. Management of bleeding complications

The different NOACs share the fact that specific and rapid (routine) quantitative measurements of their anticoagulant effects are missing, with the exception of aPTT of diluted thrombin tests (Hemoclot®) in case of dabigatran emergencies (see also 'How to measure the anticoagulant effect of NOACs?' section). Chromogenic FXa assays are presently more difficult to provide on a 24/7 basis. Howevere, both ECT-derived tests (for dabigatran) and chromogenic assays may be implemented on routine lab systems in the near future, providing much faster availability of coagulation tests. One has to realize, however, that restoration of coagulation does not necessarily equal good clinical outcome. The Phase III NOAC studies have shown that the bleeding profile of NOACs is more favourable than that of warfarin, in particular concerning intracranial and other life-threatening bleeding. Not only was there non-inferiority or even superiority for bleeding incidence, but outcome of bleedings under NOACs was also shown to be more benign than for bleedings under VKA treatment.[133,134] Also, less bleeding events under NOAC therapy will lead to less change in anticoagulant therapy, which also leads to reduced early and late mortality. Nevertheless, as more patients will start using one of the NOACs, the number of bleeding-related events is expected to increase.

Reversal of VKAs through the administration of vitamin K has a slow onset (i.e. at least 24 h). Administration of fresh frozen plasma more rapidly restores coagulation but is less effective then the use of PCCs as assessed by both INR values and assays of vitamin K-dependent clotting factors.[135] In case of NOACs, however, the plasma abundance of the NOAC may block newly administered coagulation factors as well. Hence, fresh frozen plasma cannot be considered a reversal strategy. On the other hand, coagulation factor concentrates can be used for reversal, as discussed below. Although there is a growing number of reports about anecdotal experience with bleeding in NOAC-treated patients, and increasing information about the effects of prothrombin concentrates, prospective randomized data are lacking.[136] Therefore, recommendations on bleeding management are still mainly based on preclinical information and experts' opinions.

A specific reversal agent for dabigatran (idarucizumab, a humanized antibody fragment that specifically binds dabigatran)[137] is approaching expedited approval after the REVERSE-AD trial showed a nearly complete reversal of the anticoagulant effects of dabigatran within minutes.[138] Similar agents for FXa inhibitors are under development, such as andexanet alfa (a recombinant human FXa analogue that competes for the FXa inhibitors with FXa) and aripazine, a small synthetic molecule that seems to have more generalized antagonistic effects.[139–141] In healthy volunteers, idarucizumab showed immediate and complete reversal of the anticoagulation effect of dabigatran, without any increase in procoagulant biomarker levels.[137,142] Moreover, it allowed restart of dabigatran 24 h after its idarucizumab administration, restoring normal peak and trough plasma levels.[138,142,143] When idarucizumab would not be readily available during a bleeding complication under dabigatran, or in case bleeding occurs in a patient treated with any of the FXa inhibitors, one can resort to non-specific reversal strategies, as discussed below.

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 9* and *Figure 5* 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.[144] This underscores the importance to inquire about the prescribed dosing regimen, the exact time of last intake, factors influencing plasma concentrations (like P-gp therapy, CKD, and others, see also *Table 6*), and other factors influencing haemostasis (like concomitant use of antiplatelet 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.[39,145,146] Moreover, the risks of bleeding at puncture sites for dialysis need 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 CKD on maintenance haemodialysis, the mean fraction of drug removed by dialysis was 62% at 2 h and 68% at 4 h.[122] Recently, its use in an emergency surgery setting has been reported.[147] Whether enhanced removal of dabigatran from plasma is possible via haemoperfusion over a charcoal filter is under evaluation.[39]

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. This has been confirmed for edoxaban and apixaban.[148,149]

Life-threatening bleeding

In patients treated with dabigatran, idarucizumab is the preferred reversal agent when it becomes available. The pilot trial was not designed to compare outcome data, but the investigators considered haemostasis in most patients presenting with serious bleeding or requiring urgent surgery as restored after administration of idarucizumab.[138]

Animal studies have shown bleeding prevention under dabigatran by administration of concentrates of coagulation factors II (VII), IX, and X [prothrombin complex concentrate (PCC); some brand names are Cofact®, Confidex®, Octaplex®, and Beriplex®].[150–152] Prothrombin complex concentrate also normalized anticoagulation parameters (aPTT and thrombelastographic clotting time) in rivaroxaban-treated animals, although it did not reverse bleeding.[153] In healthy volunteers, PCC dose-dependently reversed the anticoagulant effects of FXa inhibitors, with incomplete reversal by 25 U/kg and complete reversal by 50 U/kg.[154–156] *In vitro* testing, using blood samples from volunteers taking rivaroxaban,

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Table 9 Possible measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, and rivaroxaban)
None 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).[122] Charcoal haemoperfusion can be considered (based on preclinical data)	Inquire last intake + dosing regimen. Normalisation 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) 50 U/kg (with additional 25 U/kg if clinically needed) (but no clinical ata). Activated PCC 50 U/kg; max 200 U/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) Idarucizumab 5 g IV (approval waiting)	All of the above. Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (healthy volunteer data) Activated PCC 50 U/kg; max 200 U/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.

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.[157–159]

The efficacy of PCC or aPCC in patients who are actively bleeding has not been firmly established (i.e. that they reduce blood loss and improve outcome),[160] and one has to to balance the potential prothrombotic effects against the potential anticoagulant benefits.[161,162] The administration of PCC or aPCC can be considered in a patient with life-threatening bleeding if immediate haemostatic support is required. Clinical trials and registry data with NOACs have shown that this is rarely needed, however.[136,163,164] The choice between PCC and aPCC may depend on their availability and the experience of the treatment centre. Based on studies with PCCs in healthy volunteers, administration could start at a dose of 50 U/kg, with an additional 25 U/kg 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 U/kg, with a maximum of 200 U/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. We do not believe that currently it deserves priority over PCC or aPCC.[145]

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 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).

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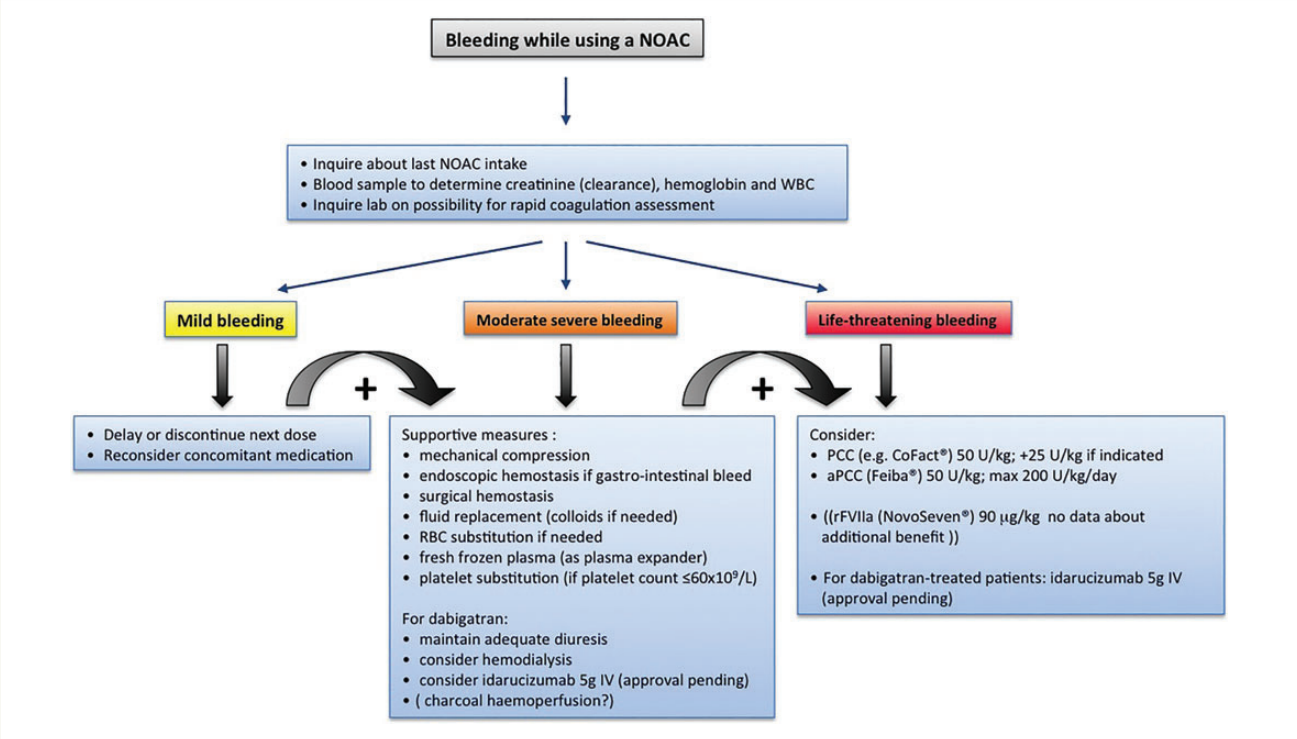

Figure 5 Management of bleeding in patients taking NOACs. Possible therapeutic measures in case of minor or severe bleeding in patients on NOAC therapy. Based on van Ryn *et al.*[39]

10. Patients undergoing a planned surgical intervention or ablation

When to stop non-vitamin K antagonist anticoagulants?

Surgical interventions or invasive procedures that carry a bleeding risk require 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.[163] Both patient characteristics (kidney function, age, history of bleeding complications, and concomitant medication) and surgical factors should be taken into account on when to discontinue and restart the drug, as indicated in *Table 10*. Bridging with LMWH or heparin, as was proposed in AF patients with higher thrombo-embolic risk treated with VKAs,[4] 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.[164] Moreover, the BRIDGE trial has now shown that also in VKA-treated patients, bridging with LMWH has no benefit regarding thromboembolism but is inferior concerning major bleeding.[165] European Heart Rhythm Association and other societies have formulated extensive advice on antithrombotic management in patients undergoing EP procedures, including temporary cessation of NOAC therapy.[166,167] Registry data have shown that bridging is still inappropriately used in NOAC patients, leading to a significantly higher peri-procedural bleeding rate (without lower thrombo-embolic rate).[164]

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 carries 'no clinically important bleeding risk' and/or when adequate local haemostasis is possible, as with 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 OD 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 post-procedural 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 up to 5 days.

For procedures 'with a minor bleeding risk' (i.e. with a low frequency of bleeding and/or minor impact of a bleeding, of which some have been listed in *Table 11*), it is recommended to take the last dose of NOAC 24 h before the elective procedure in patients with normal kidney function (*Table 10*). In the case of procedures that carry a 'risk for major bleeding' (i.e. with a high frequency of bleeding and/or important clincial impact),[168] it is recommended to take the last NOAC 48 h before. In patients with a CrCl of

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Table 10 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban–edoxaban–rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥ 80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl < 15 mL/min	No official indication for use			
There is no need for bridging with LMWH/UFH				

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.
Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk with a high frequency of bleeding and/or important clincial impact. See also *Table 11*.
CrCl, creatinine clearance.
[a]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 (i.e. 15 mg OD) or edoxaban (i.e. 30 mg OD).

15–30 mL/min, we recommend consideration of earlier interruption than 24 h for any of the FXa inhibitors, both for interventions with low and high risk for bleeding, i.e. last intake ≥36 h respectively ≥48 h before the procedure.

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 10*.

Procedures such as spinal anaesthesia, epidural anaesthesia, and lumbar puncture may require complete haemostatic function, and fall under the 'high risk of bleeding' category. This writing group does not recommend neuraxial anaesthesia in the presence of uninterrupted NOAC use.

Although the aPTT and PT may provide a semi-quantitative assessment of dabigatran and FXa inhibitors, respectively (see 'How to measure the anticoagulant effect of NOACs?' section), a strategy that includes normalization of the aPTT or PT prior to elective/urgent interventions has not been validated, nor has such a strategy been studied with more specific coagulation tests like dTT or chromogenic assyas.

When to restart the non-vitamin K antagonist 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 (e.g. 0.5 mg/kg/day of enoxaparin) or intermediate dose of LMWHs (e.g. 1 mg/kg/day of enoxaparin) 6–8 h after surgery if adequate haemostasis has been achieved, whereas full therapeutic anticoagulation by restarting NOACs is deferred 48–72 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.

Special considerations concerning atrial fibrillation ablation procedures

Pulmonary vein isolation (PVI) constitutes an intervention with a risk of serious bleeding. Tamponade or haemothorax may occur secondary to transseptal puncture or extensive manipulation and ablation in the left atrium. Pulmonary vein isolation also qualifies as a procedure with a risk for frequent bleeding complications. Tamponade or haemothorax was reported to be around 1.3% in the worldwide AF ablation survey,[169] although their incidence is decreasing in recent trials. Separate data on major groin bleedings were not presented, but are not uncommon. On the other hand, ablation is performed in a pro-thrombotic setting, while endocardial ablation lesions further increase thrombo-embolic risk.[167,170,171]

Recent international consensus statements recommend performing PVI in VKA-treated patients without VKA interruption, since such strategy is associated not only with less thrombo-embolic events but also with less bleeding.[4,172] These expert recommendations have been confirmed in a large controlled trial comparing interrupted and uninterrupted warfarin therapy.[173] There has been a recent shift towards performing AF ablation on uninterrupted VKA therapy with target INR of 2.0–2.5. Whether such an approach is safe in patients on NOAC therapy is less clear.

There have been numerous reports on outcome of PVI patients under NOAC therapy, although many were small series, often observational and even with historical control data. Moreover, the protocols used were very heterogeneous (ranging from timed cessation as described under 'When to stop non-vitamin K antagonist anticoagulants?' section, to fully uninterrupted NOAC administration). Meta-analysis has demonstrated similar thrombo-embolic and bleeding rates with dabigatran compared with uninterrupted

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Table 11 Classification of elective surgical interventions according to bleeding risk

Interventions not necessarily requiring discontinuation of anticoagulation
Dental interventions
Extraction of one to three 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, etc.)
Interventions with minor bleeding risk (i.e. infrequent or with low clinical impact)
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or catheter ablation for right-sided supraventricular tachycardia
Non-coronary angiography (for coronary angiography and ACS: see 'Patient with atrial fibrillation and coronary artery disease' section)
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
Interventions with major bleeding risk (i.e. frequent and/or with high impact)
Catheter ablation of simple left-sided supraventricular tachycardia (e.g. WPW)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopaedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy
Extracorporeal shockwave lithotripsy (ESWL)
Interventions with major bleeding risk AND increased thrombo-embolic risk[a]
Complex left-sided ablation (PVI; some VT ablations)

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.
[a]Last intake can vary from ≥24 to 1 h before intervention: see text.

VKA.[174–178] Similar meta-analysis findings were reported for rivaroxaban, even with a slight bleeding benefit for the NOAC.[179] Observational studies comparing uninterrupted rivoraxaban or apixaban (until the evening before or even the morning of the ablation; in one study with only 2.5 mg apixaban given at that time) and uninterrupted VKA, also found similar thrombo-embolic and bleeding outcomes in both groups.[50,180–182] Randomized trials with all NOACs are on their way, usually comparing NOAC administration up until the evening before the ablation with uninterrupted VKA. The first, Venture-AF (with rivaroxaban) showed similar event rates, both bleeding and ischaemic, albeit in a rather small population leading to an underpowered trial.[183]

Therefore, while awaiting data from prospective trials, we recommend an institutional protocol for NOAC patients undergoing AF ablation. This may consist of changing patients to uninterrupted VKA, of uninterrupted NOAC therapy, or of well-planned cessation of NOAC. A number of factors should be considered for the timing of last intake, such as renal function, CHA_2DS_2-VASc risk of the patient, experience of the operator, type and extent of additional ablation beyond PVI, and the presence of peri-procedural imaging to guide transseptal puncture. Meta-analysis data indicate that a last intake of NOAC 24 h before the procedure is a viable strategy. Continued intake until the evening before the procedure or even the morning of the procedure seems to be equally safe, especially in experienced centres but more data are needed to make firm statements on the best strategy. When NOAC is last taken ≥36 h before the intervention, a transoesophageal echocardiography (TOE) should be considered before ablation. The same applies if adherence to correct NOAC intake in the weeks before ablation is doubtful. Transoesophageal echocardiography can be performed shortly before the ablation procedure, or at its onset so that it can also guide transseptal puncture. Note that some operators prefer systematic TOE in every patient with elevated CHA_2DS_2-VASc risk at the initiation of the ablation procedure.

During the ablation, IV heparin should be administered to achieve an ACT of 300–350 s.[167] It seems reasonable to use the same target ACT levels for heparine titration in NOAC-treated patients as in patients on (uninterrupted) VKA, as has been done by many investigators.[46,50,181,183] It has been noted that even in patients in whom the last NOAC dose was given in the morning of the procedure, the total need for heparin was higher and the time to target ACT lasted longer than in uninterrupted VKA patients.[46,50,181,183] This likely reflects a difference in whole blood coagulability rather than a direct interaction between NOACs and the ACT test.

Non-vitamin K antagonist oral anticoagulant intake can be resumed a 3–4 h after sheath removal if adequate haemostasis and the absence of pericardial effusion have been confirmed.[167]

Special considerations concerning device implantation procedures

Also for patients undergoing device implantation, recent prospective and randomized data in VKA-treated patients have confirmed prior observations of lower thrombo-embolic and bleeding rates if VKA is continued in an uninterrupted fashion, at least in patients with an increased embolic risk.[184] For NOAC-treated patients, we do not see a reason to deviate from the global scheme as presented in *Tables 9* and *10*, i.e. with timed cessation before intervention, without bridging, and restarting a few hours up until 2 days afterwards (depending on CHA_2DS_2-VASc risk). Smaller studies did not show a benefit of uninterrupted NOAC (and even a trend for more bleeding).[185–187] An extensive overview of data and recommendations can be found in the recent EHRA/HRS/APHRS consensus document.[167] A larger randomized trial, BRUISECONTROL2 (NCT01675076), is underway, evaluating uninterrupted dabigatran 110 mg BID vs. discontinuation (of any dose dabigatran) before implantation (24–48 h depending on kidney function).

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11. Patients requiring 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. Data from RE-LY have shown that the bleeding rate in dabigatran patients requiring urgent surgery 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).[163] Evaluation of common coagulation tests (aPTT for DTIs; sensitive PT for Factor Xa inhibitors) or of specific coagulation tests (dTT for DTI; chromogenic assays for FXa inhitibors) can be considered if there is concern about the PK waning of the anticoagulant effect (e.g. renal insufficiency and/or concomitant conditions as in *Table 6*; see also 'Drug–drug interactions and pharmacokinetics of non-vitamin K antagonist anticoagulants' section). There are anecdotal reports of emergency surgery in dabigatran-treated patients after a normal aPTT was confirmed.[45] Such a strategy, however, has never been tested systematically. Moreover, some have reported normal aPTT values despite prolonged TTs.[188]

If surgery cannot be delayed, reversal of the anticoagulant may be considered. As mentioned in 'Management of bleeding complications' section, data in healthy volunteers have shown that PCC or aPCC dose-dependently reverse the anticoagulant effects of NOACs in healthy volunteers.[154,155] Despite isolated experience of their use in emergency surgery settings,[136] this has never been evaluated prospectively.

First results with idarucizumab, a specific antibody fragment, showed that in 39 patients under dabigatran therapy requiring urgent surgery, there was a rapid and near maximal reversal of the anticoagulant effects by idarucizumab, with normal intraoperative haemostasis in all except for two and one patients with mildly to moderately abnormal hemostasis as judged by the operator.[138] The agent is under consideration for expedited approval by EMA and FDA. A prospective open-label Phase III trial with andexanet alfa, a recombinant FXa inhibitor antidote, is enrolling patients experiencing an acute major bleed under therapy but not patients requiring urgent surgical interventions (Clinicaltrials.gov NCT02329327).

12. Patient with atrial fibrillation and coronary artery disease

The combination of AF and CAD not only is a common clinical setting, it is also a complex setting to deal with anticoagulation and antiplatelet therapy, and it is associated with significantly higher mortality rates.[189–191] Unfortunately, there are not sufficient data available to optimally guide clinical practice in such settings, which is recognized by other recent documents by the ESC.[192–194] This text is in line with the aforementioned documents, but focuses specifically on NOAC treatment. There is no randomized study comparing VKAs and NOACs in patients with AF undergoing PCI for acute coronary syndromes (ACSs) or for stable CAD, i.e. patients who have an indication to receive single or DAPT. Moreover, new antiplatelet agents such as ticagrelor and prasugrel have entered the market for ACS. So far, there are no large-scale randomized studies published evaluating these newer antiplatelet agents in patients with AF receiving eiter VKAs or NOACs, adding to the uncertainty on how to use these antithrombotics in combination when both CAD (ACS or stable disease) and AF converge in a given patient. The lack of large outcome trials and the large number of possible combinations are reflected in the wide variety of practices across Europe in a recent survey by the EHRA.[195] For the sake of clarity, we have opted to define three clinical scenarios (see 'Scenario 1: coronary interventions in atrial fibrillation patients already on non-vitamin K antagonist oral anticoagulants', 'Scenario 2: management of the patient with a recent acute coronary syndrome (<1 year) who develops new-onset atrial fibrillation', and 'Scenario 3: a stable coronary artery disease patient (acute coronary syndrome ≥1 year ago) develops atrial fibrillation' sections). For background information and key scientific data that form the basis of the guidance spelled out here, see 'Key 'scientific' data on the use of non-vitamin K antagonist oral anticoagulant in acute coronary syndromes, percutaneoous coronary intervention, or stable coronary artery disease plus atrial fibrillation' section below.

Key 'scientific' data on the use of non-vitamin K antagonist oral anticoagulant in acute coronary syndromes, percutaneoous coronary intervention, or stable coronary artery disease plus atrial fibrillation

(i) Atrial fibrillation complicating an ST-elevation (STE) or non-STE (NSTE) ACS and vice versa is relatively frequent, and is associated with significantly higher mortality rates as well as higher rates of ischaemic and bleeding events.[189,191,196,197] Atrial fibrillation 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.

(ii) 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; new-generation drug-eluting stents (DESs) or bare-metal stents (BMSs) to minimize the duration of triple therapy; and a radial approach for interventional procedures (reducing at least the risk of access site bleeding). In the recent EHRA survey,[195] 81% preferred a radial approach in such setting.

(iii) Vitamin K antagonist treatment is protective after an ACS.[198] Warfarin plus aspirin reduces the risk of recurrent ischaemic events after an ACS, compared with aspirin alone. 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 + aspirin (with an INR between 2 and 2.5).[199] Low-intensity VKA (or poor INR control) does not appear to be protective.[200–202]

(iv) In stable CVD patients receiving OAC for AF, it appears to be unnecessary to add antiplatelet agents.[193,203] Recent data from a large Danish registry ($n = 8700$) adding an antiplatelet agent to VKA in stable CAD patients (i.e. beyond 12 months

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after an ACS) did not result in fewer recurrent atherothrombotic or thrombo-embolic events, but clearly increased bleeding risk.[204]

(v) Other registry data confirm a high risk of major bleeding with triple therapy.[205,206] To date, only two trials, WOEST[207] and ISAR-TRIPLE,[208] randomized patients requiring chronic anticoagulation and undergoing PCI to triple therapy (i.e. aspirin, clopidogrel, and VKA) or dual therapy (clopidogrel plus VKA). In WOEST, almost 70% received OAC because of AF, but only a minority of patients had an ACS. WOEST demonstrated that triple therapy (continued for a full year) doubles the risk of bleeding complications compared with a single antiplatelet (SAPT) agent (clopidogrel) plus VKA. Although this small open-label study was underpowered for evaluation of efficacy outcomes, clopidogrel plus VKA was associated with an intriguing significantly lower mortality rate, the mechanism of which remains elusive.[207] Of note, no data are available on how SAPT therapy with aspirin + VKA would have performed. In ISAR-TRIPLE, 6 weeks of triple therapy (i.e. aspirin + VKA + clopidogrel) was compared with a 6-month strategy with the same therapy in patients exclusively treated with a DES.[209] There was no significant difference in both bleeding or thrombotic events, or their combination, between the two strategies. However, there were fewer bleedings (classified as BARC types 1–5) between 6 weeks and 6 months with the shorter duration regimen. A nationwide Danish registry studied antithrombotic combinations in MI patients with AF.[205] Both triple therapy and VKA plus a SAPT agent significantly increased the risk of bleeding in these patients, compared with DAPT or VKA in monotherapy; the excess risk was especially high during the first 3 months, but persisted throughout 1 year. There was a slightly higher bleeding risk with clopidogrel + OAC than with aspirin + OAC, as also prior data had indicated.[205] 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, MI, or stroke). In addition, in the AFCAS registry ($n = 914$), propensity-adjusted major adverse cardiac or cerebrovascular event rates were numerically (but not statistically) higher with triple therapy compared with VKA and clopidogrel.[190] Taken together, these data indicate that triple therapy should be kept as short as possible. Which would be that SAPT (aspirin, clopidogrel, or a newer P2Y12 inhibitor) by preference remains unclear.

(vi) Triple therapy with DAPT and NOACs at least doubles the risk of major bleeding after an ACS.[91–93,210,211] As a rule of thumb, adding a SAPT drug to (any type of) oral anticoagulation increases the major bleeding risk by 60–80%; adding dual antiplatelet drugs increases major bleeding with at least 130% over anticoagulation only.[211]

(vii) There are currently three ongoing large-scale outcome studies evaluating combinations of NOAC or VKA and antiplatelets in patients with AF that undergo a PCI with stenting (elective or due to an ACS), providing hope that within the next few years there will be more evidence in this field.

(a) The PIONEER AF PCI study (NCT01830543) evaluates the safety of two different rivaroxaban treatment strategies vs. VKA: (i) 15 mg rivaroxaban OD plus clopidogrel; (ii) 2.5 mg BID plus low-dose aspirin 75–100 mg plus clopidogrel, prasugrel or ticagrelor, followed by rivaroxaban 15 mg OD (or 10 mg for subjects with moderate renal impairment) plus aspirin for 12 months; or (iii) VKA treatment strategy utilizing similar combinations of antiplatelet therapy.

(b) The RE-DUAL PCI study (NCT02164864) evaluates dual antithrombotic therapy regimens of (i) 110 mg dabigatran BID plus clopidogrel or ticagrelor, or (ii) 150 mg dabigatran BID plus clopidogrel or ticagrelor, with (iii) a triple antithrombotic therapy combination of warfarin plus clopidogrel or ticagrelor plus low-dose aspirin for 1–3 months.

(c) Finally, apixaban will be evaluated vs. VKA in AF patients with a recent ACS in the AUGUSTUS trial (NCT02415400). All patients will be receiving a P2Y12 inhibitor and will be randomized in a 2 × 2 factorial design to 6 months of apixaban 5 mg BID vs. VKA, and aspirin vs. placebo.

(d) A similar trial with edoxaban, EVOLVE-AF-PCI, is likely to start.

(viii) Although the above-mentioned clinical trials are ongoing, it is currently unknown whether SAPT/DAPT plus NOAC is safer in post-ACS or stable patients than SAPT/DAPT plus VKA or vice versa. There was no interaction with (dual) antiplatelet therapy on both efficacy and bleeding in the AF trials. Therefore, awaiting ongoing trials, it might be assumed that the respective advantages of the NOAC over VKA are maintained in dual or triple therapy.

(ix) In addition, several new antiplatelets and anticoagulants have recently been shown to be beneficial when separately evaluated for either ACS or AF.[212,213] 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.

(x) Prolonged antiplatelet therapy even beyond 1 year after ACS or DES implantation has been suggested based on recent large-scale randomized clinical trials. In the DAPT trial, patients were randomized 12 months after a PCI with DES to aspirin plus clopidogrel or aspirin alone, up to 30 months after the PCI.[214] In the PEGASUS TIMI 54 trial, patients were randomized 1–3 years after an MI to aspirin plus ticagrelor or aspirin alone, and followed for a median of 33 months.[215] However, patients in need of long-term oral anticoagulation therapy were excluded from both studies, making the results of less relevance for treatment of AF patients.

(xi) Dabigatran and edoxaban have 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 MIs 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).[216] However, the net clinical benefit and mortality benefit of dabigatran over VKA was maintained in AF patients with a previous MI, and the relative effects of dabigatran vs. VKA on myocardial ischaemic events were consistent in patients with or without a previous MI or CAD.[217] No excess of MI was observed in a Danish

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registry,[100] and in an FDA conducted US Medicare registry[218] comparing dabigatran vs. VKA in more than 134 000 patients. There were numerically more MIs with the low-dose regimen of edoxaban in ENGAGE-AF[28] and in HOKUSAI, the VTE trial with edoxaban.[219] Also in the North American subgroup of ROCKET-AF, in which the TTR was higher than in the overall trial, there was a numerical excess of MIs compared with the VKA group.[29] However, no trial with FXa inhibitors showed a statistically significant excess of MI.[26,28,29,193]

(xii) After ACS, DAPT on top of apixaban at a dose proven to be protective in AF significantly increases major and fatal bleeding risk including ICH, without clear evidence of reduction in ischaemic events including stroke.[93] Also a Phase II trial with dabigatran in combination with DAPT after ACS, showed a dose-dependent increase in bleeding events.[210]

(xiii) Very low-dose rivaroxaban (2.5 mg BID) on top of DAPT significantly improves ischaemic outcome after ACS, but is also associated with increased major and intracranial bleeding risk.[92] The risk of stroke was not reduced with this dose of rivaroxaban on top of DAPT in non-AF ACS patients. A study in stable AF patients undergoing PCI is on underway (PIONEER AF PCI; NCT01830543).

(xiv) In VKA-treated patients, a PCI seems safe without bridging and without additional peri-procedural heparin.[220] It is unknown if this applies also to NOACs, since all clinical studies have suggested interruption of NOAC therapy at PCI. A small pilot study in 50 stable patients undergoing planned PCI and on DAPT suggests that preprocedural dabigatran provides insufficient anticoagulation during PCI.[221] A similar study with rivaroxaban however showed suppressed coagulation activation after elective PCI, without increased bleeding.[222] The four-fold increased risk of (early) stent thrombosis with bivalirudin in the HORIZONS-AMI[223] and HEAT-pPCI[224] primary PCI trials also suggest that only direct thrombin inhibition might be insufficient in STE myocardial infarction (STEMI) patients, who are known to have delayed onset of action of P2Y12 inhibitors.[225] Similarly, the increased risk of catheter thrombosis with fondaparinux in OASIS-5/6,[226,227] indicated that peri-procedural solitary parenteral FXa inhibition was insufficient. In contrast, peri-procedural rivaroxaban, given 2–4 h before the procedure, appeared to be safe and effective in suppressing coagulation activation in stable patients on DAPT in another recent small mechanistic study.[222] Larger studies evaluating clinical outcomes are warranted.

Scenario 1: coronary interventions in atrial fibrillation patients already on non-vitamin K antagonist oral anticoagulants

Whereas guidelines recommend to maintain VKA patients uninterrupted on their treatment, both during elective or urgent PCI, NOACs should preferably be temporarily discontinued for elective interventions and upon presentation with ACS, as has been done during the Phase III AF trials. Performing a PCI (scheduled or not) under NOAC is different than under VKA for many reasons: uncertainty about the last dose; uncertainty about adherence; uncertainty about the extent of anticoagulation in the absence of mainstream tests, and hence uncertainty about stacking or additional peri-procedural anticoagulants; variability in renal function (especially when unknown in an acute setting); singular anti-factor II or X blockade vs. multifactor antagonism, etc. Limited experience with dabigatran in a small Phase II trial in patients undergoing an elective PCI suggests that dabigatran might not provide sufficient anticoagulation in such setting.[221] Temporary discontinuation of the short-acting NOACs allows safe initiation of antiplatelet therapy and standard local anticoagulation practices peri-procedurally. A recent consensus document issued by the ESC on antithrombotic combination therapies in AF patients undergoing PCI or having an ACS, in general discourages the inclusion of ticagrelor or prasugrel in triple therapy strategies since their bleeding risk in association with NOACs is not known (Class III, LoE C). However, it leaves the opportunity to use one of these antiplatelets with a (N)OAC under certain circumstances such as prior stent thrombosis while under a combination of aspirin, clopidogrel, and OAC.[193]

Acute in-hospital management

A general flow diagram, indicating possible scenarios, has been provided in *Figure 6*.

Elective coronary intervention (stable coronary artery disease)

New-generation DES or BMSs are preferred to shorten exposure to dual or triple therapy after the procedure (see below). Sole balloon angioplasty or bypass surgery should always be considered in patients in need for chronic anticoagulation, since they reduce the need for long-term dual or triple therapy.

There is no rationale for switching a NOAC to VKA after (or just prior) to elective PCI, since this may be associated with a clearly increased bleeding and thrombo-embolic risk compared with restarting the NOAC, as the correct dosing of VKA is unknown.

The NOAC should be discontinued before patients are taken to the cath lab and the NOAC effect should have disappeared (i.e. 24 h or longer after last intake; see 'Patients undergoing a planned surgical intervention or ablation' section). Peri-procedural anticoagulation should be used per local practice. Unfractionated heparin (70 IU/kg) or bivalirudin rather than enoxaparin is preferred.[228] Unfractionated heparin should be administered to target ACT or aPTT levels per standard clinical practice. Bivalirudin may be an attractive alternative because of its very short therapeutic half-life. In high-risk patients, bivalirudin is safer than the combination of UFH plus glycoprotein IIb/IIIa inhibitors.[229]

ST-elevation myocardial infarction

In the absence of contraindications, all NOAC patients developing an ACS should receive low-dose aspirin immediately at admission (150–300 mg loading dose) as well as a P2Y12 inhibitor. As clopidogrel as well as the newer P2Y12 inhibitors[225] takes considerable time to achieve its maximal antiplatelet effect in unstable patients, P2Y12 inhibition *without* aspirin cannot be recommended. In frail patients at high bleeding risk, aspirin only might be a safer initial therapy awaiting invasive management, when indicated.

In case of an STEMI, primary PCI via a radial approach is strongly recommended over fibrinolysis. It is recommended to use additional parenteral anticoagulation (i.e. UFH, enoxaparin, or bivalirudin, but

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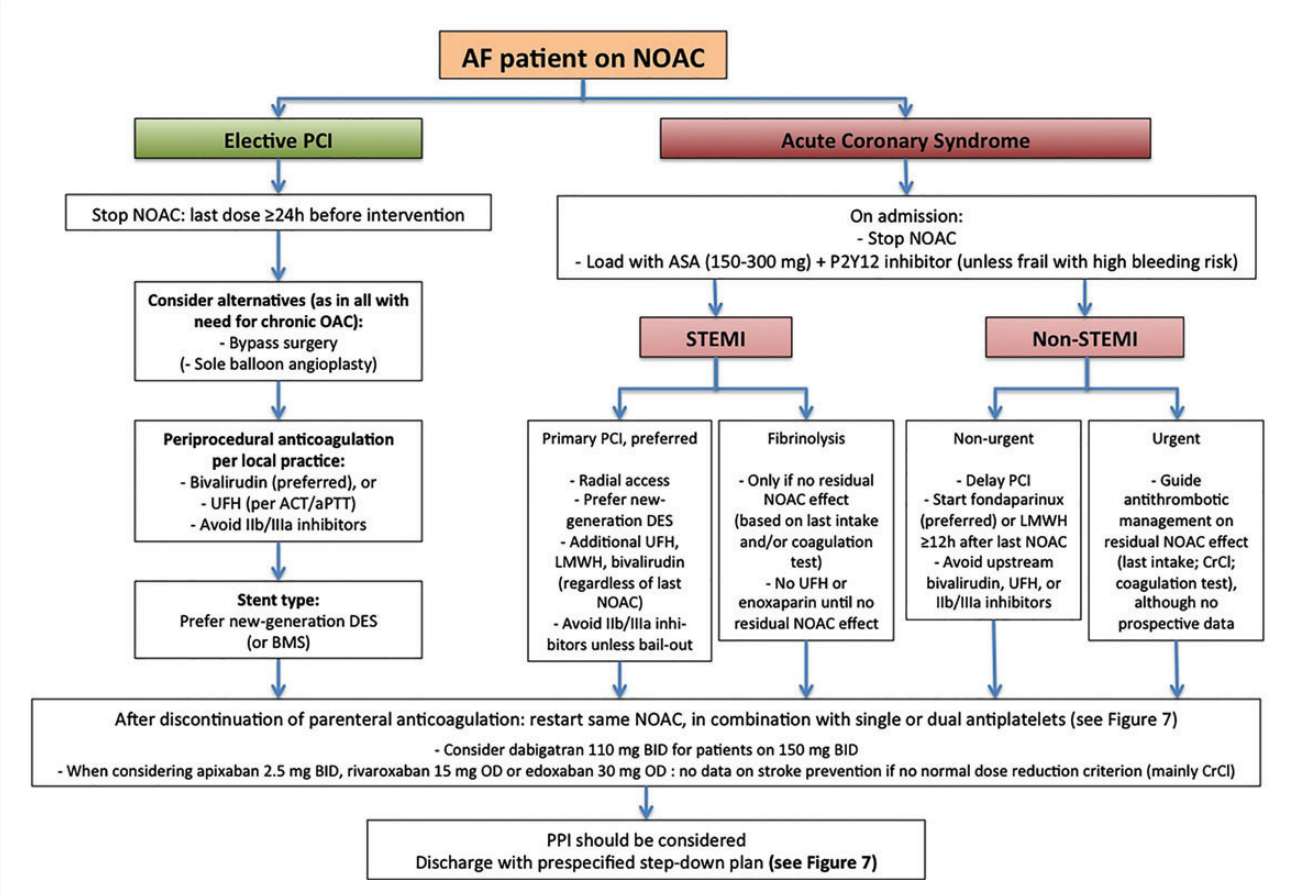

Figure 6 Acute management of revascularization or ACS in AF patients treated with NOAC. See text for further discussion.

not fondaparinux), regardless of the timing of the last dose of NOAC. Unless for bail-out situations, routine glycoprotein IIb/IIIa inhibitors should generally be avoided.

If fibrinolysis is the only available reperfusion therapy, it may be considered if the NOAC-treated patient presents with dTT, ECT, aPTT (for DTI), or PT (for FXa inhibitors) not exceeding the upper limit of normal. Also additional UFH or enoxaparin in addition to fibrinolysis should be avoided until the NOAC effect has decreased (12 h or longer after last intake).

Non-ST-elevation myocardial infarction

After discontinuing the NOAC and waning of its effect (12 h or longer after last intake; see 'Patients undergoing a planned surgical intervention or ablation' section), fondaparinux (preferred) or enoxaparin can be initiated. The use of upstream glycoprotein IIb/IIIa inhibitors should be avoided in this setting. In the ESC consensus document, UFH or bivalirudin is only recommended in bail-out situations, awaiting an intervention (class IIb C).[193] To reduce the risk of access site bleeding, a radial approach is preferred.

In more urgent situations, assessment of the NOAC effect might be considered (see 'How to measure the anticoagulant effect of NOACs?' section) to guide the antithrombotic peri-procedural management. However, because of uncertainty about the interpretation of routine coagulation tests in NOAC patients, and since such a strategy has never prospectively been evaluated, such an approach should be discouraged at this time.

Post-procedural 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 stopped. It is reasonable to restart the NOAC that the patient was taking before the ACS or elective procedure. There are no data to recommend switching to VKA (which may even be associated with higher bleeding and thrombo-embolic risks, especially in VKA-naive patients in whom the correct VKA dose is unknown), or to one particular NOAC. The same applies for AF patients after coronary bypass grafting.

As at least one antiplatelet agent is required, in dabigatran-treated patients the lower dose (110 mg BID) should be considered, as this dose has been shown to be non-inferior to VKA for stroke prevention but has a lower risk of major bleeding compared with VKA and dabigatran 150 mg BID, also in patients receiving antiplatelet treatment.[91]

Although in patients on therapy with FXa inhibitors needing the combination with antiplatelets, also the lower dose of NOAC (i.e. apixaban 2.5 mg BID, rivaroxaban 15 mg OD, or edoxaban 30 mg OD) might be considered to reduce bleeding risk, these dosages have been evaluated only in a subset of patients in the Phase III trials based on prespecified dosing algorithms. Their benefit in stroke

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prevention in patients with a normal renal function is uncertain (rivaroxaban and apixaban) or was inferior to VKA (edoxaban 30 mg). That needs to be taken into account when considering these dose reductions as part of combination antithrombotic treatment in AF patients deemed to have high bleeding risk due to combination therapy (i.e. not fulfilling the criteria used for dose reduction in the clinical studies.)

The patient needs to be discharged with a prespecified planned downgrade schedule of antithrombotic agents to reduce the longer term risk of bleeding while protecting against coronary events, as described below. Proton pump inhibitors should be considered in all patients with a combination of antiplatelets and anticoagulants.

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

Combining SAPT or DAPT with chronic anticoagulation (NOAC as well as VKA) significantly increases bleeding risk, regardless of any of the large variety of possible combinations.[91,204,210,230] There is no randomized study comparing VKA vs. NOAC in this setting, and there is no ideal combination fitting every patient. The type and level of anticoagulation as well as SAPT vs. DAPT and its duration need to be highly personalized, based on atherothrombotic risk, cardioembolic risk, and bleeding risk.[231] It is highly recommended to formally assess stroke and ischaemic event risk using validated tools such as the CHA_2DS_2-VASc and GRACE[232] scores. Estimating the bleeding risk, e.g. by the HAS-BLED score, should lead to efforts to correct or reduce reversible bleeding risk factors.[4,5] Reducing the time exposed to triple or even dual therapy needs to drive the physician's choice between the myriad of possible combinations for long-term therapy.

Given the many possible options (see 'Key 'scientific' data on the use of non-vitamin K antagonist oral anticoagulant in acute coronary syndromes, percutaneous coronary intervention, or stable coronary artery disease plus atrial fibrillation' section), we have opted to define guidance based on 'default scenarios', and modifiers that would indicate lengthening or shortening of the periods on triple and double therapy. *Figure 7* serves as a backbone for patient tailored decisions.

In patients **after elective PCI**, we propose a *default time of triple therapy of 1 month* (for a BMS or newer DES), thereafter stepping down to double therapy (with OAC and either aspirin or clopidogrel) until 1 year. Factors that weigh in to shorten triple therapy with earlier switch to dual therapy are a high (uncorrectable) bleeding risk or an estimated low atherothrombotic risk (as e.g. calculated

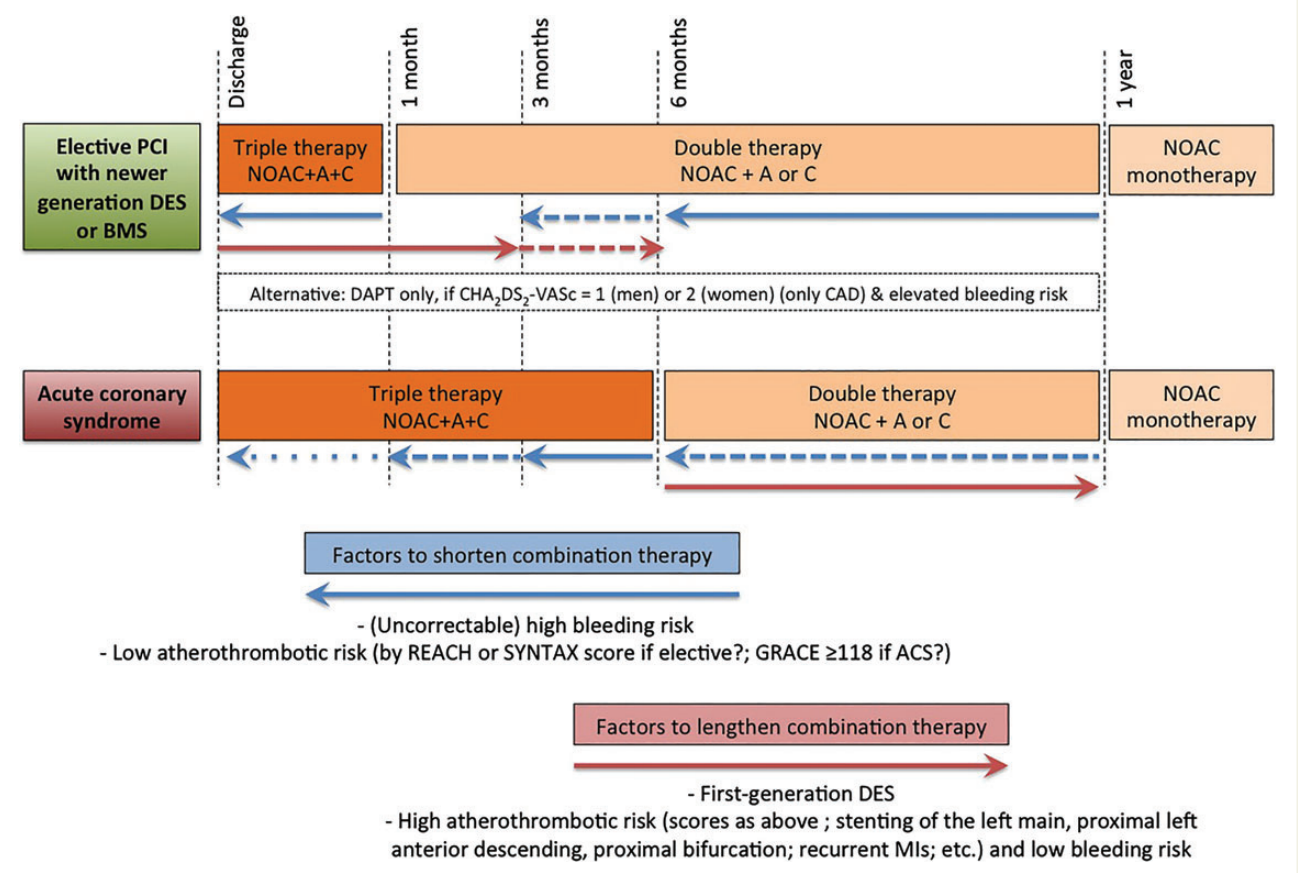

Figure 7 Default scenarios and criteria for adaptation for long-term treatment of patients on NOAC therapy after revascularization or ACS. There are innumerable possible variations on this global theme, as discussed in the text. Patient characteristics and institutional practices should be taken into account to individualize the approach. This figure wants to create a 'backbone' as guidance for such tailored approaches. A: aspirin 75–100 mg OD; C: clopidogrel 75 mg OD.

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with the Syntax or REACH score, although prospective validation is missing in such combination scenarios). The same factors may lead to the decision to discontinue all antiplatelets and provide anticoagulation in monotherapy, after 3–6 months (instead of 1 year). In a small subset of patients with a low stroke risk (CHA_2DS_2-VASc of 1 in males or 2 in females, i.e. only CAD) and elevated bleeding risk, one could opt to even treat with only DAPT, without anticoagulants, from the onset (although in ACTIVE-W there were numerically more MIs with aspirin plus clopidogrel compared with warfarin).[233] On the other hand, longer triple therapy (3–6 months) may be considered in those receiving a first-generation DES, or those with a combination of high atherothrombotic risk and low bleeding risk.

In patients **after an ACS**, treated medically or with PCI, *6 months of triple therapy* should be the current default before stepping down to double therapy. In those with a high (uncorrectable) bleeding risk, the duration of triple therapy can be shortened from 6 to 1 months, or even to immediate double therapy (with either aspirin or clopidogrel) in highly selected cases. Even longer triple therapy (up to 12 months) may be considered in individual cases receiving a first-generation DES or those with a combination of very high atherothrombotic risk (as e.g. calculated by a GRACE score $\geq$118; again without existing evaluation of this value in this setting) and low bleeding risk (HAS-BLED).

For all CAD patients with AF, the default is to step down to *anticoagulation in monotherapy after 1 year*, except for those with a very high risk for coronary events and an acceptably low bleeding risk. See also Scenario 3 below.

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 DAPT for up to 1 year after the acute event in patients without indication for OAC, and recent data indicate that even longer DAPT might be beneficial.[214,215] If AF develops during this time window, and there is an indication for thrombo-embolic prevention with anticoagulation, the question on starting (i.e. adding) VKAs or NOACs emerges. We refer to the default schedules described in 'Chronic setting (from discharge to 1 year after acute coronary syndrome)' section for guidance.

Although a low dose of rivaroxaban (2.5 or 5 mg BID) decreases ischaemic events including stent thrombosis in ACS patients on DAPT (albeit with an increase in bleeding), its protective effect against AF-related stroke is undetermined.[92,234] Therefore, such policy certainly cannot be defended in AF patients with higher thrombo-embolic risk, awaiting ongoing study addressing this combination (PIONEER AF-PCI; NCT01830543).

Scenario 3: a stable coronary artery disease patient (acute coronary syndrome $\geq$1 year ago) develops atrial fibrillation

Stable CAD patients developing AF should receive anticoagulation, depending on their CHA_2DS_2-VASc score. Based on studies showing that VKAs alone are superior to aspirin post-ACS, and VKAs + aspirin may not be more protective but associated with excess bleeding (see above), anticoagulation only without additional antiplatelet agents is considered sufficient for most AF patients with stable CAD.[192,204,235]

Are the NOACs safe and effective alternatives in such patients? About 15–20% of patients in the four Phase III 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. Also for dabigatran, the net clinical benefit was maintained and total myocardial ischaemic events were not increased, which was further supported by the very large registry follow-up in 134 000 elderly patients treated with dabigatran or VKA which did not reveal any increased risk for MI.[33,217] Since direct comparative data are lacking, there is no strong argument for choosing one NOAC over another in this setting.

13. Cardioversion in a non-vitamin K antagonist anticoagulant-treated patient

Based on the ESC guidelines,[4] in patients with AF of >48 h duration (or AF of unknown duration) undergoing cardioversion, effective oral anticoagulation should be given for at least 3 weeks prior to cardioversion, or TOE should be performed to rule out left atrial thrombi. After cardioversion, continuous oral anticoagulation is mandatory for at least another 4 weeks, irrespective of CHA_2DS_2-VASc score.[4,8,237] Different scenarios have to be distinguished: electrical cardioversion in a patient who is being treated with NOAC for a longer time and now requires a new cardioversion for a new bout of AF, and cardioversion in a patient newly diagnosed with AF in whom one wants to start anticoagulation with NOAC. For the latter scenario, only data are available in those with AF of >48 h duration. Therefore, we consider a third scenario, with AF of $\leq$48 h duration in an anticoagulation-naive patient (*Figure 8*).

Cardioverting an atrial fibrillation patient being treated for $\geq$3 weeks with non-vitamin K antagonist oral anticoagulant

Subgroup analyses from RE-LY (dabigatran), ROCKET-AF (rivaroxaban), and ARISTOTLE (apixaban) suggest that electrical cardioversion in patients treated with NOACs has a similar (and very low) thrombo-embolic risk as under warfarin.[237–239] The recently published X-VeRT trial confirmed the low peri-cardioversion stroke risk in patients treated with rivaroxaban compared with warfarin in a prospective, controlled trial, albeit with insufficient patient numbers to demonstrate statistically sound non-inferiority.[240] According to these data, a cardioversion without TOE seems reasonably safe under regular and continued NOAC intake, provided that good anticoagulation has been present for $\geq$3 weeks before cardioversion as stated in the Guidelines.[4] As there is no coagulation assay available for any NOAC that provides information on effective

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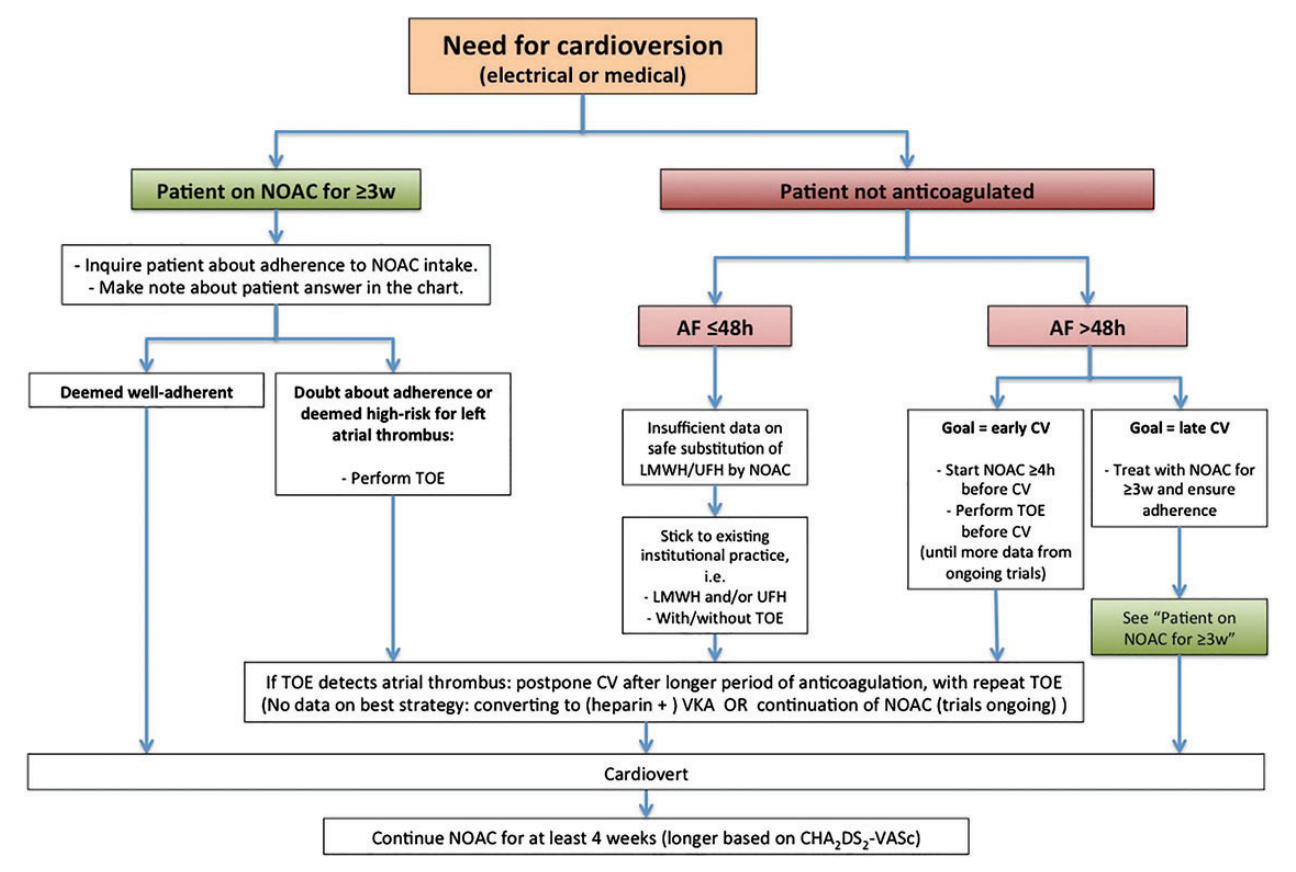

Figure 8 Cardioversion work-flow in AF patients treated with NOAC, depending on the duration of the arrhythmia and prior anticoagulation.

anticoagulation over the past 3 weeks, it is mandatory to explicitly ask the patient about adherence over the last weeks and to document the answer in their file. If in doubt about adherence, a TOE should be performed prior to cardioversion under a NOAC. Also, it has to be kept in mind that left atrial thrombi can also form in spite of adequate long lasting oral anticoagulation with a VKA or NOAC. Therefore, it remains an individual decision whether to perform a cardioversion with or without prior TOE. For this decision, the individual thrombo-embolic risk of a patient according to the $CHADS_2$ or CHA_2DS_2-VASc score can be considered: in 1.6–2.1% of therapeutically anticoagulated patients a TOE prior to AF ablation revealed thrombi or sludge in the left atrium and the risk of thrombus correlated with the $CHADS_2$ score (thrombus incidence $\leq$0.3% in $CHADS_2 = 0$ patients, thrombus incidence $>$5% in $CHADS_2 \geq 2$ patients).[241–243]

Cardioverting atrial fibrillation of >48 h in a patient not on non-vitamin K antagonist oral anticoagulant

For the scenario of cardioversion in an AF patient that is not on NOAC already, the X-VeRT study with rivaroxaban has been presented, and studies with the other NOACs are ongoing. In X-VeRT, 1504 AF patients with AF of $>$48 h or of unknown duration, scheduled for cardioversion, were prospectively randomized to receive rivaroxaban or VKA in a 2:1 fashion.[240] The cardioversion strategy was either early (with TOE, or without TOE in case the patient was known to be anticoagulated with VKA or NOAC for $\geq$3 weeks) or delayed (with 3–8 weeks anticoagulation before cardioversion). In the early group, the target was to cardiovert within 1–5 days after randomization. In rivaroxaban patients, the drug was started at least 4 h before cardioversion. Four hundred and sixty-two anticoagulation-naive patients entered the early strategy arm, of whom 305 received rivaroxaban. The median time to cardioversion was 1 day after randomization. There was no difference in ischaemic or bleeding events between anticoagulant or timing groups. Note that 64.7% of the entire early group underwent TOE, of whom 4.4% had an LA thrombus that precluded early cardioversion. Therefore, a strategy with at least a single NOAC dose $\geq$4 h before cardioversion is safe and effective in patients with AF of $>$48 h duration, provided that a TOE is performed prior to cardioversion.

Cardioverting atrial fibrillation of $\leq$48 h in an anticoagulation-naive patient

X-VeRT did not provide information on whether intake of at least 1 pill of NOAC is a feasible strategy in patients with AF of $\leq$48 h duration, who are currently often cardioverted after a single dose of LMWH (with continuation of anticoagulation for $\geq$4 weeks later on, especially when they have an elevated CHA2DS2-VASc score).

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Some of these patients are being included in ongoing trials such as ENSURE-AF (with edoxaban; clinicaltrials.gov NCT02072434) and EMANATE (with apixaban; NCT02100228). In the absence of further data, we recommend adherence to your current institutional practice with heparin/LMWH with/without TOE in such patients.

Management of a patient with documented left atrial appendage thrombus

Patients in whom TOE identifies a left atrial thrombus should not undergo cardioversion. Observational and prospective data did not show a different thrombus incidence in patients treated with NOAC or VKA.[237–240] There are no data on the best strategy when a thrombus is detected on either form of anticoagulant, but there may be a preference to treat the patient with rigorously followed-up INR monitoring under VKA therapy until resolution of the thrombus (with heparin bridging if necessary). Trials are ongoing to address this clinical scenario, such as RE-LATED_AF (with dabigatran; NCT02256683) and X-TRA (with rivaroxaban; NCT01839357)[244] the latter of which will report first.

14. Patients presenting with acute stroke while on non-vitamin K antagonist anticoagulants

The acute phase

Patients with acute brain haemorrhage (intracerebral haemorrhage)

Patients undergoing treatment with VKAs constitute 12–14% of patients with ICH, a risk which is even greater in Asian patients.[17,245] Apart from its direct reserved prognosis, ICH is also associated with later ischaemic stroke and mortality, partly due to the cessation of anticoagulation after the ICH.[246,247] Recommendations for the treatment of ICH under oral anticoagulants were recently published.[248–250] 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. Until the new antidotes for NOACs become available, the first treatment strategy is discontinuation of the drug and supportive therapy. If the intake of NOAC is $\leq$2 h ago, oral activated charcoal can be given (see also 'Patients with chronic kidney disease' section). The data on the use of specific pro-coagulants such as PCC, aPCC, and aFVII for severe bleeding associated with NOACs are discussed in 'Management of bleeding complications' section. The efficacy and safety of this strategy applied for ICH need to be further evaluated in clinical studies.[150,250] In essence, the situation is not different from 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, aPCC 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).[251]

In patients without evidence for ongoing bleeding or bleeding expansion, conservative treatment and observation can be advised, given the short half-life of NOACs. If rapid normalization is not expected, the steps outlined in 'Management of bleeding complications' and 'Patients requiring an urgent surgical intervention' sections can be taken.

Patients with acute ischaemic stroke

According to current guidelines and official labelling, thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA), which is approved within a 4.5 h time window from onset of stroke symptoms, is not recommended in patients under therapy with anticoagulants (like with an INR >1.7 if under VKA therapy). As plasma half-life of NOACs ranges between 8 and 17 h, thrombolytic therapy cannot be given within 24(–48) h after the last administration of NOAC (corresponding to two to four plasma half lives depending also on renal function), balancing the expected benefit of thrombolysis vs. its risk. This is an arbitrary recommendation, which has yet to be tested. In case of uncertainty concerning last NOAC administration, a prolonged aPTT (for dabigatran) indicates that the patient is anticoagulated (see 'How to measure the anticoagulant effect of NOACs?' section) and thrombolysis should not be administered. A reliable biomarker for the NOACs which can be measured in the emergency room is not yet available. 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 'How to measure the anticoagulant effect of NOACs?' section) is within the normal reference range, the use of rt-PA can be considered. We urge for the implementation of easy-to-use point-of-care testing for the emergency setting. There are no current data (not even pre-clinical) on whether specific NOAC antidotes might enable more rapid thrombolysis although this scenario was eligible for inclusion in the REVERSE-AD trial with idarucizumab.[138]

If NOACs have been administered within the last 24–48 h and appropriate coagulation tests are not available or abnormal, mechanical recanalization of occluded vessels with stent retrievers may be considered as an alternative treatment option. No prospectively collected data exist in patients under NOAC therapy, but the recent European Stroke Organization recommendations mention the use of mechanical thrombectomy in patients with contraindication for IV thrombolysis in light of the many recent positive studies on thrombectomy (http://2014.strokeupdate.org/consensus-statement-mechanical-thrombectomy-acute-ischemic-stroke).[252–254]

Management of the post-acute phase

Intracranial bleeding

As mentioned above, trial-based guidelines regarding NOACs in intracranial bleeding are missing. It will always be a very difficult individual decision to make whether or not to reintroduce anticoagulation of any type in patients who have experienced an anticoagulation-related intracranial bleeding. By analogy to the use of VKAs, administration of NOACs may be restarted 4–8 weeks if cardioembolic risk is high and the risk of new intracerebral haemorrhage is estimated to be low.[248,249] For patients with low

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cardioembolic risk and high bleeding risk, the indication for oral anticoagulation should be reconsidered. In practice, however, the same factors that are predictive for embolic stroke (age, hypertension, previous stroke, and others) are also predictive for intracerebral haemorrhages.[255] We should not forget that according to the labelling of VKAs and also of the NOACs, a history of a spontaneous intracranial bleed constitutes a contraindication against anticoagulation, unless the cause of the bleeding has been reversed. Reversible or treatable causes of intracerebral haemorrhage constitute uncontrolled hypertension, triple therapy, and INR >4–5 in patients on VKAs.

Arguments for not resuming or initiating anticoagulation after ICH would be older age, persistent uncontrolled hypertension, lobar bleeds, severe white matter lesions, multiple microbleeds on magnetic resonance angiography (>30), chronic alcoholism and need for DAPT after PCI. Patients with cortical bleeds have a much higher risk of recurrent bleeding and should not be anticoagulated.[256] This is also true after an intracerebral bleeding in a patient with amyloid angiopathy. Amyloid angiopathy can be assumed when there is a family history of ICH <60 years and/or early dementia. Severe small vessel disease and a high number of microbleeds are also suggestive of amyloid angiopathy.

Epidural haematomas are always traumatic, with skull fractures. In this case, it would be safe to start or reinitiate anticoagulation after 4 weeks although there are no specific data. The same applies to traumatic subdural haematoma, except for at least one-third of these patients who are chronic alcoholics. For spontaneous subdural haematomas in the context of uncontrolled INR (i.e. >3), anticoagulation can reasonably be restarted after 4 weeks. If the iNR was normal, however, or the patient was not anticoagulated, oral anticoagulation is contraindicated.

Non-pharmacological prevention strategies such as occlusion of the left atrial appendage should be considered as potential substitutes for the contra-indicated resumption of long-term anticoagulation.[4,5,257]

Ischaemic stroke

If adherence to medication intake and therapeutic effect of coagulation have been assured (i.e. the stroke must have occurred under adequate anticoagulation), alternative causes for the ischaemic stroke should be investigated, like large vessel disease, lacunar stroke, or others.[258]

Continuation or discontinuation of NOACs after ischaemic stroke depends on the infarct size and stroke severity. If in patients with mild stroke 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. Since NOACs have a faster onset of action compared with VKA, no bridging with heparins is required. Aspirin has no place in secondary stroke prevention.[4,5] Clinical study data regarding timing of reinstitution of anticoagulation after transient ischaemic attack (TIA) or stroke are missing. Therefore, recommendations on the initiation of anticoagulation are based on consensus opinion, in what is known as the '1-3-6-12 day rule': in patients with TIA and AF, oral anticoagulation can be initiated at day 1 or in patients who were on anticoagulation, it can be continued. In patients with mild stroke (NIHSS <8, National Institute of Health Stroke Scale), oral anticoagulation can be initiated after 3 days, or after intracranial haemorrhage is excluded by imaging (CT or MRI). In patients with moderate stroke (NIHSS 8–16), anticoagulation can be started after 5–7 days, and in severe stroke (NIHSS >16) after 12–14 days. In the last scenario, repeat cerebral imaging has to be performed to rule out significant haemorrhagic transformation of the initial ischaemic stroke (*Figure 9*). Ongoing trials like RE-SPECT ESUS (clinicaltrials.gov NCT02239120) have implemented this empirical 'rule' as a prospective strategy, which will be important for its validation.

Patients with transient ischaemic attack of cardioembolic origin

In patients with TIA, anticoagulation treatment with NOACs can be started immediately. With respect to the fast onset of action, bridging with heparin or LMWH is not recommended. Aspirin is no alternative option: in AF patients considered not suitable for VKA thrombo-embolic preventive treatment, the FXa inhibitor apixaban was shown to be superior to aspirin in stroke prevention with the same major bleeding risk.[27]

Patients with atrial fibrillation and concomitant atherosclerotic carotid disease

Patients with AF and known carotid athorosclerosis with mild to moderate asymptomatic stenosis can be treated with anticoagulants only, without the need for additional antiplatelet therapy, as in stable coronary heart disease (see 'Patient with atrial fibrillation and coronary artery disease' section).

Patients with AF and symptomatic high-degree stenosis of the internal carotid artery should be operated and not stented. This avoids prolonged triple therapy with high risk of major bleeding in stented patients. In patients undergoing endarterectomy, addition of aspirin is recommended immediately prior to and for 10 days after surgery.[258]

15. Non-vitamin K antagonist anticoagulants vs. vitamin K antagonists in atrial fibrillation patients with a malignancy

Many cancers occur in elderly patients, as does AF. 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, and although there were a few patients with cancer in the Phase III AF trials, the absence of type and stage of cancer information precluded any subgroup analysis. A combined analysis of the Einstein-DVT and -PE trials showed that 7.2% of the patients had cancer ($n = 597$; 5.2% at baseline, 2% diagnosed during the trial).[259] Although rates of recurrent DVT and major bleeding were higher in cancer patients, the efficacy and safety of rivaroxaban were similar in patients with cancer as in the full trial cohort, i.e. with a non-inferior DVT prevention rate compared with enoxaparin/heparin treatment but with a significantly lower major bleeding rate. Despite the small subgroup, the net clinical benefit of rivaroxaban was significantly more favourable due to the reduced bleeding rate than with the classical heparin treatment regimen.[259] A similar analysis from the

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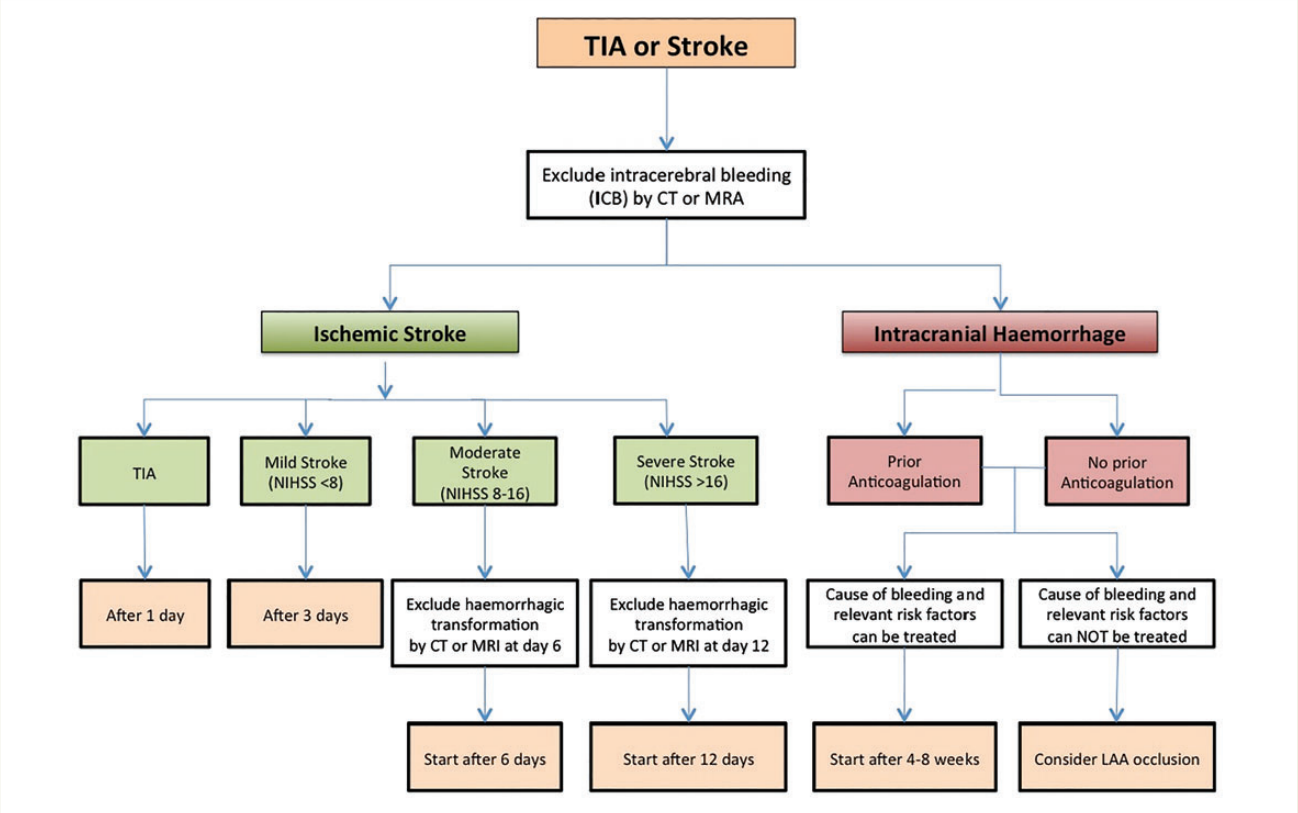

Figure 9 Flowchart for the initiation or re-initiation of anticoagulation after TIA/stroke or intracerebral haemorrhage.

RE-COVER trials with dabigatran showed no significant differences compared with VKA, both for VTE recurrence and for bleeding.[260] Based on these preliminary results of subgroup analyses and meta-analyses, it is suggested that NOACs could represent a better alternative than conventional anticoagulation in VTE patients with active cancer.[261,262] In how far this applies to AF requires more data. Antithrombotic therapy in patients with AF and suffering a malignancy definitely needs discussion between cardiologist and oncologist, taking into consideration the impact of the cancer on morbidity and mortality, the specific oncologic therapy used, and the anticipated effects of tumour and therapy on both thrombo-embolic risk and bleeding risk.

Patients with malignancies are at increased risk for thrombo-embolic events

Many forms of cancer interact directly or indirectly with the coagulation system. Some tumours directly secrete pro-thrombotic 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.

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).[263] Moreover, many malignancies are associated with increased risk of mucosal bleeding, e.g. bronchial carcinoma, urogenital cancers, gastrointestinal 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.

Practical suggestions

(i) Patients with malignancies and AF require multidisciplinary care by cardiologists and oncologists including a careful planning of antithrombotic therapy.

(ii) The presence of a malignancy in patients with AF increases stroke risk. If the AF patients are on prior NOAC therapy,

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its continuation may be possible, even in patients with malignancies who receive moderately myelosuppressive therapies. Possible drug–drug interactions on plasma levels (e.g. from antibiotics or antifungal therapy) should be considered (see *Table 6*).

(iii) When anticoagulant therapy needs to be newly initiated in a patient with malignancy developing AF, 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.

(iv) 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 routinely needed (such as LMWHs) in anticoagulated cancer patients.

(v) 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 'Patients undergoing a planned surgical intervention or ablation' section).

(vi) 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).

(vii) 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.

(viii) As mentioned in 'Choice of anticoagulant therapy and its initiation' section, gastric protection with PPI or H2 blockers should be considered in all patients treated with anticoagulants.

(ix) Patients with malignancies on NOACs should be instructed to carefully monitor signs for bleeding (petechiae, haemoptysis, and black stools) and be instructed to contact their therapy centre should those signs develop.

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