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SPECIAL ARTICLE

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

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The current manuscript is the second update of the original Practical Guide, published in 2013 [Heidbuchel *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**:625–651; Heidbuchel *et al.* Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015;**17**:1467–1507]. Non-vitamin K antagonist oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with atrial fibrillation (AF) and have emerged as the preferred choice, particularly in patients newly started on anticoagulation. Both physicians and patients are becoming more accustomed to the use of these drugs in clinical practice. However, many unresolved questions on how to optimally use these agents in specific clinical situations remain. The European Heart Rhythm Association (EHRA) set out to coordinate a unified way of informing physicians on the use of the different NOACs. A writing group identified 20 topics of concrete clinical scenarios for which practical answers were formulated, based on available evidence. The 20 topics are as follows i.e., (1) Eligibility for NOACs; (2) Practical start-up and follow-up scheme for patients on NOACs; (3) Ensuring adherence to prescribed oral anticoagulant intake; (4) Switching between anticoagulant regimens; (5) Pharmacokinetics and drug–drug interactions of NOACs; (6) NOACs in patients with chronic kidney or advanced liver disease; (7) How to measure the anticoagulant effect of NOACs; (8) NOAC plasma level measurement: rare indications, precautions, and potential pitfalls; (9) How to deal with dosing errors;

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(10) What to do if there is a (suspected) overdose without bleeding, or a clotting test is indicating a potential risk of bleeding; (11) Management of bleeding under NOAC therapy; (12) Patients undergoing a planned invasive procedure, surgery or ablation; (13) Patients requiring an urgent surgical intervention; (14) Patients with AF and coronary artery disease; (15) Avoiding confusion with NOAC dosing across indications; (16) Cardioversion in a NOAC-treated patient; (17) AF patients presenting with acute stroke while on NOACs; (18) NOACs in special situations; (19) Anticoagulation in AF patients with a malignancy; and (20) Optimizing dose adjustments of VKA. Additional information and downloads of the text and anticoagulation cards in different languages can be found on an EHRA website (www.NOACforAF.eu).

Abbreviations

ACS	Acute Coronary Syndrome,
ACT	Activated Clotting Time,
AF	Atrial Fibrillation,
AMPLIFY	Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy,
ANNEXA	Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors study,
aPCC	Activated Prothrombin Complex Concentrates,
aPTT	Activated Prothrombin Time,
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation,
ATLAS ACS–TIMI	Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction,
AUGUSTUS	Apixaban Versus Vitamin K Antagonist in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention,
AXAFA-AFNET	Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy – Atrial Fibrillation Network,
BMI	Body Mass Index,
BMS	Bare metal stent,
BRIDGE	Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery,
CAD	Coronary artery disease,
CKD	Chronic kidney disease,
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies,
CrCl	Creatinine clearance,
DAPT	Dual antiplatelet therapy,
DES	Drug-eluting stent,
dTT	Diluted thrombin time,
ECA	Ecarin chromogenic assay,
EHRA	European Heart Rhythm Association,
ELDERCARE-AF	Edoxaban low-dose for elder care AF patients,
ELIMINATE-AF	Evaluation of Edoxaban compared with VKA in subjects undergoing catheter ablation of non-valvular atrial fibrillation,
EMANATE	Eliquis evaluated in acute cardioversion compared to usual treatments for anticoagulation in subjects with NVAF,
ENGAGE AF-TIMI 48	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation - Thrombolysis in Myocardial Infarction 48,
ENSURE-AF	Edoxaban versus warfarin in subjects undergoing cardioversion of Atrial Fibrillation,
ENTRUST AF-PCI	Evaluation of the Safety and Efficacy of an Edoxaban-Based Compared to a Vitamin K Antagonist-Based Antithrombotic Regimen in Subjects With Atrial Fibrillation Following Successful Percutaneous Coronary Intervention With Stent Placement,
ESC	European Society of Cardiology,
GFR	Glomerular filtration rate,
ICB	Intracranial bleeding,
INR	International Normalized Ratio,
ISTH	International Society of Thrombosis and Hemostasis,
LMWH	Low molecular weight heparin,
MI	Myocardial infarction,
NOAC	Non-Vitamin K Antagonist Oral Anticoagulant,
Non-STEMI	Non- ST-elevation myocardial infarction,
NSAID	Non-steroidal anti-inflammatory drug,
PAUSE	Perioperative Anticoagulant Use for Surgery Evaluation,
PCC	Prothrombin Complex Concentrates,
PCI	Percutaneous Coronary Intervention,
P-gp	P-glycoprotein,
PIONEER AF-PCI	Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention,
PPI	Proton pump inhibitor,

PT	Prothrombin time,
RCT	Randomized clinical trial,
RE-CIRCUIT	Randomized Evaluation of Dabigatran Etexilate Compared to Warfarin in Pulmonary Vein Ablation: Assessment of an Uninterrupted Periprocedural Anticoagulation Strategy,
RE-DUAL PCI	Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention,
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy,
RE-VERSE AD	Reversal Effects of Idarucizumab in Patients on Active Dabigatran,
ROCKET AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation,
SEE	Systemic embolic event,
SmPC	Summary of product characteristics,
STEMI	ST-elevation myocardial infarction,
TIA	Transient ischaemic attack,
TT	Thrombin time,
TTR	Time in therapeutic range,
UFH	Unfractionated heparin,
VENTURE-AF	Active-controlled multi-center study with blind-adjudication designed to evaluate the safety of uninterrupted Rivaroxaban and uninterrupted vitamin K antagonists in subjects undergoing catheter ablation for non-valvular Atrial Fibrillation,
VHD	Valvular heart disease,
VKA	Vitamin K Antagonist,
VTE	Venous thromboembolic event,
WOEST	What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting,
X-VeRT	Explore the efficacy and safety of once-daily oral rivaroxaban for the prevention of cardiovascular events in patients with non- valvular atrial fibrillation scheduled for cardioversion

Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with atrial fibrillation (AF) and have emerged as the preferred choice, particularly in patients newly started on anticoagulation.[1–3] The term NOAC has been used for many years, is used by the current European Society of Cardiology (ESC) AF guidelines[3] and is widely recognized. Therefore, even though some authors refer to these drugs as 'direct oral anticoagulants',[4] we prefer to continue to use NOAC. Ultimately, both terms are interchangeable when referring to the direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban as well as the direct thrombin inhibitor dabigatran.

Non-vitamin K antagonist oral anticoagulants have an improved efficacy/safety ratio, a predictable anticoagulant effect without need for routine coagulation monitoring, and fewer food and drug interactions compared with VKAs. However, the proper use of NOACs requires a carefully considered approach to many practical aspects. Whereas the ESC Guidelines[3] mainly discuss the indications for anticoagulation in general and of NOACs in particular, they offer less guidance on how to deal with NOACs in specific clinical situations. Moreover, there are still several less well researched aspects of NOAC use, which are nonetheless relevant when these drugs are used by cardiologists, neurologists, geriatricians, general practitioners, and other healthcare providers in daily clinical practice. 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. The first edition of the Practical Guide was published in 2013 to supplement the AF guidelines as guidance for safe and effective use of NOACs when prescribed; a first update was published in 2015.[1,2] This text is the 2018 update to the original Guide.

A writing group formulated practical answers to 20 clinical scenarios, based on available and updated knowledge. The writing group was assisted by medical experts from the manufacturers of the NOACs, who 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 final responsibility of this document resided entirely with the EHRA writing group. In some instances, the authors opted to make recommendations that do not fully align with all SmPCs, 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, on perioperative management, and others).

An EHRA website, www.NOACforAF.eu, accompanies the Practical Guide. The Practical Guide is summarized in a Key Message booklet which can be obtained through EHRA and ESC; the website also provides EHRA members with a downloadable slide kit on the Practical Guide.

We hope that with the current revision the practical tool that EHRA envisioned has further improved. The authors realize that there will be gaps, unaddressed questions, and areas of uncertainty and 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 with the ultimate goal of improving patient care and outcome.

1. Eligibility for non-vitamin K antagonist oral anticoagulants

Non-vitamin K antagonist oral anticoagulants are approved for stroke prevention in non-valvular atrial fibrillation. Strictly, the term 'non-

Table 1 Selected indications and contraindications for non-vitamin K antagonist oral anticoagulant therapy in atrial fibrillation patients

Condition	Eligibility for NOAC therapy
Mechanical prosthetic valve	Contraindicated
Moderate to severe mitral stenosis (usually of rheumatic origin)	Contraindicated
Mild to moderate other native valvular disease (e.g., mild-moderate aortic stenosis or regurgitation, degenerative mitral regurgitation etc.)	Included in NOAC trials
Severe aortic stenosis	Limited data (excluded in RE-LY) Most will undergo intervention
Bioprosthetic valve (after > 3 months post operatively)	Not advised if for rheumatic mitral stenosis Acceptable if for degenerative mitral regurgitation or in the aortic position
Mitral valve repair (after > 3 months post operatively)	Some patients included in some NOAC trials
PTAV and TAVI	No prospective data yet May require combination with single or dual antiplatelet therapy
Hypertrophic cardiomyopathy	Few data, but patients may be eligible for NOACs

Hatched—limited data.
PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.

valvular AF' refers to AF in the absence of a mechanical prosthetic heart valve or moderate to severe mitral stenosis (usually of rheumatic origin) (*Table 1*),[3,5,6] which were exclusion criteria for all Phase III NOAC vs. warfarin trials in AF. In order to avoid confusion, the term 'non-valvular' has been eliminated in the 2016 ESC guidelines on the management of patients with AF, and reference is made to the specific underlying valvular heart disease (VHD).[3,6] However, the term is still found in the individual SmPCs of each of the NOACs due to the original wording used in the exclusion criteria of the clinical trials on which their regulatory approval was based.

Based on these new developments, a novel classification has recently been suggested where a functional EHRA (*E*valuated *H*eartvalves, *R*heumatic or *A*rtificial) categorization is proposed, depending on the type of OAC use in patients with AF.[6] In this scheme, EHRA Type 1 refers to AF patients with VHD needing therapy with a vitamin K antagonist (VKA), including in particular moderate–severe mitral stenosis of rheumatic origin and mechanical prosthetic valve replacement. In contrast, EHRA Type 2 valvular heart disease refers to VHD patients needing thromboembolic prevention therapy for AF with a VKA or a NOAC, including essentially all other native valvular stenoses and insufficiencies as well as mitral valve repair, bioprosthetic valve replacements and transaortic valve intervention (TAVI).[6] Patients with EHRA Type 2 valvular heart disease were variously included in these trials and NOACs demonstrated a comparable relative efficacy and safety vs. warfarin in patients with vs. without valvular disease, except for a higher risk of bleeding with rivaroxaban vs. warfarin in patients with valvular heart disease in a *post hoc* analysis of the ROCKET-AF trial.[6–12] Non-vitamin K antagonist oral anticoagulants may therefore be used in such patients (*Table 1*).[3,6,13]

Atrial fibrillation in patients with biological valves or after valve repair constitute a grey area, even though these patients were included in some of the landmark NOAC trials.[6,7,9,10] Since most of these patients do not require long-term oral anticoagulation following their valve procedure, the use of a NOAC for the management of concomitant AF is considered to be a valid option. One exception may be AF in the presence of a biological mitral prosthesis implanted for rheumatic mitral stenosis. Although mitral valve flow is normalized post-mitral valve replacement in these patients, their atria usually remain large and severely diseased. As such, VKA may be the preferred option over NOACs in these patients, but more data are needed.

There are no prospective data available yet on NOACs in patients after percutaneous aortic valve interventions [percutaneous transluminal aortic valvuloplasty or transcatheter aortic valve implantation (TAVI)] in the presence of AF. Percutaneous transluminal aortic valvuloplasty or TAVI usually requires single or even transient dual antiplatelet therapy (DAPT).[5] The addition of an anticoagulant increases the bleeding risk, and the optimal combination and duration is the subject of ongoing studies, in analogy to the situation in acute coronary syndrome (ACS) patients (see **chapter 14**).

In hypertrophic (obstructive) cardiomyopathy (HCM), AF is associated with a high rate of thromboembolism. There is limited experience with NOACs in this condition.[14,15] In contrast to patients with AF in the setting of mechanical valves or rheumatic mitral stenosis, however, there does not seem to be a mechanistic rationale why NOACs should be inferior to warfarin in HCM. On the contrary, AF in HCM shares many similarities of HFpEF related AF, for which there has been no indication that NOAC would be inferior to VKA.[16–18] Moreover, NOACs

demonstrate a sustained efficacy over VKA also in other high risk subgroups (e.g. patients with a high CHA_2DS_2-VASC score). As such, patients with HCM may be eligible for NOAC therapy.

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

Choice of anticoagulant therapy and initiation

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

Before prescribing a NOAC to a patient with AF, it needs to be decided that anticoagulation is indicated based on a risk/benefit analysis.[3] The choice of anticoagulant (VKA or NOAC; choice of NOAC) should be made on the basis of indications approved by regulatory authorities and specified within guidelines from professional societies. Knowledge of kidney function is required, since all NOACs have precautions and contraindications based on creatinine clearance (CrCl) (see **chapter 6**). Also product characteristics (as explained in the SmPCs), patient-related clinical factors, and patient preference need to be taken into account.[3,19,20]

European guidelines have expressed a preference for NOACs over VKA in stroke prevention for AF patients, especially if newly initiated. This recommendation (Class I, level of evidence A) is based on the overall clinical benefit of NOACs.[3]

In some countries, NOAC therapy can only be prescribed (and/or are reimbursed) if international normalized ratio (INR) control with VKA has been shown to be suboptimal (i.e. after a failed 'trial of VKA'). There is evidence that clinical scores such as SAMe-TT_2R_2 may be able to predict poor INR control.[21–27] However, further prospective studies would be required to validate and implement such strategies (which are not generally needed from a medical perspective, but may be a reasonable cost containment strategy). For the majority of patients, and in accordance with current ESC guidelines, NOACs need to be considered as the first choice anticoagulation based on the positive results of the large outcome trials.[3,28–31]

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

With four NOACs available in different dosages for different indications and with different dose reduction criteria, identification of the correct dose has become more complicated and is one of the key challenges in the daily use and individualization of treatment (see **chapter 15**). Non-vitamin K antagonist oral anticoagulants do not have precisely the same rules for prescription and availability in every country. Local factors, such as regulatory approval, formulary committees and the cost of therapy, may influence NOAC availability.

All NOACs have been tested in large randomized prospective trials and resulted in documented efficacy and safety of the respective agent. Testing of different doses, however, was carried out differently. In ARISTOTLE (using apixaban) and ROCKET-AF (using rivaroxaban), patients received one dose which was reduced in the presence of predefined patient characteristics.[29,30] In contrast, in RE-LY (with dabigatran) and ENGAGE-AF (with edoxaban) both a lower and a higher dose were tested in fully powered patient cohorts (with further dose reduction for edoxaban in certain patients, see **chapter 15**).[28,31] Dose reduction of NOACs is primarily recommended only according to the dose reduction criteria investigated in the large phase III trials (see **chapter 15**). Whenever possible, the tested standard dose of NOACs should be used. In addition, it is also important to consider co-medications, some of which may be contraindicated or result in unfavourable drug–drug interactions (see **chapter 5**). Also, patient age, weight, renal function (see **chapters 6 and 18**), and other comorbidities influence the choice. In some patients, proton pump inhibitors (PPIs) may be considered to reduce the risk for gastrointestinal (GI) bleeding, especially in those with a history of GI bleeding or ulcer and patients requiring concomitant use of (dual) antiplatelet therapy.[32,33] This gastroprotective effect was especially demonstrated in patients receiving antiplatelet or VKA therapy,[34–36] while data on the preventive effects in NOAC treated patients are limited.[37] Decision aids are available to guide clinicians about which NOAC may be best suited for a specific target group.[38–41]

An anticoagulation card for non-vitamin K antagonist oral anticoagulants and the importance of education

Patients on VKAs have routinely been advised to carry information about their anticoagulant therapy to alert any healthcare provider about their treatment. It is equally important that those treated with NOACs carry details of this therapy. Each manufacturer provides proprietary information cards to be completed by physicians and carried by patients; however, we recommend that a uniform card should be used instead. The proposed NOAC card presented in this version of the Practical Guide has been updated and will be available for download in various languages at www.NOACforAF.eu.

It is critically important to educate patients at each visit about the modalities of intake [once daily (OD) or twice a day (BID); intake with food in case of 15 mg/20 mg of rivaroxaban], the importance of strict adherence to the prescribed dosing regimen, how to deal with any lapse in dosing, and to be careful not to leave their medication behind when travelling. Key educational aspects are also listed on the NOAC anticoagulation card. Education sessions can be further facilitated using specific checklists.[3,20,42,43]

How to organize follow-up?

The follow-up of AF patients who are taking anticoagulant therapy needs to be carefully specified and communicated among the different caregivers of the patient. The use of any anticoagulant is associated with some drug–drug interactions which may increase the risk of serious bleeding or diminish stroke protection. Treatment requires vigilance due to potentially severe complications, particularly as the target patient population tends to be of older age and frail. Patients' treatment should be reviewed on a regular basis (preferably after 1 month initially and at least every 3 months thereafter). As clinical experience with NOACs grows,[44,45] follow-up intervals may become longer, based on individual (patient-specific) or local (centre-specific) factors. Patient follow-up may be undertaken by general

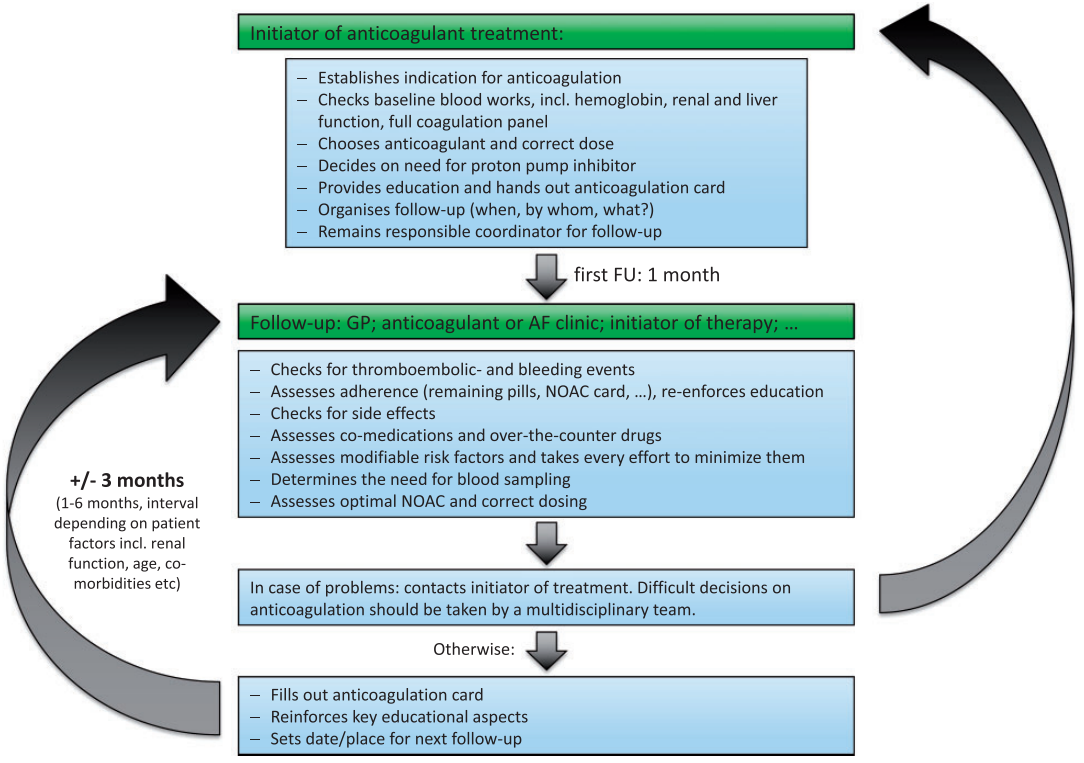

Figure 1 Structured follow-up. Initiation and structured follow-up of patients on non-vitamin K antagonist oral anticoagulants. It is mandatory to ensure safe and effective drug intake. The anticoagulation card is intended to document each planned visit, each relevant observation or examination, and any medication change, so that every person following up the patient is well-informed. Moreover, written communication between different healthcare providers is required to inform them about the follow-up plan and execution. FU, follow-up.

practitioners with experience in this field and/or by appropriate secondary care physicians (*Figure 1*). Growing evidence shows that nurse-coordinated AF clinics may be very helpful in this regard.[46–50] Each caregiver, including specially trained 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.

Table 2 and *Figure 1* list the appropriate timing of the relevant aspects which need to be systematically assessed during follow-up. Importantly, the individual patient profile needs to be taken into consideration; for example, renal function needs to be assessed more frequently (*Table 2*) in compromised individuals including older patients (≥75 years), frail patients,[52,53] or in those where an intercurrent condition (such as infection or cancer), which may affect hepatic or renal function. Also stroke risk factors alter over time and need to be reassessed at every patient visit.[54] Bleeding risk should be systematically assessed, e.g. by the HAS-BLED score, which has also been validated in patients on NOACs[55] and has shown a better prediction than an approach based only on modifiable bleeding risk factors.[56–60] Also other bleeding risk scores have been proposed.[59,60] Importantly, however, a high bleeding risk in itself should not automatically result in the decision not to anticoagulate as stroke risk tracks along with bleeding risk.[3,61] For the practical management, correcting and minimizing modifiable risk factors is of critical importance in order to minimize the risk of bleeding while on treatment with a NOAC. This approach is also the one recommended by current AF guidelines.[3] Similarly, frailty and risk of falling should not generally be a reason not to anticoagulate patients, but rather to ensure careful education on the best choice of (N)OAC and dose selection, and follow-up of the patient (see **chapter 18**).

3. Ensuring adherence to prescribed oral anticoagulant intake

Strict adherence to NOAC intake is crucial as its anticoagulant effect wanes within 12–24 h after the last intake.[62] Non-vitamin K antagonist oral anticoagulant plasma level as well as general coagulation tests cannot be considered as tools to monitor adherence since they only reflect intake over the last 24(–48) h and the measured level is heavily dependent on the time between last intake and sampling (see **chapter 7**). The absence of a need for routine plasma level monitoring means that NOAC patients are likely to be less frequently seen for follow-up compared with VKA patients. However, there are arguments in favour of regular follow-up assessment for patients on

Table 2 Checklist during follow-up contacts of atrial fibrillation patients on anticoagulation

	Interval	Comments
1. Adherence	Each visit	• Instruct patient to bring NOAC card and complete list of medication: make note and assess average adherence • Re-educate on importance of strict intake schedule • Inform about adherence aids (special boxes; smartphone applications; . . .). Consider specific adherence measuring interventions (review of pharmacy refill data; electronic monitoring[51]; special education session; . . .)
2. Thromboembolism	Each visit	• Systemic circulation (TIA, stroke, peripheral) • Pulmonary circulation
3. Bleeding	Each visit	• 'Nuisance' bleeding: preventive measures possible? Motivate patient to diligently continue anticoagulation • Bleeding with impact on quality-of-life or with risk: prevention possible? Need for revision of anticoagulation indication, dose or timing?
4. Other side effects	Each visit	Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation, or change of anticoagulant drug
5. Co-medications	Each visit	• Prescription drugs; over-the-counter drugs (Pharmacokinetics and drug–drug interactions of non-vitamin K antagonist oral anticoagulants section). • Careful interval history: also temporary use can be risky
6. Blood sampling (incl. hemoglobin, renal and liver function)	Yearly	Patients other than those specified below
	6-monthly	≥75 years (especially if on dabigatran) or frail (see **chapter 2**)
	x-monthly	If renal function CrCl ≤60 mL/min: recheck interval = CrCl/10
	If needed	If intercurrent condition that may impact renal or hepatic function
7. Assessing and minimizing modifiable risk factors for bleeding	Each visit	• As recommended by current guidelines[3] • Particularly: uncontrolled hypertension (systolic >160 mmHg), medication predisposing for bleeding (e.g. aspirin, NSAIDs), labile INR (if on VKA), excessive alcohol intake)
8. Assess for optimal NOAC and correct dosing	Each visit	Especially based on the above, re-assess whether a. The chosen NOAC is the best for the patient b. The chosen dose is correct

For frequency of visits: see *Figure 1*.
CrCl, creatinine clearance (preferably measured by the Cockcroft–Gault method); NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; TIA, transient ischaemic attack.

NOACs, particularly in case of relevant co-morbidities such as renal failure, older age, multiple comorbidities, or frailty.

Available 'real world' data suggest variable adherence to NOAC intake from 38% to 99% depending on the setting and definition.[63–78] Although caution is needed when interpreting these results, low adherence rates severely diminish the benefit of treatment. Some of these concerns have been alleviated by recent 'real world' implementation data which mostly confirm the improved risk/benefit profile in patients treated with NOACs vs. VKAs as observed in the randomized controlled trials suggesting adequate adherence also in daily clinical practice.[66,72,79–98] Although there is evidence for significantly lower discontinuation rates with NOACs than with VKAs, discontinuation is still a relevant issue.[67,76,77,84,95,99–107] Despite limited data on how NOAC adherence can best be optimized, all means possible should be considered.

Practical considerations (Figure 1)

(1) Patient education on the need for oral anticoagulation therapy and the importance of strict adherence is important.[19,20,42,63,108–111] Many simultaneous approaches can be employed to provide education including leaflets and instructions at initiation of therapy, a patient anticoagulation card, group sessions, and 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 UK (www.anticoagulationuk.org), and AFNET (http://www.kompetenznetz-vorhofflimmern.de/de/vorhofflimmern/patienteninformation-vorhofflimmern). Education may be more effective if directed to specific knowledge gaps of the patient, measured by validated questionnaires which can be administered to the patient at the time of a visit, or even via online platforms.[64,109,112]

(2) Family members should be involved in the care of the patient, so that they understand the importance of adherence and help the patient in this regard.

(3) There should be a pre-specified follow-up schedule for the NOAC patient (as suggested in *Figure 1*) known to and shared by general practitioners, cardiologists, pharmacists, anticoagulation clinics, and other professionals providing care. Each of those involved has a responsibility to reinforce adherence. Everyone's efforts should be communicated to the others, e.g. by filling out a line on the NOAC anticoagulation card (see **chapter 2**). Nurse-coordinated AF centres may be helpful in coordinating patient follow-up and checking on adherence.[46–50]

(4) 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. It has been shown that an increased follow-up and adherence monitoring by pharmacists may improve NOAC adherence.[113]

(5) Many technological aids are being explored to enhance adherence: the day-marked blister pack format; medication boxes (conventional or with electronic verification of intake); smartphone applications[114] with reminders and/or SMS messages to alert the patient about the next intake some even requiring confirmation that the dose has been taken. Popular apps for both Android and iOS devices are Medisafe Pill Reminder (also available for watchOS), Dosecast, MyMeds, CareZone, and many others.[115] Again, the long-term effects of such tools are unknown and one tool may not suit all patients.

(6) Once daily dosing regimens generally results in greater adherence vs. BID regimens in cardiovascular patients.[116–118] Most, but not all studies evaluating adherence for NOACs indicate that an OD dosing regimen is superior from a total tablet count perspective.[66,67,70–74,95,112,119,120] However, it is still uncertain whether any regimen is superior in guaranteeing the clinical thromboembolic preventive effects and safety profile as seen in the clinical trials.[73,83–86,90–95,121,122] Although there are modelling data suggesting that there is potentially a larger fluctuation in the anticoagulant activity when a single dose is omitted from an OD dosing regimen compared with when a single or even two doses are omitted from a BID regimen,[123] the clinical relevance of these fluctuations is unknown.[124] Therefore, it is essential to ensure that drugs are taken according to the prescribed regimen.

(7) In cases where suboptimal adherence is suspected, electronic monitoring may help to educate the patient by exposing patterns of missed doses. Electronic medication intake monitoring can even be set up as a telemonitoring service, with the possibility of faster feedback to the patient.[51] The health-economic validity of such an approach needs further study.

(8) Some patients may explicitly prefer INR monitoring to no monitoring, or VKA over NOAC therapy. Patient education needs to discuss these preferences in the context of available clinical trial data (including reduction in ICH with NOACs even in the setting of high TTR).[19,42]

(9) In NOAC patients in whom low adherence is suspected despite proper education and additional tools, conversion to VKAs may be considered. It needs to be kept in mind, however, that poor adherence in VKA treated patients is equally associated with INR fluctuations and less preferable outcomes.

4. Switching between anticoagulant regimens

When switching between different anticoagulant therapies, it is important to ensure the continuation of anticoagulant therapy while minimizing the risk for bleeding. This requires insights into the pharmaco-kinetics and -dynamics 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 [half-lives for acenocoumarol 8–24 h, warfarin 36–48 h, phenprocoumon 120–200 h (6 days)]. The proposed scheme (also shown in *Figure 2*, top panel) tries to unify different specifications from the SmPCs, which state that NOAC can be started when INR is ≤3 for rivaroxaban, ≤2.5 for edoxaban, and ≤2 for apixaban and dabigatran.

Non-vitamin K antagonist oral anticoagulant (NOAC) and Vitamin K antagonist (VKA)

Because of the slow onset of action of VKAs, it may take 5–10 days before the INR is in the therapeutic range, with large individual variations (see also **chapter 20**). Therefore, the NOAC and VKA should be administered concomitantly until the INR is in a range that is considered appropriate (*Figure 2*, lower panel)—similar to the situation when low molecular weight heparins (LMWHs) are administered during VKA initiation. A loading dose is not recommended for acenocoumarol and warfarin, but is appropriate with phenprocoumon (see **chapter 20**).

As NOACs may have an impact on INR measurements, it is important that the INR (i) is measured just before the next intake of the NOAC during concomitant administration and (ii) is re-measured early after stopping the NOAC (i.e. reflecting solely VKA therapy) to assure adequate anticoagulation. It is also recommended to closely monitor INRs within the first month until stable values have been attained (i.e. three consecutive measurements 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 the INR was within range, in combination with the above intensive INR testing strategy.[125] Switching according to this scheme

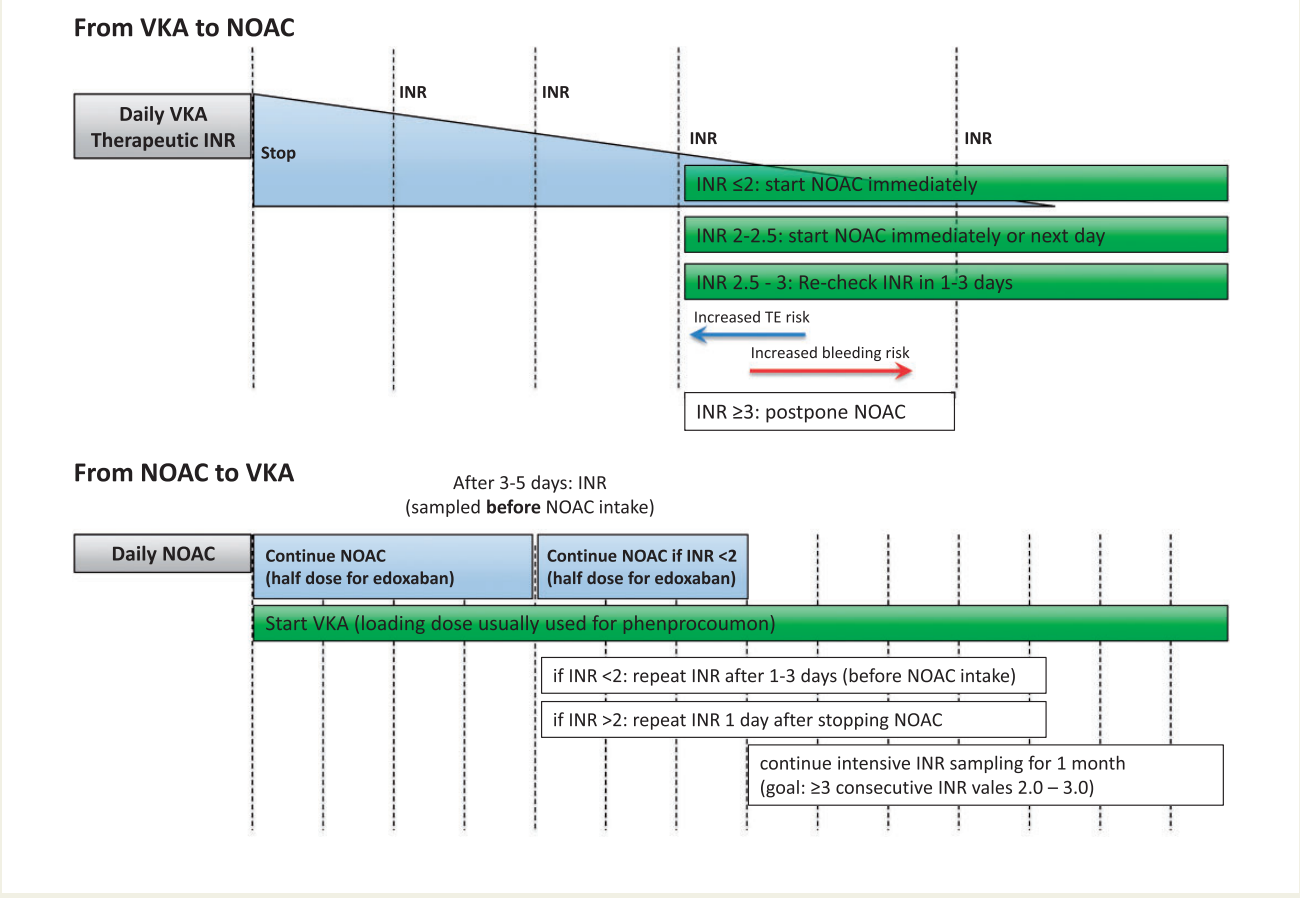

Figure 2 Switching between vitamin K antagonists and non-vitamin K antagonist oral anticoagulants and vice versa. TE, thromboembolic.

has proven to minimize the risks of stroke and bleeding[125] while, conversely, inadequate transitioning was associated with increased stroke rates.[126,127] Whether the half-dose bridging regimen also applies to transitioning of NOACs other than edoxaban is unknown.

When concomitant administration of a NOAC during the initiation of the VKA is not deemed appropriate, initiation of the VKA can be performed after switching the NOAC to LMWH (see below), which may be considered especially in patients with a high thromboembolic risk.

Non-vitamin K antagonist oral anticoagulant to parenteral anticoagulants

The parenteral anticoagulant [unfractionated heparin (UFH) and LMWH] can be initiated when the next dose of the NOAC would be due.

Parenteral anticoagulant to non-vitamin K antagonist oral anticoagulant

Intravenous UFH: NOACs can usually be started 2 (to 4) h after intravenous UFH (half-life 2 h) is discontinued.

Low molecular weight heparin: NOACs can be initiated when the next dose of LMWH would be due. Care should be taken in patients with renal impairment where the elimination of LMWH may be prolonged.

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

The alternative NOAC can be initiated when the next dose of the initial NOAC 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 in between NOACs is recommended.

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 (see **chapter 14**).

5. Pharmacokinetics and drug–drug interactions of non-vitamin K antagonist oral anticoagulants

Treatment with VKAs requires careful consideration of multiple food and drug–drug interactions. Despite fewer interactions with the

NOAC drugs, physicians should consider the pharmacokinetic interactions of accompanying drugs and 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. Knowledge regarding 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 absorption, distribution, metabolism, and excretion of the different NOACs are summarized in the previous version of the guide.[2] An important interaction mechanism for all NOACs consists of significant gastrointestinal re-secretion over a P-glycoprotein (P-gp) transporter after absorption in the gut. Competitive inhibition of this pathway will result in *increased* plasma levels. The P-gp transporter is also involved in renal clearance.[128] Many drugs used in AF patients are P-gp inhibitors (e.g. verapamil, dronedarone, amiodarone, and quinidine). CYP3A4-type cytochrome P450-dependent elimination is relevantly involved in the hepatic clearance of rivaroxaban and apixaban.[129] Strong CYP3A4 inhibition or induction may affect plasma concentrations, and should be evaluated in context (see *Tables 3–5* and colour coding, discussed below). Non-metabolic clearance of apixaban is diverse (including excretion of the unchanged compound by >50%), which reduces the potential for drug–drug interaction.[130] In general, NOAC use is not recommended in combination with drugs that are strong inhibitors of both CYP3A4 and P-gp. Conversely, strong inducers of P-gp and/or CYP3A4 (such as rifampicin, carbamazepine, etc.) will markedly *reduce* NOAC plasma levels; such combinations should be avoided or used with great caution and surveillance.

Specific dosing algorithms for the different NOACs have been evaluated in large Phase III clinical trials and resulted in documented efficacy and safety of the respective agent. Of note, only one Phase III study prospectively used concomitant therapy with certain drugs as a dose reduction criterion (dose reduction of edoxaban in ENGAGE-AF in patients treated with potent P-gp inhibitors verapamil, quinidine, or dronedarone). Dose reduction of all NOACs is primarily recommended along the published dose reduction criteria (see **chapter 15**). Whenever possible, the tested standard doses of NOACs should be used.

However, there is some 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 based on a combination of factors.[3,151–154] Prospective clinical trial data only exist for 'lower doses' of dabigatran (110 mg BID) and edoxaban (30/15 mg OD; but not approved). For dabigatran 110 mg BID, a similar stroke risk and reduced major bleeding vs. warfarin was observed[28]; however, this was in an unselected AF population and not in selected high-risk patients in whom plasma levels may be increased and the benefit of a reduction in major bleeding may be lost.[152,155] For edoxaban 30/15 mg OD a 41% higher ischaemic stroke risk compared with a well-controlled warfarin arm (median TTR >68%) was observed leading to non-approval of this dosing regimen; at the same time, a reduction in major bleeding, cardiovascular- and all-cause mortality was observed compared with warfarin.[31,153] These data represent the only available RCT evidence of a 'lower dose' of a NOAC for stroke prevention in AF on hard clinical endpoints.[28,31] In contrast, no 'lower dose' arm was included in ROCKET-AF (for rivaroxaban) or ARISTOTLE (for apixaban) and as such, no clinical outcome data are available for the use of these doses outside the tested dose reduction algorithms. (Of note, a small study in Japanese patients investigated the use of 15 mg rivaroxaban as standard dose for stroke prevention in Japanese patients with apparently preserved efficacy, but the implications of these results outside this setting are unclear.)[156]

The use of plasma level monitoring for NOAC dose-adjustment or in the setting of 'off label' lower dose prescription (see **chapters 7 and 8**) is discouraged for the vast majority of patients due to the lack of outcome data to support such an approach. Indeed, an increased risk of bleeding frequently goes along with an increased risk of stroke due to the overlapping risk factors (including advanced age, frailty etc.), and inappropriate use of a reduced dose may result in lack of stroke prevention.[157] However, in rare cases of potentially substantial drug–drug interactions or special situations in which a certain NOAC is preferred for certain reasons (e.g. patients after transplantation, patients on HIV medication etc.) this may be considered (*Figure 3*). Importantly, this approach should be limited to centres with extensive experience in the performance and interpretation of such assays as well as in the care of NOAC-treated patients.

In summary, possible drug–drug interactions, especially when combined with other clinical risk factors affecting NOAC plasma levels are important aspects for choosing a specific NOAC for a specific patient. *Table 3* gives an overview of the effect of various frequently used agents on NOAC plasma levels; *Table 4* focusses on common cancer drugs (see also **chapter 19**), *Table 5* on antiepileptic drugs (see also **chapter 18.4**). Taking into consideration these factors as well as the setup and results from the large randomized NOAC outcome trials the algorithm shown in *Figure 3* may assist in a rational selection of a specific NOAC and/or a 'reduced dose' based on drug–drug interactions and other clinical risk factors. Unfortunately, for many potential interactions with drugs that are often used in AF patients no detailed information is available yet (hatched in the tables).

Food intake, antacids, and nasogastric tube administration

Rivaroxaban 15 mg/20 mg for stroke prevention in AF needs to be taken with food [the area under the curve (AUC) plasma concentrations increases by 39% to a very high bioavailability of almost 100%], while there is no food interaction with the other NOACs. The concomitant use of PPIs and H2-blockers leads to a small reduction in bioavailability of dabigatran, but without effect on clinical efficacy.[158,159] There is also no relevant antacid interaction for the other NOACs.[140,160,161] There are no pharmacokinetic data on fish oil supplements for any of the NOACs, but interaction is unlikely.

Data have shown that administration in crushed form, e.g. via a nasogastric tube, does not alter the bioavailability for apixaban, rivaroxaban, and edoxaban.[162–164] Also an oral solution of apixaban 5 mg (12.5 mL of 0.4 mg/mL oral solution administered via oral syringe together with 240 mL of water) has been developed, which has shown comparable exposure as the tablet formulation.[165] In contrast, dabigatran capsules must not be opened as it results in a substantial increase in drug bioavailability (+75% per SmPC).

Table 3 Effect of drug–drug interactions and clinical factors on NOAC plasma levels ('area under the curve')

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[131]
Antiarrhythmic drugs					
Amiodarone	moderate P-gp competition	+12 to 60%[SmPC]	No PK data[a]	+40%[132–134]	Minor effect[a]
Digoxin	P-gp competition	No effect[SmPC]	No effect[135]	No effect	No effect[SmPC]
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[SmPC]	+40%[136]	No data yet	No effect
Dronedarone	P-gp competition and CYP3A4 inhibition	+70 to 100% (US: 2 × 75 mg if CrCl 30–50 mL/min)	No PK or PD data: caution	+85%[b]	Moderate effect, should be avoided
Quinidine	P-gp competition	+53%[SMPC]	No data yet	+77%[137] (no dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12 to 180%[SmPC] (if taken simultaneously)	No PK data	+53% (SR)[137,142] (no dose reduction required by label)	No effect
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	No relevant interaction	No data yet	No effect	No effect
Ticagrelor	P-gp competition	+25%[SmPC] (give loading dose 2h after dabigatran)[d]	No data	No data	No data
Antibiotics					
Clarithromycin; Erythromycin	Moderate P-gp competition and strong CYP3A4 inhibition	+15 to 20%	+60% AUC +30% C_{max}	+90%[SmPC]	+34% (Erythromycin)/ +54% (Clarithromycin) SmPC129
Rifampicin	P-gp/BCRP and CYP3A4/ CYP2J2 inducers	Minus 66%[SmPC]	Minus 54%[138]	Minus 35%, but with compensatory increase of active metabolites	Up to minus 50%[SmPc]
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%[129]

Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[SmPC]
Itraconazole; Ketoconazole; Voriconazole	potent P-gp and BCRP competition; CYP3A4 inhibition	+140 to 150% (US: 2 x 75 mg if CrCl 30–50 mL/min)	+100%[136]	+87 to 95%[132] (reduce NOAC dose by 50%)	Up to +160%[SmPc]
Posaconasole	Mild to moderate P-gp inhibition	SmPC	SmPC		SmPC
Others					
Naproxen	P-gp competition; pharma-codynamically increased bleeding time	No data yet	+55%[139]	No effect	No data yet
H2B; PPI; Al-mg-hydroxide	GI absorption	Minus 12–30%	No effect	No effect[SmPc]	No effect[140]
St. John's wort	P-gp/BCRP and CYP3A4/CYP2J2 inducers				
Other factors					
Age ≥80 years	Potential for Increased plasma levels		b	c	
Age ≥75 years	Potential for Increased plasma levels			c	
Weight ≤60 kg	Potential for Increased plasma levels		b	b	
Renal function	Increased plasma level	See *Figure 4*			
Other increased bleeding risk		• Concomitant antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants • History of GI bleeding • Recent surgery on critical organ (brain; eye) • Frailty/falls risk • St.p bleeding or predisposition (anaemia, thrombocytopenia)			

The hatched colour coding indicates no clinical or PK data available, and recommendations are based on the respective NOAC SmPC (where available) or expert opinion.
White: No relevant drug–drug interaction anticipated.
Yellow: Consider dose adjustment or different NOAC if 2 or more 'yellow' factors are present (see *Figure 3*).
Orange: Consider dose adjustment or different NOAC (see *Figure 3*).
Red: contraindicated/not recommended.
Brown: Contraindicated due to *reduced* NOAC plasma levels.
Blue: The label for edoxaban mentions that co-administration is possible in these cases, despite a decreased plasma level, which are deemed not clinically relevant. Since not tested prospectively, however, such concomitant use should be used with caution, and avoided when possible.
BCRP, breast cancer resistance protein; NSAID, non-steroidal anti-inflammatory drugs; H2B, H2-blockers; PPI, proton pump inhibitors; P-gp, P-glycoprotein; GI, gastrointestinal.
[a]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 end-points in the Phase-3 clinical trials.[29,30] No direct PK interaction data available.
[b]Dose reduction based on published criteria (see *Table 13*, *Figure 3*).
[c]Age had no significant effect after adjusting for weight and renal function.
[d]Data from Phase I study. Evidence from Re-DUAL PCI indicate safety in the (small) subgroup on dabigatran and ticagrelor.[141]

Table 4 Anticipated effects of common anticancer drugs on non-vitamin K antagonist oral anticoagulants plasma levels

	Via[142]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		**Yes**	**Yes**	**Yes**	**Yes**
CYP3A4 substrate		**No**	**Yes (≈25%)**	**No (<4%)**	**Yes (≈18%)**
Antimitotic agents					
Paclitaxel	Moderate CYP3A4 induction; CYP3A4/P-gp competition				
Vinblastine	Strong P-gp induction; CYP3A4/P-gp competition				
Docetaxel, Vincristine	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Vinorelbine	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Antimetabolites					
Metotrexate	P-gp competition; no relevant interaction anticipated				
Pemetrexed, Purine analogs, Pyrimidine analogs	No relevant interaction anticipated				
Topoisomerase inhibitors					
Topotecan	No relevant interaction anticipated				
Irinotecan	CYP3A4/P-gp competition; No relevant interaction anticipated				
Etoposide	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Anthracyclines/Anthracenediones					
Doxorubicin	Strong P-gp induction, mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Idarubicin	Mild CYP3A4 inhibition; P-gp competition				

Daunorubicin	P-gp competition; No relevant interaction anticipated				
Mitoxantrone	No relevant interaction anticipated				
Alkylating agents					
Ifosfamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Ciclophosphamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Lomustine	Mild CYP3A4 inhibition				
Busulfan	CYP3A4 competition; No relevant interaction anticipated				
Bendamustine	P-gp competition; No relevant interaction anticipated				
Chlorambucil, Melphalan, Carmustine, Procarbazine, Dacarbazine, Temozolomide	No relevant interaction anticipated				
Platinum-based agents					
Cisplatin, Carboplatin, Oxaliplatin	No relevant interaction anticipated				
Intercalating agents					
Bleomycin, Dactinomycin	No relevant interaction anticipated				
Mitomycin C	No relevant interaction anticipated				
Tyrosine kinase inhibitors					
Imatinib, Crizotinib	Strong P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition				
Nilotinib, Lapatinib	Moderate-to-strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Vemurafenib	Moderate CYP3A4 induction; CYP3A4/P-gp competition				

Dasatinib	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Vandetanib, Sunitinib	Strong P-gp induction; CYP3A4 competition				
Erlotinib, Gefitinib	CYP3A4 competition; No relevant interaction anticipated				
Monoclonal antibodies					
Brentuximab	CYP3A4 competition; No relevant interaction anticipated				
Rituximab, Alemtuzumab, Cetuximab, Trastuzumab, Bevacizumab	No relevant interaction assumed				
Hormonal agents					
Abiraterone	Moderate CYP3A4 inhibition, strong P-gp inhibition; CYP3A4/P-gp competition				
Enzalutamide	Strong CYP3A4 induction, strong P-gp inhibition; CYP3A4/P-gp competition				
Bicalutamide	Moderate CYP3A4 inhibition				
Tamoxifen	Strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4 competition				
Anastrozole	Mild CYP3A4 inhibition				
Flutamide	CYP3A4 competition; No relevant interaction anticipated				
Letrozole, Fulvestrant	CYP3A4 competition; No relevant interaction anticipated				
Raloxifene, Leuprolide, Mitotane	No relevant interaction anticipated				
Immune-modulating agents					
Cyclosporine	Strong-to-moderate P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC	SmPC	+73%[143]	

Dexamethasone	Strong CYP3A4/P-gp induction; CYP3A4/P-gp competition				
Tacrolimus	Strong-to-moderate P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC			
Prednisone	Moderate CYP3A4 induction; CYP3A4 competition				
Temsirolimus, Sirolimus	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Everolimus	CYP3A4 competition; No relevant interaction anticipated				

Purine analogs: Mercaptopurine, Thioguanine, Pentostatin, Cladribine, Clofarabine, Fludarabine.
Pyrimidine analogs: Fluorouracil, Capeticabine, Cytarabine, Gemcitabine, Azacitadine, Decitabine.
Anticipated effects of common anticancer drugs on NOACs plasma levels.[144]
The hatched colour coding indicates no clinical or PK data available, and recommendations are based on the respective NOAC SmPC (where available) or expert opinion. Some of the colour codes will likely require adaptation as more data become available over time.
White: No relevant drug–drug interaction anticipated.
Yellow (light): Caution is needed in case of polypharmacy or in the presence of ≥2 bleeding risk factors.
Yellow: Consider dose adjustment or different NOAC if 2 or more 'yellow' factors are present (see *Figure 3*).
Orange: Consider dose adjustment or different NOAC (see *Figure 3*).
Red: contraindicated/not recommended.
Brown (dark): Contraindicated due to *reduced* NOAC plasma levels.
Brown (light): Use with caution or avoid. Either expert opinion or the NOAC label mentions that co-administration is possible despite a decreased plasma level, which is deemed not clinically relevant (nevertheless, since not tested prospectively, such concomitant use should be used with caution, and avoided when possible).
Where no data or SmPC instructions were available, expert opinion was based on the following principles:

- Strong CYP3A4 and/or P-gp inducer—should not be used (dark brown).
- Moderate CYP3A4 or P-gp inducer—use with caution or avoid (light brown).
- Strong CYP3A4 and/or inhibitor—should not be used (red).
- Moderate CYP3A4 or P-gp inhibitor—use with caution, consider dose reduction or different NOAC (orange).
- Mild CYP3A4 and/or P-gp inducers or inhibitors—caution is needed with polypharmacy or in the presence of ≥2 bleeding risk factors (yellow).

Rate and rhythm control drugs

Possible interactions are listed in *Table 3*. The P-gp inhibiting effects of verapamil on dabigatran levels are dependent on the verapamil formulation: when an immediate release preparation is taken within 1 h prior to dabigatran intake, plasma levels of dabigatran may increase up to 180%. Separating both drugs' intake ≥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 concentration. Pharmacokinetic data from the RE-LY trial showed an average 23% increase in dabigatran levels in patients taking verapamil.[166] It is advised to use the lower dose dabigatran (110 mg BID) when combining it with verapamil ('orange', *Table 3*).

A similar interaction had initially been noted for edoxaban.[167] However, after analysis of Phase III data, this interaction was considered not to be clinically relevant and no dose reduction is recommended in the European label. However, caution might be warranted in combination with other factors ('yellow', *Table 3*). On a more general level, these findings underline the difference between changes in plasma levels and influence on hard clinical endpoints. There are no specific interaction pharmacokinetic data available for apixaban or rivaroxaban with verapamil. Diltiazem has a lower inhibitory potency of P-gp, resulting in non-relevant interactions,[166] although there is a 40% increase in plasma concentrations of apixaban ('yellow'; *Table 3*).[136]

For edoxaban a 40% increase in AUC was observed in patients on amiodarone with normal renal function.[132] Of note, there was a significant interaction for amiodarone on the efficacy of the low-dose edoxaban regimen in the Phase III trial, exemplifying the potential impact of changed plasma levels.[133] Nevertheless, dose reduction is not recommended in case of concomitant administration.

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 dronedarone intake was a dose reduction criterion in the ENGAGE-AF protocol.[31] There are no interaction pharmacokinetic 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') or avoidance (for rivaroxaban). Interestingly, a recent analysis of NOAC plasma levels before surgical

Table 5 Anticipated effects of common antiepileptic drugs on non-vitamin K antagonist oral anticoagulants plasma levels

	Via[142,145,146]	Dabigatran etexilate	Apixaban[130]	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	SmPC	−50%[SmPC]	−35%[SmPC]	SmPC, Ref.[147]
Ethosuximide	CYP3A4 competition; No relevant interaction known/assumed				
Gabapentin	No relevant interaction known/assumed				
Lamotrigine	P-gp competition; No relevant interaction known/assumed				
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/P-gp induction; P-gp competition		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC, Ref.[148]	SmPC	SmPC	SmPC
Pregabalin	No relevant interaction known/assumed				
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction				Ref.[149]
Zonisamide	CYP3A4 competition; No relevant interaction known/assumed				

Anticipated effects of common antiepileptic drugs on NOACs plasma levels.[147,150]
The hatched colour coding indicates no clinical or PK data available, and recommendations are based on the respective NOAC SmPC, where available, or expert opinion. Some of the colour codes will likely require adaptation as more data become available over time.
White: No relevant drug–drug interaction anticipated.
Brown (dark): Contraindicated due to *reduced* NOAC plasma levels.
Brown (light): Use with caution or avoid—either the label for the respective NOAC mentions that co-administration is possible despite a decreased plasma level, which are deemed not clinically relevant (nevertheless, since not tested prospectively, such concomitant use should be used with caution, and avoided when possible) or expert opinion.
Where no data or SmPC instructions were available, expert opinion was based on the following principles:

- Strong CYP3A4 and/or P-gp inducer—should not be used (dark brown).
- Moderate CYP3A4 or P-gp inducer—use with caution or avoid (light brown).
- Strong CYP3A4 and/or inhibitor—should not be used (red).
- Moderate CYP3A4 or P-gp inhibitor—use with caution, consider dose reduction or different NOAC (orange).
- Mild CYP3A4 and/or P-gp inducers or inhibitors—caution is needed with polypharmacy or in the presence of ≥2 bleeding risk factors (yellow).

intervention demonstrated that concomitant intake of verapamil, dronedarone, or amiodarone was significantly associated with higher pre-operative plasma levels.[168]

Other drugs

Table 3 also lists the potential interaction mechanisms for other drugs and their possible clinical relevance. Since some drugs are inhibitors of both CYP3A4 and P-gp, they may have an effect on NOAC plasma levels although the P-gp and/or CYP3A4 effect in itself is less pronounced. In general, although NOACs are substrates of CYP enzymes or P-gp/breast cancer resistance protein (BCRP), they do not inhibit or induce any of them.

Co-administration of NOACs with other substrates of CYP3A4 (e.g. midazolam), P-gp (e.g. digoxin), or both (e.g. atorvastatin) does not significantly alter plasma levels of these drugs.

The platelet inhibitor ticagrelor is a P-gp inhibitor. Concomitant administration of ticagrelor 180 mg loading dose with dabigatran 110 mg increased dabigatran C_{max} by 65% (AUC +49%), compared with dabigatran given alone. When a loading dose of 180 mg ticagrelor was given 2 h after 110 mg dabigatran etexilate, the increase of

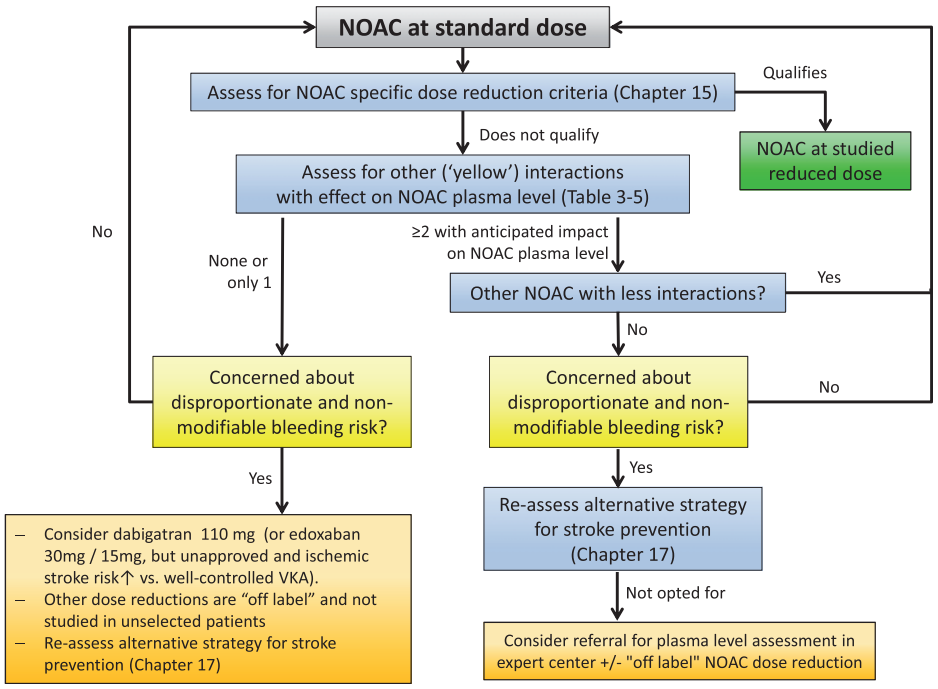

Figure 3 NOAC selection based on drug–drug interactions and/or risk of bleeding. Use of plasma level measurements to guide dosing is generally discouraged and should only be used in rare cases of potentially substantial interactions or special situations, and only in centres with great experience in the performance and interpretation of such assays as well as the care of NOAC-treated patients.

dabigatran C_{max} and AUC was reduced to +23% and +27%, respectively, compared with dabigatran given alone. As per the dabigatran SmPC, this staggered intake is the recommended administration strategy for starting with the loading dose of ticagrelor. Concomitant administration of 90 mg ticagrelor BID (maintenance dose) with 110 mg dabigatran increased the adjusted dabigatran AUC and C_{max} by 26% and 29%, respectively, compared with dabigatran given alone. These data are based on a Phase I study; the use of ticagrelor and dabigatran post-percutaneous coronary intervention (PCI) as studied in the RE-DUAL PCI study is discussed in detail later (see **chapter 14**).[141]

Of note, 'herbal' medicines are frequently underestimated regarding their potential for interaction, including the potent CYP3A4 and P-gp inducer St. John's wort, although relevant interactions have been published (also outside the anticoagulation field).[169] Due to the relevant decrease in NOAC levels, the concomitant use of St. John's wort is not recommended.

Pharmacodynamic interactions

Apart from the pharmacokinetic interactions, co-administration of NOACs with other anticoagulants, platelet inhibitors (e.g. aspirin, clopidogrel, ticlopidine, prasugrel, ticagrelor, others), and non-steroidal anti-inflammatory drugs increases the risk of bleeding.[170–172] Therefore, such combinations should be carefully balanced against the potential benefit in each clinical situation. Co-administration of NOACs with dual antiplatelet drugs requires active measures to reduce time on triple therapy (see **chapter 14**).

Polypharmacy

Polypharmacy is a well-established risk factor for adverse events resulting from drug–drug interactions.[173–175] In ROCKET-AF and ARISTOTLE, patients concomitantly taking several (≥5 or ≥9) medications experienced similar outcomes and consistent treatment effects of either NOAC relative to warfarin.[174,175] Although reassuring, these findings are derived from *post hoc* analyses with many limitations. In addition, concomitant use of strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) or inducers (e.g. phenytoin, rifampicin) was not allowed. Conversely, event rates with warfarin also increase in patients with polypharmacy, likely not only due to interactions but also due to the higher baseline risk of these patients. While polypharmacy in itself is not a contraindication for the use of NOACs, special care needs to be taken when treating these vulnerable patients (*Tables 3–5*; *Figure 3*).

6. Non-vitamin K antagonist oral anticoagulants in patients with chronic kidney disease or advanced liver disease

Kidney and liver function both play an important role in the metabolism and elimination of NOACs.

Oral anticoagulation in chronic kidney disease

There is a bidirectional interaction between AF and chronic kidney disease (CKD): AF facilitates the development or progression of CKD, and the prevalence and incidence of AF increases with decreasing renal function.[176–179] Patients with AF and CKD have an increased morbidity and mortality due to their excessive risk for both thromboembolic and severe bleeding events, making risk stratification and treatment challenging.[180,181] In addition, all four NOACs are at least partly eliminated by the kidneys. Dabigatran has the greatest extent of renal elimination (80%), whereas 50%, 35%, and 27% of edoxaban, rivaroxaban, and apixaban, respectively, are cleared via the kidneys as unchanged drug (*Table 6*).

Clinical decisions on how to treat an AF patient with CKD who needs OAC requires the assessment of renal function. Basic information on the diagnosis/staging of CKD and assessment of renal function is provided in *Table 7*. Several equations are available to gauge a patient's renal function, all with inherent strengths and limitations. The CKD-EPI equation estimating the glomerular filtration rate is recommended by the *National Kidney Foundation* because it has been shown to be reliable across the range of CKD stages.[187] However, in the context of NOAC treatment, renal function should preferably be estimated by calculating the CrCl using the Cockcroft–Gault method, which was used in most NOAC trials and therefore also in this *Practical Guide*. Importantly, CKD can only be diagnosed and assessed in stable situations and must not be confused with acute renal failure. In the latter case, serum creatinine levels and calculated CrCl may indicate mildly reduced (or even normal) renal function when in reality it is severely impaired. In situations with acute renal failure, any NOAC therapy needs to be discontinued and parenteral anticoagulation initiated (after careful risk-benefit analysis).

In patients on NOACs, renal function needs to be monitored diligently, 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), a more frequent evaluation is recommended (e.g. by dividing CrCl by 10 to obtain the minimum frequency of renal function testing in months; *Table 2*). In patients with additional risk factors (e.g. older age, frail, multiple co-morbidities etc.), it may be evaluated even more frequently, especially if on dabigatran. Intercurrent acute illness (like infections, acute heart failure, etc.) may transiently affect renal function and should also trigger re-evaluation; importantly, patients need to be alerted that in such situations they should seek contact with their healthcare provider. This guidance is also presented in the updated NOAC Card.

On the other side of the spectrum, a possibly decreased efficacy of edoxaban 60 mg OD compared with warfarin was observed in patients with a CrCl of >95 mL/min.[31] Interestingly, as a result of these findings, further *post hoc* analyses revealed a similar effect also for Rivaroxaban[188] and Apixaban.[189] In 2015 the FDA issued a warning about the use of edoxaban in individuals with such a high-normal CrCl, and recommended the use of other oral anticoagulants in these patients. Also the EMA advised that 'edoxaban should only be used in patients with high CrCl after a careful evaluation of the individual thromboembolic and bleeding risk'. A *post hoc* analysis of the ENGAGE AF data showed that despite the trend towards a decrease in relative efficacy of edoxaban 60 mg OD in the upper range of CrCl in an exploratory (not pre-defined) subgroup analysis, the safety and net clinical benefit of edoxaban compared with warfarin were consistent across the spectrum of renal function.[190]

Oral anticoagulant therapy in patients with mild or moderate CKD (CrCl ≥30 mL/min)

The benefit of VKAs in terms of reduced stroke and mortality is well established in AF patients with *mild to moderate* CKD.[191–194] Compared with warfarin, all four NOACs showed consistent efficacy and safety in patients with *mild to moderate* CKD compared with non-CKD patients in the respective Subgroup analyses of pivotal NOAC trials.[190,195–199] In addition, the ARISTOTLE trial data analysis suggests that the bleeding benefit with apixaban compared with warfarin becomes significantly more prominent at lower CrCl values, while the stroke reduction benefit is maintained.[181,197] In contrast, the bleeding benefit of 110 mg dabigatran over warfarin is lost in patients with CrCl <50 mL/min while maintaining a similar stroke risk reduction compared with VKA.[195]

A *post hoc* analysis of the RE-LY trial data showed a significantly faster rate of decline in renal function during the trial in patients on warfarin (especially at lower TTRs) compared with those on dabigatran[200] suggesting that it may delay the decline in renal function compared with warfarin. Moreover, it has been suggested that warfarin use may be associated with increased vascular calcification and/or the development of acute warfarin-related nephropathy with or without clinically overt haematuria.[201]

Appropriate dosing is an essential issue to be addressed when using NOACs in patients with CKD (*Figure 4*). While rivaroxaban, apixaban, and edoxaban doses were reduced according to renal function in their respective randomized clinical trials (RCTs), patients in the RE-LY trial were randomized to dabigatran 150 mg BID or 110 mg BID without dose reduction for renal insufficiency. Per SmPc, a recommendation for the use of dabigatran 110 mg BID is made in patients with CrCl< 50 mL/min at high risk of bleeding. With the availability of three FXa inhibitors with less pronounced renal clearance, the use of the latter may be preferred in this patient population. The use of NOAC doses inconsistent with drug labelling has been associated with worse outcome; for example, underdosing of apixaban in patients with normal or only mildly reduced renal function has been associated with less effectiveness (i.e. higher stroke rates) and no additional safety benefit in a large 'real-world' AF cohort.[202]

Oral anticoagulant therapy in patients with a CrCl of 15–29 mL/min

There are no RCT data on the use of NOACs for stroke prevention in AF patients with severe CKD or on renal replacement therapy (RRT) since all landmark NOACs trials essentially excluded patients with a CrCl of <30 mL/min (except for a few patients on apixaban with CrCl 25–30 mL/min). However, VKA have also never been prospectively assessed in a RCT in this patient population.

Rivaroxaban, apixaban, and edoxaban (but not dabigatran) are approved in Europe for the use in patients with severe CKD (Stage 4, i.e. a CrCl of 15–29 mL/min), with the reduced dose regimen (see **chapter 15** and *Figure 4*). In view of the individual NOACs' pharmacokinetics, dose-reduction criteria and available evidence from RCTs,

Table 6 Absorption and metabolism of the different NOACs

	Dabigatran[158,182]	Apixaban[183]	Edoxaban[184]	Rivaroxaban[185,186]
Bioavailability	3–7%	50%	62%	15 mg/20 mg: 66% without food, 80–100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose	20%/80%	73%/27%	50%/50%	65%/35%
Plasma protein binding	35%	87%	55%	95%
Dialysability	50–60% (in part dialysable)	14% (in part dialysable)	n.a. (in part dialysable)	n.a. (in part dialysable)
Liver metabolism: CYP3A4 involved	No	Yes [elimination, moderate contribution (≈25%)[a]]	Minimal (<4% of elimination)	Yes (hepatic elimination ≈18%)[131]
Absorption with food	No effect	No effect	6-22% more; minimal effect on exposure	+39% more (see above)
Absorption with H2B/PPI	-12% to 30% (not clinically relevant)	No effect	No effect	No effect
Asian ethnicity	+25%[166]	No effect	No effect	No effect
Elimination half-life	12–17 h	12 h	10–14 h	5–9 h (young)
				11–13 h (elderly)
Other	Dyspepsia (5–10%)			Intake of 15 mg/20 mg with food mandatory

[a]Hepatic metabolism in total of ≈25%, mostly via CYP3A4, with minor contributions of CYP1A2, 2J2, 2C8, 2C9, and 2C19.

the use of either apixaban or edoxaban may be preferable in these patients. Apixaban is least renally cleared (27%), and the dose is reduced by 50% in rather stringent conditions according to its dose reduction algorithm; furthermore the relative safety of apixaban vs. warfarin has been demonstrated to increase with decreasing renal function.[197] Edoxaban is 50% renally cleared, but its dose reduction to 50% is applied more rapidly and was tested in a large subgroup. Rivaroxaban has an intermediate renal clearance (33%), and its dose is reduced less (by 25%) under similar conditions as edoxaban. In the US (but not in Europe), a low dose dabigatran 75 mg BID regimen has been approved for patients with severe CKD (a CrCl of 15–29 mL/min), based on pharmacokinetic simulations. Further randomized trial data are urgently required for these difficult to treat patients.

Oral anticoagulant therapy in patients with a CrCl of ≤15 mL/min and on dialysis

Numerous observational studies yielded conflicting results for VKA regarding efficacy without a clear consistent benefit of VKA in patients with severe renal dysfunction,[192–194,203] Most studies confirmed a significantly lower incidence of stroke and embolism under warfarin, but also a markedly increased bleeding risk.[192–194] The only registry that assessed the net benefit found no changes in overall-mortality for warfarin in dialysis-dependent patients.[193] Of note, the use of warfarin in patients with end-stage renal failure may in some cases result in calciphylaxis, a painful and often lethal condition caused by calcification and occlusion of cutaneous arteries and arterioles.[204–208]

The efficacy and safety of NOACs in patients with end-stage renal dysfunction and on dialysis is unclear and subject to ongoing studies. Registry data have shown a higher incidence of hospitalization or death from bleeding in dialysis-dependent patients started on off-label dabigatran or rivaroxaban compared with VKA.[209] In the US (but not in Europe) apixaban 5 mg BID is currently approved in chronic, stable dialysis-dependent patients. However, plasma levels with apixaban 5 mg BID were recently shown to be supra-therapeutic.[210] Levels similar to those in patients with normal renal function on the respective NOACs were found for apixaban 2.5 mg BID in a small number of patients on dialysis,[210] for edoxaban 15 mg OD (in Japanese patients with severe renal insufficiency)[211] and rivaroxaban 10 mg OD in end-stage renal disease patients.[212] It needs to be kept in mind, however, that plasma levels are a surrogate endpoint. In the absence of hard endpoint studies (which are currently ongoing, e.g. NCT02942407, NCT02933697), the routine use of NOACs in patient with severe

Table 7 Criteria for diagnosing chronic kidney disease; estimation of renal function and categories of renal dysfunction

Decreased GFR[a]	GFR <60 mL/min/1.73 m^2		
Markers of kidney damage (≥1)	• Excessive albuminuria (AER ≥30 mg/24 h; ACR ≥30 mg/g or ≥3 mg/mmol) • Urine sediment abnormalities • Electrolyte or other abnormality caused by tubular disorders • Abnormal histology • Structural abnormalities detected by kidney imaging • History of kidney transplantation		
GFR category	CKD stage	GFR[a]	Descriptions
G1	1	≥90	Normal or high
G2	2	60–89	Mildly decreased
G3a	3	45–59	Mildly to moderately decreased
G3b		30–44	Moderately to severely decreased
G4	4	15–29	Severely decreased
G5	5	<15	Kidney failure (requires renal replacement therapy – dialysis or kidney transplantation)

Estimation of renal function in NOAC patients best by Creatinine Clearance (Cockroft–Gault):

$$\text{CrCl [mg/dl]} = \frac{(140 - \text{age}) \times \text{weight (in kg)} \times [0.85 \text{ if female}]}{72 \times \text{serum creatinine (in mg/dL)}}$$

Online calculators available at (e.g.): www.kidney.org/professionals/kdoqi/gfr_calculator; www.nephron.com/cgi-bin/CGSI.cgi; www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation; https://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault.
Popular Apps are NephroCalc, MedMath, MedCalc, Calculate by QxMD, and Archimedes.
CKD, chronic kidney disease; GFR, glomerular filtration rate; AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CrCl, creatinine clearance.
[a]mL/min/1.73 m^2.

renal dysfunction (CrCl <15 mL/min) as well as in patients on dialysis is best avoided. In fact, given the lack of strong evidence also for VKA in this patient population, the decision to anticoagulate remains a very individualized one requiring a multidisciplinary approach considering and respecting patients' preferences.[180,208,213]

There are no data on the use of NOACs in AF patients after kidney transplantation. If NOACs are used in such patients, the dosing regimen should be selected according to the estimated renal function, and caution is needed with respect to possible drug–drug interactions between the NOAC and concomitant immunosuppressive therapies (see **chapter 5**).

Non-vitamin K antagonist oral anticoagulants in liver disease

Advanced liver disease is associated with increased bleeding risk, but is also a prothrombotic disorder.[214] In addition, significant liver disease can profoundly affect hepatic clearance and drug metabolism, and altered functionality of the liver enzymes and transporters may alter drug response and facilitate drug-induced liver injury.[215]

The use of VKAs in patients with advanced liver disease and coagulopathy (*Table 8*) is challenging due to intrinsically elevated INR values and difficulties in selecting appropriate VKA dosing.[216] Patients with significant active liver disease including cirrhosis, or those with persistent (as confirmed by repeated assessment ≥1 week apart) elevation of the liver enzymes or bilirubin [e.g. alanine transaminase or aspartate transaminase ≥2(–3) times the upper limit of normal (ULN) or total bilirubin ≥1.5 times the ULN] were excluded from the landmark NOAC trials in AF.[28–31] Consequently, all four NOACs are contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Turcotte-Pugh C cirrhosis (*Table 8*). Rivaroxaban should also not be used in AF patients with Child B liver cirrhosis due to a >two-fold increase in drug exposure in these patients.[217] Dabigatran, apixaban and edoxaban may be used with caution in patients with Child B cirrhosis (*Table 8*).[218,219] Initiation and follow-up at a specialised centre in a multidisciplinary team (including a hepatologist and a haematologist) is recommended.

Due to the withdrawal/non-approval of the direct thrombin inhibitor ximelagatran from the market in 2006 as a result of its hepatotoxic side effects,[220] there had been some concern about the potential of NOACs to cause drug-induced liver injury. However, no signal for increased hepatotoxicity has been observed in any of the NOAC trials.[221] In fact, the risk of liver injury may even be lower than with VKA.[222–224]

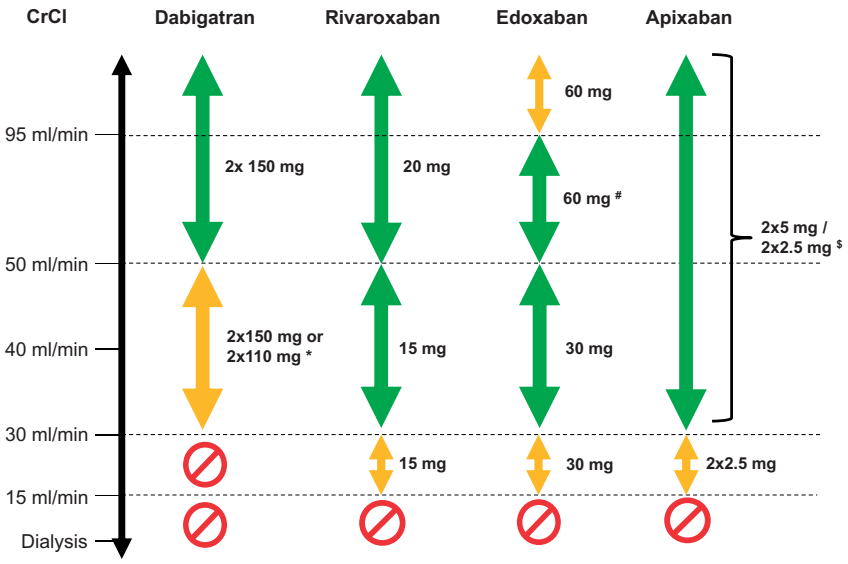

Figure 4 Use of non-vitamin K antagonist oral anticoagulants according to renal function. *2 × 110 mg in patients at high risk of bleeding (per SmPc). #Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). $2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function); see text for details.

Table 8 Calculation of the Child-Turcotte-Pugh score and use of NOACs in hepatic insufficiency

Parameters	1 point	2 points	3 points
Encephalopathy	No	Grade 1–2 (suppressed with medication)	Grade 3–4 (refractory/chronic)
Ascites	No	Mild (diuretic-responsive)	Moderate–severe (diuretic-refractory)
Bilirubin	<2 mg/dL	2–3 mg/dL	>3 mg/dL
	<34 µmol/L	34–50 µmol/L	>50 µmol/L
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
	>35 g/L	28–35 g/L	<28 g/dL
INR	<1.7	1.71–2.30	>2.30

Child–Pugh category	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
A (5–6 points)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B (7–9 points)	Use with caution	Use cautiously	Use cautiously	Do not use
C (10–15 points)	Do not use	Do not use	Do not use	Do not use

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

Routine coagulation tests [prothrombin time (PT) and activated partial thromboplastin time (aPTT)] generally do not provide an accurate assessment of NOAC anticoagulant effects. In contrast, the latter can be measured via specific coagulation assays developed for the quantification of NOAC plasma levels.[225–227] Most routine coagulometers are capable of measuring NOAC plasma levels within ≤30 min. Institutions are recommended to consider 24/7 availability of these tests for emergency situations. In contrast, point-of-care tests are not yet available for patients on NOACs.[228]

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. The absence of anti-Xa activity with these assays excludes clinically relevant drug levels. Conversely, the diluted thrombin time (dTT) test as well as the ecarin chromogenic assay (ECA) display a direct linear relationship with dabigatran concentration and are suitable for the quantitative assessment of dabigatran concentrations.

The use of appropriate calibrators allows for the determination of plasma concentrations of all NOACs. Even though levels in clinical trials were measured using HPLC/MS, drug measurement and monitoring can be closely approximated using a calibrated dTT/ECA assay for dabigatran or chromogenic anti-FXa assay for FXa-inhibitors. It is recommended to primarily use plasma concentrations rather than anti-FXa activity or dTT to quantitatively assess the concentration of a NOAC. An overview of the expected peak and trough levels in patients on NOACs can be found in *Table 9*. When interpreting a coagulation assay in a patient treated with a NOAC, it is important 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 approximately (1-)2–3 h after intake for each of these drugs (*Table 9*).

Of note, NOACs affect routine coagulation test (PT and aPTT), and also more specialized assays (such as lupus anticoagulant assays and coagulation factors) can be altered.

Specific considerations

Dabigatran

For dabigatran, the aPTT may provide a qualitative assessment of dabigatran level and anticoagulant activity. The relationship between dabigatran and the aPTT is curvilinear.[229] An aPTT in the normal range does not exclude dabigatran levels in the 'on therapy' range, but excludes drug levels above the 'on therapy' range when a sensitive assay is used.

Dabigatran has little effect on the PT and INR at clinically relevant plasma concentrations, which are therefore unsuitable for the assessment of the anticoagulant activity of dabigatran.[228]

The thrombin time (TT) is very sensitive to the presence of dabigatran and a normal TT excludes even very low levels of dabigatran. The TT is not suited for the quantitative assessment of dabigatran plasma concentrations in the range expected with clinical use. In contrast, dTT tests and the ECA allow for the measurement of dabigatran levels in the range that is clinically relevant.

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

Table 9 Plasma levels and coagulation assays in patients treated with non-vitamin K antagonist oral anticoagulants

	Dabigatran[229,230]	Apixaban[231], SmPc	Edoxaban[184,232]	Rivaroxaban[131,186]
Expected plasma levels of NOACs in patients treated for AF (based on dTT/ECA for dabigatran and anti-FXa activity for Xa inhibitors)				
Expected range of plasma levels *at peak* for standard dose (ng/mL)[a]	64–443	69–321	91–321	184–343
Expected range of plasma levels *at trough* for standard dose (ng/mL)[a]	31–225	34–230	31–230	12–137
Expected impact of NOACs on routine coagulation tests				
PT	↑	(↑)	↑(↑)	↑↑ (↑)
aPTT	↑↑(↑)	(↑)	↑	↑
ACT	↑(↑)	↑	↑	↑
TT	↑↑↑↑	—	—	—

Ranges indicate the P5/95 percentiles for dabigatran, rivaroxaban, and apixaban, and the interquartile ranges for edoxaban.
The reagents influence the sensitivity of the PT for FXa inhibitors and of the aPTT for dabigatran. When a sensitive assay is used, normal aPTT excludes above on-therapy levels in dabigatran-treated patients, and normal PT excludes above on-therapy levels in rivaroxaban and edoxaban, but not apixaban treated patients. Point-of-care INR devices developed to monitor vitamin K antagonists do not accurately reflect the anticoagulant status of NOAC treated patients.
ACT, activated clotting time; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECA, ecarin clotting assay; INR, international normalized ratio; PT, prothrombin time.

evaluation of FXa inhibitory effect because of the limited prolongation, variability of assays, and paradoxical response at low concentrations.[233] Although Factor Xa-inhibitors demonstrate a concentration-dependent prolongation of the PT, the effect 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, vitamin K deficiency).[233] For apixaban, the PT cannot be used for assessing the anticoagulant effect. For rivaroxaban and to a lesser extent edoxaban, the PT may provide some quantitative information, even though the sensitivity of the different PT reagents varies importantly and may be insensitive for the anti-FXa effect.[226] Assessment of the sensitivity of the employed PT reagent for the Xa-inhibitors is strongly recommended.

Importantly, conversion of PT to INR does not correct for the variation and even increases the variability. The INR (especially a point-of-care determined INR) is unreliable for the evaluation of FXa inhibitory activity. Furthermore, the prolongation of the PT/INR by NOACs can be misleading during the transition of a NOAC to a VKA. Therefore, switching needs to be executed diligently, as discussed in **chapter 4**.

Impact of non-vitamin K antagonist oral anticoagulants on other coagulation assays

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

The activated clotting time (ACT) test is used as a point-of-care test in settings where high heparin doses are administered and where the aPTT is too sensitive (e.g. bypass surgery, coronary interventions, ablation procedures, etc.). It is a test on whole blood, based on contact activation. Dabigatran increases the ACT in a curvilinear fashion, consistent with the effects on aPTT.[229] The ACT has not been investigated to gauge dabigatran anticoagulant activity in clinical practice. There is a small dose-dependent effect of apixaban, edoxaban, and rivaroxaban on the ACT.[234,235] It seems reasonable to use the same target ACT levels for heparin titration in NOAC-treated patients undergoing interventions. However, since ACT is a non-standardized test, ACT target levels require centre validation. The ACT cannot be used to gauge FXa anticoagulant activity.

8. Non-vitamin K antagonist oral anticoagulant plasma level measurement: rare indications, precautions and potential pitfalls

Non-vitamin K antagonist oral anticoagulants do not require monitoring of coagulation: neither the dose nor the dosing intervals need to be altered in response to changes in coagulation parameters for the currently registered indications. However, laboratory assessment of drug exposure and anticoagulant effect may help clinicians in emergencies as well as in special situations. Laboratory monitoring to guide long-term use can also be considered in exceptional patients with special characteristics. This, however, should only be done under the guidance of a coagulation expert and in the knowledge that hard clinical outcome data do not exist for such a strategy.

Measurement in emergencies

In emergencies such as bleeding (**chapter 11**), urgent procedures (**chapter 13**), or an acute stroke (**chapter 17**), routine coagulation tests are rapidly available and may quickly inform the clinician on recent exposure; specific assays may provide accurate assessment of plasma levels (**chapter 7**).

In case of serious bleeding, coagulation tests may help the clinician to support haemostasis (**chapter 11**). Coagulation tests may also uncover associated bleeding disorders. In case of urgent surgery as well as in exceptional cases of planned surgery with high-bleeding risk, coagulation tests may help the clinician define the timing of surgery (see **chapters 12 and 13**).

Information on drug exposure may also guide treatment in patients who present with acute thrombotic events, particularly in patients with acute ischaemic stroke for whom thrombolysis is considered (**chapter 17**). Other emergency situations where assessment of anticoagulant activity may be valuable include suspected overdosing or intoxication.

Measurement before elective procedures

In general, routine measurement of the anticoagulant activity is not recommended prior to elective procedures (**chapter 12**). When the timing since last intake is unknown or uncertain, or when there are concerns on the clearance of the drug because of special patient characteristics (potential drug–drug interactions, change in renal or hepatic function), it is reasonable to check the absence of clinically relevant plasma concentrations when specific assays are available.[168] Importantly, however, there are currently no prospectively validated data with hard clinical endpoints on cut-off values of any coagulation test to guide the timing of elective or urgent surgery.[236]

Monitoring during long-term exposure

The expected drug levels while on therapy, as observed in clinical trials, are shown in *Table 9*. Importantly, no studies have investigated if measurement of drug levels and dose adjustment based on laboratory coagulation parameters reduces the risk for bleeding or thromboembolic complications, e.g. by dose reduction in case of higher than expected levels or by dose increase in case of lower than expected levels, during chronic treatment. As such, routine monitoring of plasma levels and subsequent dose adaptation is generally discouraged. For the (rare) patients with multiple factors that interfere with the pharmacokinetics of a given NOAC (e.g. the very obese; uncontrolled cancer patients receiving therapy for malignancies; treatment with anti-cancer drugs with unclear/unknown pharmacokinetic interactions), a reasonable strategy could be to verify that plasma levels are within the 'on treatment' range, taken into account the different 'on therapy' range for samples taken at peak or at trough levels (*Table 9*). However, this should only be performed in the hands of a coagulation expert with sufficient experience in the performance and interpretation of these assays as well as the care of these patients.

Alternatively, reverting to VKA therapy in these very special situations may be an option.

Over- and underweight patients

Patients at the extremes of the weight spectrum (i.e. <50 kg and >120 kg) have been underrepresented in the clinical trials, and NOAC use may be a challenge in these individuals (**chapter 18**). If NOAC treatment is decided on in such a patient, assessment of plasma trough levels may be considered.

9. How to deal with dosing errors?

Questions relating to dosing errors are very common in daily practice, and patients need to be informed on what to do in such cases. To avoid dosing errors as described below, patients on NOACs should be encouraged to make use of well-labelled weekly containers, with separate spaces for each dose timing. Importantly, however, dabigatran must not be taken out of its original bottle until immediately before intake. In order to provide a more uniform and simple practical advice some of the below recommendations do not fully align with all SmPCs. Also, patients' individual risk of stroke and bleeding need to be taken into consideration.

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), a forgotten dose can be taken up until 6 h after the scheduled intake. For patients with a high stroke risk and low bleeding risk, this may be extended up until the next scheduled dose.

For NOACs with an OD dosing regimen, a forgotten dose can be taken up until 12 h after the scheduled intake. After this time point, the dose should be skipped and the next scheduled dose should be taken. The 12 h interval may be extended in patients with a high stroke risk.

Double dose

For NOACs with a BID dosing regimen, the next planned dose (i.e. after 12 h) may be left out, with BID intake restarted 24 h after the double dose intake.

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

For NOACs with a BID dosing regimen, it is generally advisable to not take another tablet/capsule, but to simply continue with the regular dose regimen, i.e. starting with the next dose at the 12 h interval.

For NOACs with an OD dosing regimen, when thrombotic risk is high (CHA_2DS_2-VASc $\geq$3), it may generally be advisable to take another tablet and then continue the planned dose regimen. In case the thrombotic risk is low (CHA_2DS_2-VASc $\leq$2), it is recommended to wait until the next scheduled dose.

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

Excessive NOAC plasma concentrations potentially expose the patient to an increased risk of bleeding. This may occur when the patient has (intentionally) taken an overdose. Also intercurrent events such as acute renal failure (especially with dabigatran) or administration of drugs with known drug–drug interactions (see **chapter 5**) may increase NOAC plasma concentrations to supratherapeutic levels. In terms of management, it is important to distinguish between an overdose with bleeding complications (**chapter 11**) and without.

In case of a suspected overdose, coagulation tests can help to determine its degree and possible bleeding risk (see **chapter 7**). A normal aPTT excludes high levels of dabigatran; similarly a normal PT excludes very high levels of rivaroxaban and edoxaban. However, these routine coagulation tests are not appropriate for a quantitative assessment of high levels of these drugs.

Given the relatively short plasma half-life of the NOACs, a 'wait-and-see' strategy can be used in most cases without active bleeding. The elimination half-life can be estimated taking into account age and renal function. As a result of limited absorption, a ceiling effect with little to no further increase in plasma exposure is seen at supratherapeutic doses of $\geq$50 mg rivaroxaban.[237] 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 $\leq$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.[238–240]

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 below (**chapter 11**) may need to be considered, including the use of a specific reversal agent.[241] Only in exceptional cases, strategies to non-specifically support haemostasis awaiting clearance of the drugs may be considered, although clearly in these situations balancing the benefit of normalizing coagulation in a non-bleeding patient needs to be carefully weighed against a possibly strong prothrombotic effect.

11. Management of bleeding under non-vitamin K antagonist oral anticoagulant therapy

The Phase III NOAC studies have consistently shown that NOACs cause less intracranial and less life-threatening bleedings than warfarin, despite the absence of reversal strategies in these trials. Not only was there similar or even a reduced bleeding incidence, but patients experiencing a major (particularly extracranial) bleeding under NOACs were also shown to have a more favourable outcome than for bleeding under VKA treatment.[240,242–245,378,379] Overall, a

reduction in all-cause mortality was observed with NOACs vs. warfarin for stroke prevention in AF.[246]

Nevertheless, as more patients are being treated with NOACs, the absolute number of NOAC-related bleeding events will increase. Importantly, any bleeding is an opportunity to review the correct choice and dosing of the NOAC (see **chapters 2, 5, 6, 15** and others) and to evaluate modifiable bleeding risk factors including suboptimally treated hypertension, labile INR (if on VKA) or erratic dosing, excessive alcohol intake and concomitant antiplatelet therapy, NSAIDs, glucocorticoids etc. (see also **chapter 14**).[3]

We recommend a hospital-wide policy concerning bleeding management under NOAC, developed in an interdisciplinary manner among cardiologists, haemostasis experts, emergency physicians/intensivists and others. This protocol should describe the availability and indications of specific coagulation tests as well as of specific and nonspecific reversal agents. Such a policy needs to be communicated well and be easily accessible (e.g. on an Intranet site, in the emergency room, in pocket-sized leaflets etc.).

Strategies to manage bleeding complications in patients treated with NOACs rely on a precise analysis of the clinical situation.

(1) The type of bleeding: nuisance/minor, major non-life threatening, or life-threatening.
(2) The patient and his/her treatment: The exact time of last NOAC intake, prescribed dosing regimen, renal function, other factors influencing plasma concentrations (incl. co-medication, see also *Table 3*), and other factors influencing haemostasis (such as concomitant use of antiplatelet drugs).

Both routine coagulation tests and assays that specifically measure plasma levels of NOACs are important pillars in the assessment of NOAC related bleeding. Normal results of dTT/ecarin clotting time (for dabigatran) and anti-Xa activity (for anti-FXa treated patients) likely exclude relevant levels of the anticoagulant. Specific assays allow for the quantification of plasma levels of the anticoagulant (**chapter 7**).[247] However, it needs to be kept in mind that restoration of coagulation does not necessarily result in improved clinical outcome. Conversely, conventional coagulation tests may be abnormal not only due to the effect of the NOAC itself, but for a variety of other reasons, particularly in the setting of severe bleeding.

Depending on the clinical scenario, the anticoagulant effects in a NOAC-treated patient who presents with bleeding can be addressed with the following strategies:

(1) *Waiting* until the anticoagulant activity of the NOAC effect wanes as a result of spontaneous clearance of the drug (*Table 6*), facilitated by maintaining (and potentially by stimulating) diuresis.
(2) *Specific reversal*: A specific reversal agent is available for dabigatran (idarucizumab, a humanized antibody fragment that specifically binds dabigatran).[248] Specific agents for FXa inhibitors are undergoing clinical testing, including andexanet alfa (a recombinant human FXa analogue that competes with FXa to bind FXa inhibitors)[249] and ciraparantag (PER 977), a small synthetic molecule that seems to have more generalized antagonistic effects.[250]
(3) *Non-specific support of haemostasis* using coagulation factors concentrates. There is increasing information about the effects of (activated) prothrombin complex concentrates in cohorts of NOAC-treated patients with bleeding.[251] In contrast, the use of fresh frozen plasma is not considered a useful reversal strategy, primarily due to the plasma abundance of NOACs which will inhibit newly administered coagulation factors upon activation and the resulting large volume that would need to be administered.[247] Vitamin K and protamine administration have no role in the management of a bleeding under NOACs, but are useful in the management of bleeding under NOACs when vitamin K deficiency is suspected or in case of concomitant treatment with heparin, respectively.

Nuisance and minor bleeding

The clinical relevance of both nuisance and minor bleedings under NOAC therapy should not be underestimated as they are a frequent cause of treatment interruptions. Patients need to be made aware of the signs and symptoms of such bleedings and instructed to alert their healthcare provider in case of such an event (see **chapter 2**). Cessation or temporary interruption without consultation needs to be discouraged due to the subsequently increased thromboembolic risk.

Nuisance bleeds can usually be managed by delaying intake or withholding the NOAC for a maximum of one dose. Minor bleedings may require more aggressive therapy with a focus aimed at treating the cause of the bleeding (e.g. PPI for gastric ulcers, antibiotics for urinary tract infection, etc.). Epistaxis and gum bleeds can be treated with local anti-fibrinolytics.

In case of recurrent minor bleeding events without causal therapeutic options, an alternative NOAC with a potentially different bleeding profile should be considered while maintaining effective stroke prevention (see **chapter 5**).

A suspected or documented occult bleeding should trigger a work-up to uncover the underlying cause and the treatment thereof whenever possible.

Non-life-threatening major bleeding

Causal therapy to stop the bleeding and standard supportive measures (such as mechanical compression, endoscopic or surgical haemostasis, fluid replacement, transfusion, and other haemodynamic support) are the main pillars in the management of non-life-threatening major bleeding. With increasing time a waning of the anticoagulant activity can be anticipated in view the relatively short elimination half-lives of all NOACs (see *Tables 6*, *10* and *Figure 5*).[252]

Adequate diuresis is recommended for all NOACs, but particularly in case of dabigatran (given the large degree of renal elimination of the drug). In addition, dialysis may be an option for non-life-threatening, severe bleeding with dabigatran in cases of severe renal failure if idarucizumab is not available.[253,254] In contrast, dialysis has no significant impact in patients treated with any of the FXa inhibitors due to their high degree of protein plasma binding.[255,256]

The use of antifibrinolytics (e.g. tranexamic acid, 1 g i.v., repeated every 6 h if needed) or desmopressin 0.3 μg/kg i.v. infusion (with a maximal dosing of 20 μg) – especially in special situations with associated coagulopathy or thrombopathy – may be considered. Tranexamic acid has proven efficacy to support haemostasis, particularly in trauma-induced bleeding, with a favourable safety profile.[257,258] Even when not yet supported by clinical data its use can therefore be considered for bleeding under NOACs, especially in situations of severe bleeding where frequently many factors of the coagulation cascade are deficient.

Table 10 Possible measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non life-threatening major bleeding	• Inquire about last intake + dosing regimen • Local haemostatic measures • Fluid replacement • RBC substitution, if necessary • Platelet substitution (in case of thrombocytopenia ≤60 × 109/L or thrombopathy) • Fresh frozen plasma not as reversal agent (may be considered as plasma expander) • Tranexamic acid can be considered as adjuvant (1 g i.v., repeat every 6 h, if necessary) • Desmopressin can be considered in special cases such as coagulopathy or thrombopathy; 0.3 µg/kg i.v. infusion (max dose 20 µg)	

	• Estimate normalization of plasma levels:
	  • 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
	• Consider idarucizumab (see below)
		• Normalization of plasma levels: 12–24 h

Life-threatening bleeding	• All of the above
	• Direct reversal: Idarucizumab 5 g i.v. in two doses a 2.5 g i.v. no more than 15 min apart
		• All of the above
		• Direct reversal: Andexanet alpha (if available and approved)[a]
		  • Bolus over 15–30 min, followed by 2-h infusion
		  • Rivaroxaban (last intake >7 h before) or apixaban: 400 mg bolus, 480 mg infusion @ 4 mg/min
		  • Rivaroxaban (last intake <7 h before or unknown) or enoxaparin or edoxaban: 800 mg bolus, 960 mg infusion @ 8 mg/min

	• Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) • 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	

RBC, red blood cells; CrCl, creatinine clearance; PCC, prothrombin complex concentrate.
[a]Andexanet alpha is currently neither approved nor available and final results of the ANNEXA-4 study are pending.

Life-threatening bleeding

Patients with life-threatening bleeding while treated with NOACs may benefit from its reversal in addition to the standard measures outlined above.

Importantly, even after direct reversal, significant NOAC concentrations may reappear in some patients and contribute to recurrent or continued bleeding (particularly after andexanet alpha, less after idarucizumab administration),[249,259] underlining the necessity for continued clinical and laboratory monitoring.

Idarucizumab

In the REVERSE-AD study, idarucizumab was successfully used in patients on dabigatran presenting with major or life-threatening bleeding, or with the necessity of emergency surgery. Idarucizumab completely reversed the anticoagulant activity of dabigatran within minutes in almost all patients.[248] It is hence recommended as first-line therapy in such situations. A total of 5 g idarucizumab is administered intravenously in two bolus doses of 2.5 g no more than 15 min apart (*Figure 6*). Continued clinical and laboratory monitoring is recommended, since a 5 g dose of idarucizumab may not completely neutralize an exceptional high level of dabigatran (e.g. in case of overdose or renal insufficiency). Also, low levels of dabigatran may reappear after 12–24 h.

After 24 h, dabigatran can be re-started if clinically indicated and feasible, with normal kinetics.

Direct reversal of apixaban, edoxaban, or rivaroxaban (FXa-inhibitors)

Based on the ongoing ANNEXA-4 study (which, in contrast to REVERSE-AD only includes patients with major/life-threatening

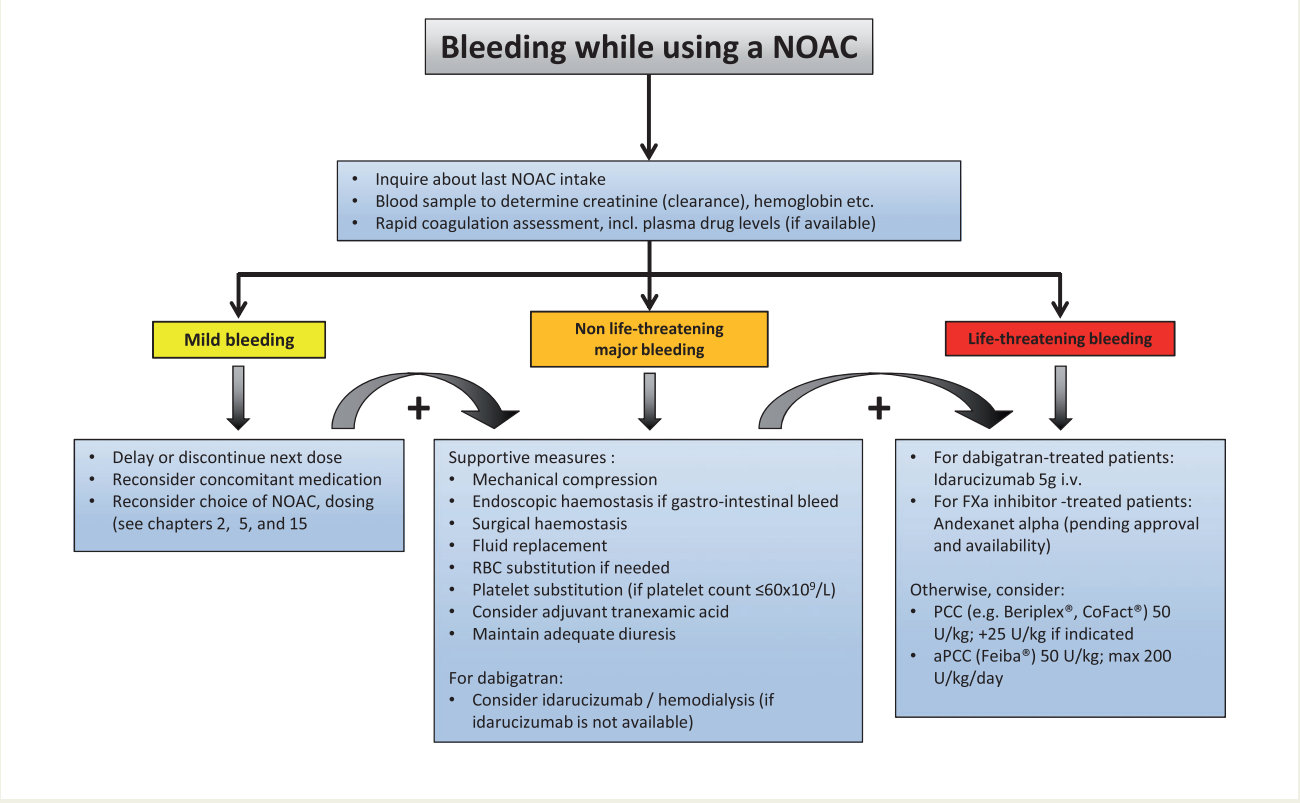

Figure 5 Management of bleeding in patients taking non-vitamin K antagonist oral anticoagulants.

bleeding),[249] andexanet alpha may become the first choice of therapy in life-threatening bleeding under FXa-inhibitor therapy (pending its regulatory approval and availability). In the ANNEXA-4 study, the drug is administered as a bolus over 15–30 min, followed by a 2-h infusion. The dosing depends on the NOAC and on the timing since last intake: For rivaroxaban (with the last intake >7 h before reversal) or apixaban, a 400 mg bolus is administered followed by a 480 mg infusion (4 mg/min). For rivaroxaban (with the last intake <7 h before reversal or unknown recent intake), edoxaban or enoxaparin, a 800 mg bolus followed by a 960 mg infusion (8 mg/min) is given (*Figure 6*). Importantly, reappearance of anticoagulant activity may occur after stopping the infusion. Therefore, it is currently less clear at what point in time and with which anticoagulant effect FXa inhibitors or heparin can be re-administered following andexanet alpha administration.

Coagulation factors

Clinical trials and registry data with NOACs have shown that administration of coagulation factors is rarely needed.[251,260] Indeed, any NOAC-antagonizing effect has to be balanced carefully against the potential prothrombotic effect. Animal experiments as well as studies in healthy volunteers have indicated the potential usefulness of PCCs and activated PCCs (aPCC) for the normalization of coagulation parameters under NOAC treatment as a surrogate for haemostatic support.[261–267] As indicated above, data from the large Phase III trials demonstrated that outcomes of bleedings under NOACs were similar (if not better) than in the VKA arm with similar treatment used (including PCC/aPCC).[240,242–243] The efficacy on clinical outcomes of PCCs or aPCCs in patients taking NOACs who are actively bleeding has not been firmly established in a RCT. However, several observational studies in patients with major bleeding have been published (with some inherent limitations including the retrospective, non-controlled setting as well as absence of a control group) indicating that (a)PCCs appeared to be efficacious in supporting haemostasis.[268,269]

The administration of PCCs or aPCCs can be considered in a patient with life-threatening bleeding if immediate haemostatic support is required, especially in situations where a specific reversal agent is not available (*Table 10*). The choice between PCC and aPCC may depend on their availability and the experience of the treatment centre. Particularly aPCC induces a strong pro-coagulant effect and should only be used by physicians experienced in their use. PCC and aPCC are preferred over recombinant activated factor VIIa (NovoSeven, 90 μg/kg) given the absence of any outcome data and the latter's pronounced pro-coagulant effect.[247,270]

Anticoagulation post-extracranial bleeding

In most cases of nuisance or minor bleeding anticoagulation can be re-started, sometimes simply by delaying or skipping a single dose. All other bleedings, particularly life-threatening bleeding episodes, require a careful re-assessment of the risks and benefits of re-initiating anticoagulation. In most cases of bleedings due to secondary (e.g. bleeding post-trauma) or reversible causes (e.g. genito-urinary

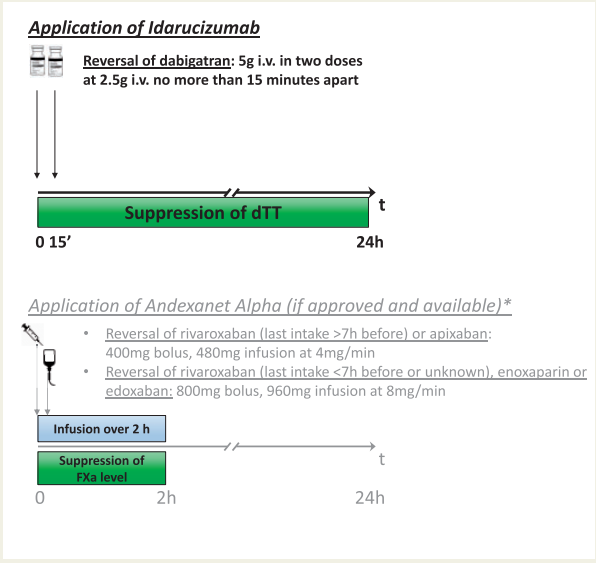

Figure 6 Application and effect of idarucizumab and andexanet alpha. *Per protocol of ANNEXA-4.[249] Andexanet alpha: The outcome study (ANNEXA-4) is still pending, the drug is not yet approved and not yet available.

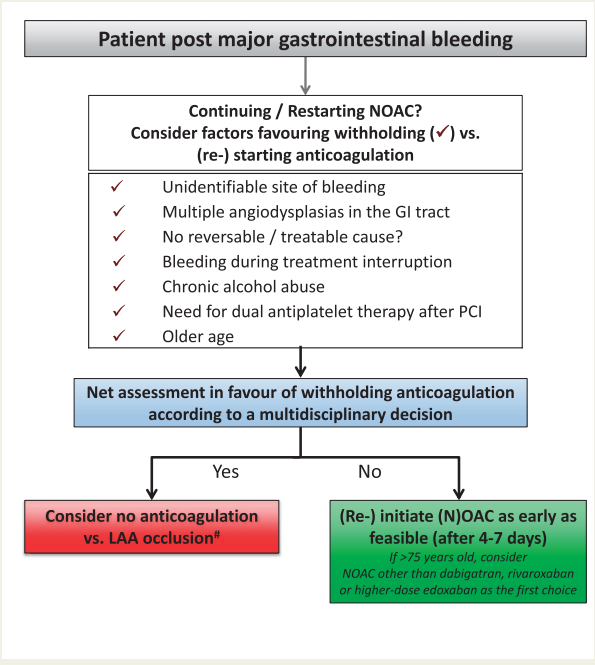

Figure 7 (Re-) initiation of anticoagulation post-gastrointestinal bleeding. #Without evidence; ideally include patient in ongoing trial.

bleed due to cancer) anticoagulation can be resumed once the cause of the bleed has been eliminated. As exemplified for GI bleedings, i.e. one of the most frequently encountered bleeds, many additional factors need to be taken into consideration (*Figure 7*). Particularly for severe and life-threatening bleedings without a clear secondary or reversible/treatable cause the risks of re-initiating anticoagulation may outweigh the benefits. In such cases, implantation of a left atrial appendage (LAA) occluder or surgical LAA occlusion may be considered as a potential substitute for long-term anticoagulation.[3] However, RCT evidence for LAA occlusion after bleeding under OAC is missing, which is why, ideally, treatment should occur wherever possible in the framework of a randomized trial to contribute to evidence for this difficult to treat population.

The approach post-intracerebral, intracranial, subdural, and epidural bleeding is outlined below (**chapter 17**).

12. Patients undergoing a planned invasive procedure, surgery or ablation

When to stop non-vitamin K antagonist oral anticoagulants?

About one quarter of anticoagulated patients require temporary cessation for a planned intervention within 2 years.[260] Awaiting the results of the ongoing Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE; NCT02228798) study, few prospective data on the management of NOACs are available.[271] Various societies have issued separate guidelines on the timing of NOAC interruption prior to surgery or interventions. It is impossible to summarize all recommendations, and healthcare providers are recommended to check this guide's recommendations against the relevant recommendations of their country/healthcare setting and professional society. The EHRA practical guide intends to provide a unified approach, which is as simplified as possible to allow its broad implementation.

Patient characteristics (including age, history of bleeding complications, concomitant medication, and kidney function) as well as surgical factors (*Table 11*) need to be taken into account to determine when to discontinue and restart a NOAC. While invasive surgical interventions require temporary discontinuation of a NOAC, many less invasive procedures carry a relatively low bleeding risk and do not necessarily require discontinuation (*Table 12*; *Figure 8*). All patients undergoing a planned intervention as well as caregivers (primary care physician etc.) should receive a written note indicating the anticipated date and time of their intervention as well as the date and time of the last intake of their NOAC (and any other medication).

Minor bleeding risk

It is recommended not to interrupt oral anticoagulation for most minor surgical procedures and those procedures where bleeding is easily controllable (*Figure 8*). In general, these procedures can be performed 12–24 h after the last NOAC intake. It may be practical to have the intervention scheduled 18–24 h after the last NOAC intake, and then restart 6 h later (skipping one dose of dabigatran or apixaban or no dose of edoxaban or rivaroxaban). The patient may only leave the ambulatory practice/outpatient clinic/hospital, if any peri-interventional bleeding has completely stopped. Moreover, the

Table 11 Timing of last non-vitamin K antagonist oral anticoagulant intake before start of an elective intervention

	Dabigatran		Apixaban – Edoxaban – Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. 12 h or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–79 mL/min	≥36 h	≥72 h	≥24 h	≥48 h
CrCl 30–49 mL/min	≥48 h	≥96 h	≥24 h	≥48 h
CrCl 15–29 mL/min	Not indicated	Not indicated	≥36 h	≥48 h
CrCl <15 mL/min	No official indication for use			
No bridging with LMWH/UFH				
Resume full dose of NOAC ≥24 h post-low bleeding risk interventions and 48 (–72) h post-high-bleeding risk interventions (see also *Figure 8*)				
Patients undergoing a planned intervention should receive a written note indicating the anticipated date and time of their intervention, and the date and time of the last intake of their NOAC (and any other medication)				

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 clinical impact. See also *Table 12*.
CrCl, creatinine clearance; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

patient has to be instructed about the normal post-procedural course and the measures to be taken in case of bleeding. The physician/dentist (or an informed colleague) has to be accessible in such a case.

Low bleeding risk

For invasive procedures with a low bleeding risk (i.e. low frequency of bleeding and/or minor impact of bleeding; *Table 11*), it is recommended to take the last dose of a NOAC 24 h before the elective procedure in patients with normal kidney function (*Table 12*, *Figure 8*). For patients on dabigatran and a CrCl <80 mL/min a graded interruption should be considered. For patients taking a FXa inhibitor and with a CrCl of 15–29 mL/min the last NOAC should be taken 36 h or more before surgery (*Table 12*). In patients taking concomitant dronedarone, amiodarone or verapamil, it may be advisable to add an extra 24 h of interruption, especially if the thromboembolic risk is not very high (CHA_2DS_2-VASc ≤3).[168] Conversely, for some procedures (e.g. cardiac device implantations, see below) a shorter interruption may be warranted, including intake of the last dose the morning of the day before the procedure. The PAUSE trial will provide more information on the relation between last intake, preprocedural plasma level and, most importantly, clinical outcome.[271]

High bleeding risk

In case of invasive procedures that carry a high risk for major bleeding (i.e. with a high frequency of bleeding and/or important clinical impact), it is recommended to take the last NOAC dose 48 h or longer before surgery. Again, the decision to halt therapy for longer should take into account the patient's thromboembolic vs. bleeding risk as well as concomitant therapy with antiarrhythmic drugs as described above. Moreover, in patients with impaired renal function longer interruption of the NOAC intake is required, especially for dabigatran (*Table 11*, *Figure 8*). In cases with combined factors that make prediction of NOAC clearance unclear, measurement of NOAC plasma levels may be considered, and only go ahead with the planned surgical intervention when the level is considered low enough (**chapter 7**, *Table 9*). However, it needs to be clearly stated that such an approach is without evidence base, including the determination of 'safe' NOAC levels in this setting as well as waiting for levels to drop into that range whilst accepting the inherent risk of thromboembolism during that time.

Bridging

Preoperative bridging with LMWH or heparin is *not* recommended in NOAC-treated patients since the predictable waning of the anticoagulation effect allows properly timed short-term cessation of NOAC therapy before surgery. On the contrary, the mixing of two anticoagulants (although with similar pharmaco-dynamics and -kinetics) has been associated with an increased bleeding risk.[272] As demonstrated in the BRIDGE trial for VKA, bridging with heparin/LMWH was associated with a significantly higher risk of major bleeding during cessation of oral anticoagulation but did not reduce cardiovascular events.[273]

Dental surgery

Dental surgery is generally considered a procedure with minor bleeding risk and with the possibility for adequate local haemostasis. Most professional statements on dental surgery advise not to suspend NOAC treatment and avoid the use of NSAIDs.[274] However, recommendations are often based on a low quality of evidence and mainly rely on available pharmacological information.[275] Dental extractions can generally be performed safely in an outpatient facility by applying

Table 12 Classification of elective surgical interventions according to bleeding risk

Interventions with minor bleeding risk
Dental interventions
Extraction of 1–3 teeth
Paradontal surgery
Incision of abscess
Implant positioning
Cataract or glaucoma intervention
Endoscopy without biopsy or resection
Superficial surgery (e.g. abscess incision; small dermatologic excisions; . . .)
Interventions with low bleeding risk (i.e. infrequent or with low clinical impact)
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or catheter ablation (except complex procedures, see below)
Non-coronary angiography (for coronary angiography and ACS: see Patients undergoing a planned invasive procedure, surgery or ablation section)
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
Interventions with high bleeding risk (i.e. frequent and/or with high impact)
Complex endoscopy (e.g. polypectomy, ERCP with sphincterotomy etc.)
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 high bleeding risk AND increased thromboembolic risk
Complex left-sided ablation (pulmonary vein isolation; some VT ablations)

For each patient, individual factors relating to bleeding and thromboembolic risk need to be taken into account, and be discussed with the operating physician.

local haemostatic measures, without interrupting anticoagulation or by just skipping the morning dose of the NOAC.[276–279] Periprocedural management includes specific haemostatic techniques including the use of oxidized cellulose or absorbable gelatin sponge, sutures, tranexamic acid mouthwashes, or compressive gauze soaked in tranexamic acid.

Device implantation procedures

Device implantations are generally considered procedures with a low bleeding risk. For patients undergoing device implantation, prospective, and randomized data in VKA-treated patients have indicated lower thromboembolic and bleeding rates if the VKA is continued in an uninterrupted fashion.[280] For NOAC-treated patients, the recently presented BRUISE-CONTROL 2 trial demonstrated similar bleeding and embolic rates in patients with a last intake 48 h before the implantation for rivaroxaban/apixaban (and based on glomerular filtration rate for dabigatran) vs. continued NOAC until the morning of the procedure (Birnie *et al.*, presented at AHA 2017). Therefore, a standard strategy as for 'low bleeding risk' procedures with intake of the last dose in the morning of the day before the procedure can be recommended in most cases, followed by restarting one day afterwards (*Table 12* and *Figure 8*). An overview of data and recommendations can be found in the recent EHRA/HRS/APHRS consensus document.[281]

Regional anaesthesia and pain medicine

Invasive procedures such as spinal anaesthesia, epidural anaesthesia, and lumbar puncture require complete haemostatic function, and fall under the 'high bleeding risk' category. European as well as North American guidelines do not recommend neuraxial anaesthesia or deep blocks in the presence of uninterrupted NOAC use and recommend interruption of NOACs for up to five half-lives (corresponding to an interruption of 3 days in FXa-inhibitors and 4–5 days for dabigatran).[282,283] NOAC therapy can usually be resumed 24 h after the intervention. On the other hand, 'low risk' procedures (such as peripheral nerve blocks or peripheral joint and musculoskeletal injections) do not necessarily require NOAC interruption and if so for only a short period (e.g. two half-lives).[284]

Lab testing before surgery or invasive procedures

Specific coagulation measurements (see **chapter 7**) prior to surgery or invasive procedures provide a direct assessment of the (residual) drug concentration[285] and may be useful in high-risk interventions and/or patients at risk for relevant residual drug concentrations such as older age, renal impairment, or certain concomitant medication (see **chapter 5**).[168] However, as indicated, such an approach is without evidence base, including the determination of 'safe' NOAC levels. For the majority of patients and procedures, a 'time-based' interruption as outlined above appears safe.

When to restart a non-vitamin K antagonist oral anticoagulant after an invasive procedure?

After a procedure with immediate and complete haemostasis, NOACs can generally be resumed 6–8 h after the end of the

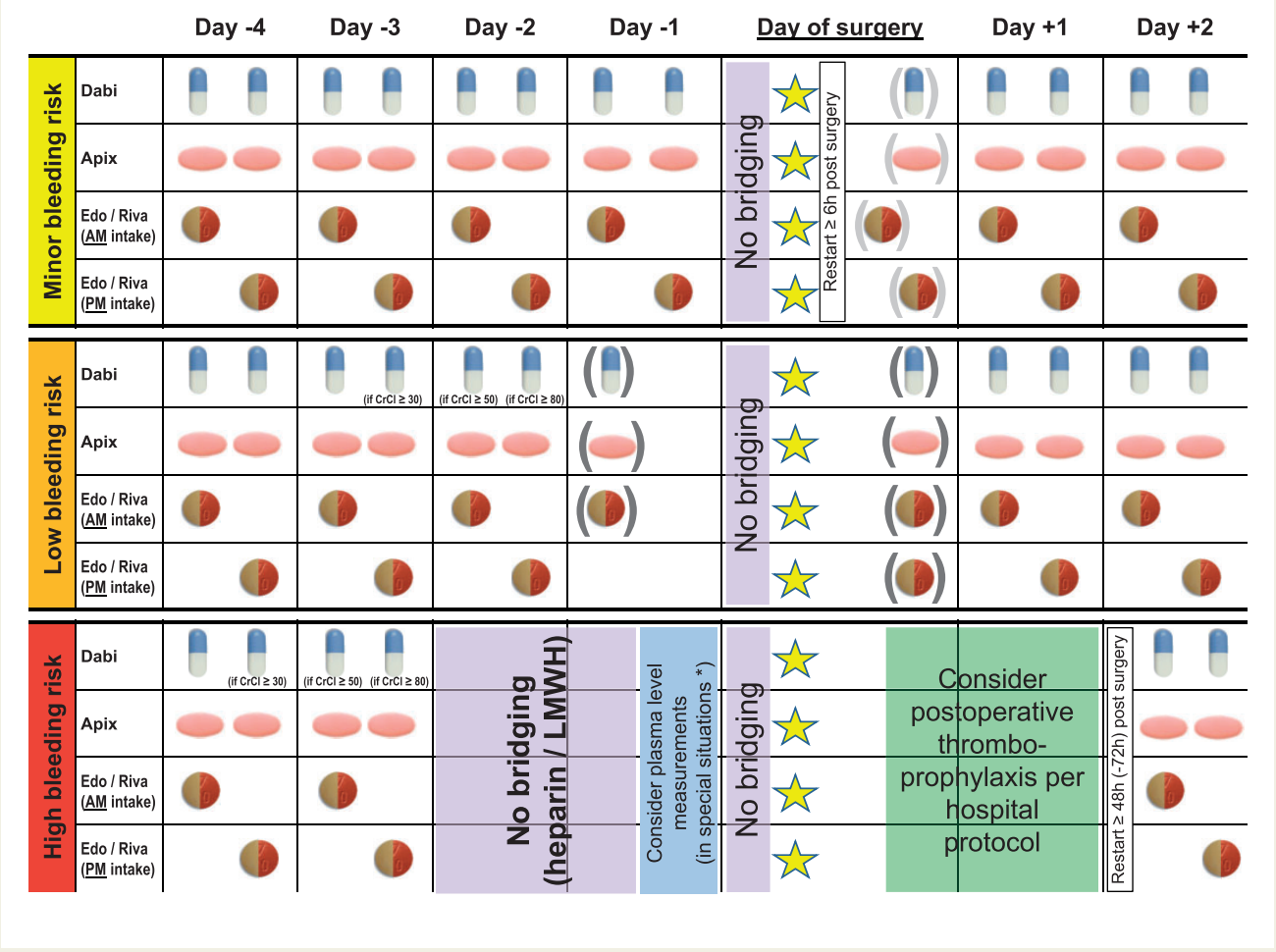

Figure 8 Stopping and re-initiation of non-vitamin K antagonist oral anticoagulant therapy in elective surgery. Yellow star, time point of the intervention/operation. Consider +24 h of interruption in situations likely resulting in increased plasma levels [e.g. patients taking verapamil, body weight <50 kg, significant interactions (see **chapter 5**)]. *Consider measurement of plasma levels (see **chapter 7**) in very special situations, e.g. highest risk neurosurgery/cardiac surgery, severe renal insufficiency, and combination of factors predisposing to higher non-vitamin K antagonist oral anticoagulant levels (see **chapter 5**). Rivaroxaban needs to be taken with food for stroke prevention in atrial fibrillation, which needs to be looked after (also) in the post-operative setting. Apix, apixaban; CrCl, creatinine clearance; Dabi, dabigatran; Edo, edoxaban; LMWH, low molecular weight heparin; Riva, rivaroxaban.

intervention. However, there are some surgical interventions in which resuming full dose anticoagulation within the first 48–72 h after the procedure carries a bleeding risk that may outweigh the risk of AF-related embolism. In such cases, initiation of post-operative thromboprophylaxis 6–8 h after surgery and restarting the NOAC 48–72 hours postoperatively (but as soon as possible) can be considered. There are, however, 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 venous thromboembolism (VTE) after hip/knee replacement) in patients with AF undergoing a surgical procedure.

It is strongly recommended to develop and implement institutional guidelines and a hospital-wide policies concerning perioperative anticoagulation management in different surgical settings, which are widely communicated and readily available.

Special considerations for atrial fibrillation ablation procedures

Left atrial catheter ablation constitutes an intervention with a risk of serious bleeding secondary to trans-septal puncture or extensive manipulation and ablation in the left atrium, although the incidence has been decreasing.[286] Major bleeds in the groin are not uncommon. On the other hand, left atrial catheter ablation implies a prothrombotic setting, increasing the risk of thromboembolic complications.[286,287] Recent international consensus statements and guidelines recommend performing left atrial catheter ablation under uninterrupted anticoagulant treatment (target INR 2–2.5),[3,286] since such a strategy was associated with less thromboembolic events and less bleeding.[288] The randomized RE-CIRCUIT (comparing dabigatran to warfarin in addition to peri-interventional heparin)[289] as well as the

VENTURE AF trial (comparing rivaroxaban to warfarin in addition to peri-interventional heparin)[290] showed a similar risk of embolism in the uninterrupted NOAC vs. VKA arms, although both studies by themselves were underpowered to detect statistically significant differences in endpoints. While in VENTURE-AF, patients preferentially received their last dose rivaroxaban in the evening before the procedure, dabigatran was routinely administered even in the morning before ablation in RE-CIRCUIT. As a result, approximately 80% of patients received their last dose <8 h before the procedure and 41% underwent ablation within 4 h of the last dabigatran dose. While a similar risk of major bleedings between rivaroxaban and warfarin was observed in VENTURE-AF, a large reduction in major bleeding was seen in RE-CIRCUIT with dabigatran compared with warfarin. Similar trials for apixaban (AXAFA-AFNET 5)[291] as well as edoxaban (ELIMINATE-AF) are ongoing. Registry data as well as a subanalysis of the ENGAGE-AF trial (with varying protocols and timings of NOAC interruption) did not indicate an increased risk of stroke or bleeding for apixaban or edoxaban in the setting of AF ablation.[292–294]

An institutional protocol for NOAC patients undergoing AF ablation should be developed to ensure a uniform approach. Whether opting to administer the last NOAC dose shortly before the procedure (i.e. 'truly uninterrupted') or to go for a short cessation period (last NOAC dose on the day before the procedure), depends on a number of factors including renal function, CHA_2DS_2-VASc score, experience of the operator, and routine practice of heparin administration prior to (first) trans-septal puncture.[2,281,286] It is reasonable to administer a last dose of NOAC 12 h before the start of the intervention, especially if trans-septal puncture is performed without periprocedural imaging (as is mostly the case in Europe). Especially, when adherence is uncertain over the weeks prior to the intervention, left atrial thrombus should be ruled out prior to ablation. A similar approach may be advisable if the last NOAC dose is taken ≥36 h before the intervention as the patient would be without adequate anticoagulation for a prolonged period of time as well as in patients at high risk for thromboembolism. During the ablation, intravenous heparin should be administered to achieve an ACT of 300–350 s.[295] It seems reasonable to use the same target ACT levels for heparin titration in NOAC-treated patients as in patients on (uninterrupted) VKA. It has been noted that the total need for heparin and the time to target ACT was higher in some NOAC treated patients.[290,296,297] This likely reflects a difference in whole blood coagulability when NOACs are stopped some time before the procedure, rather than a direct interaction between NOACs and the ACT test.

NOAC intake can be resumed 3–5 h after sheath removal if adequate haemostasis is established and pericardial effusion has been ruled out.[281]

13. Patients requiring an urgent surgical intervention

If an emergency intervention is required, the NOAC should be discontinued immediately. Specific management will then depend on the level or urgency (immediate, urgent, or expedite; *Figure 9*).[298]

(1) *Immediate procedures* (Immediate life-, limb- or organ-saving intervention, typically cardiac, vascular, and neurosurgical emergency procedures) need to be performed within minutes of the decision to operate and cannot be delayed. In these cases, reversal with idarucizumab (for dabigatran)[248] should be considered, especially in moderate- to high-haemorrhagic risk procedures.[299] While the REVERSE-AD trial with idarucizumab enrolled both bleeding patients as well as those requiring urgent surgery, the prospective open-label Phase III trial with andexanet alfa, a reversal agent for FXa inhibitors, only enrols patients experiencing an acute major bleed under therapy but not patients requiring urgent surgical interventions (Clinicaltrials.gov NCT02329327).[249] After publication of the full dataset and approval of the drug (expected by the end of 2018) its usefulness in this setting needs to be re-evaluated. If specific reversal agents are not available, PCCs or aPCCs should be considered despite the lack of evidence for efficacy and safety (see also **chapter 11** section).[269,272,283] Especially, if no specific reversal agent is available it may be advisable to perform immediate (and urgent) procedures under general rather than spinal anaesthesia in order to reduce the risk of epidural haematoma.

(2) *Urgent procedures* (e.g. intervention for acute onset or clinical deterioration of potentially life-threatening conditions, conditions that may threaten the survival of limb or organ, fixation of fractures, relief of pain, or other distressing symptoms) need to be performed within hours of the decision to operate. In these situations, surgery or intervention should be deferred, if possible, until at least 12 h and ideally 24 h after the last dose. Also, coagulation test results (see below) can be awaited in this situation to gauge the necessity for reversal or application of (a)PCCs.

(3) *Expedite procedures* (patients requiring early treatment where the condition is not an immediate threat to life, limb, or organ survival) should be performed within days of decision to operate. In these situations, interruption of NOACs should follow the proposed rules for elective surgery (see **chapter 12**).

In all such situations, particularly prior to the application of any haemostatic agents, a full panel of coagulation assays (including PT, aPTT, anti-FXa, or dTT/ECA etc.) should be obtained in order to assess the coagulation status of the patient. Even if in the emergency situation application of pro-haemostatic agents will not be postponed, results of these initial tests may have implications for further treatment during the ensuing hours. Importantly, a normal aPTT in case of dabigatran intake and a normal PT in case of rivaroxaban intake (and to a lesser extent edoxaban) may rule out high plasma levels of the respective drugs; conversely, however, normal routine coagulation tests do not exclude drug levels as expected while on therapy for all of the NOACs (see **chapter 7**). Specific coagulation tests (dTT or ECA for dabigatran; anti-FXa chromogenic assays for FXa inhibitors) and assessment of plasma levels may help in interpreting the current anticoagulant status as well as the waning of any anticoagulant effect, particularly in situations with potentially increased anticoagulant levels [e.g. in older age (see **chapter 18.1**), renal insufficiency (see **chapter 6**), and/or certain co-medications (see **chapter 5**)].

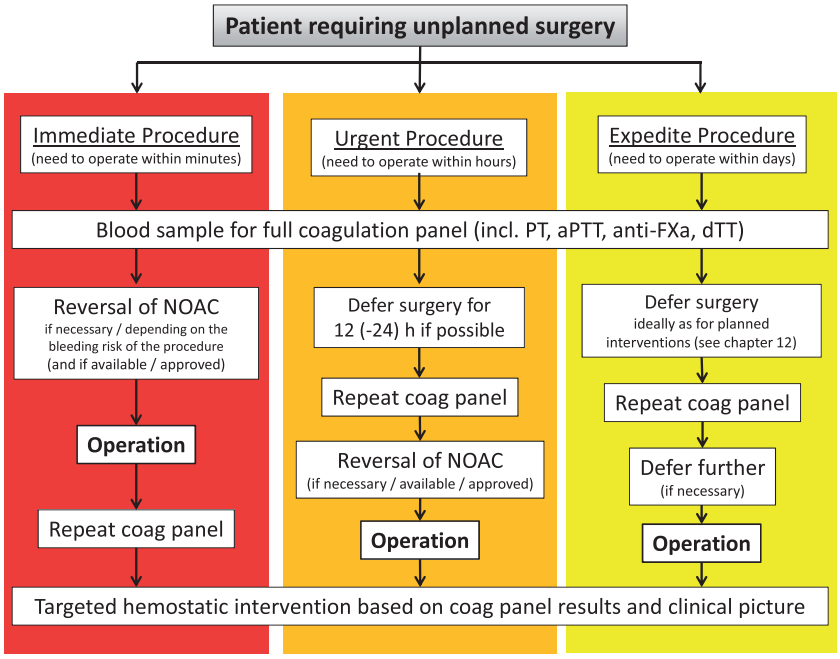

Figure 9 Non-vitamin K antagonist oral anticoagulant management in the setting of unplanned surgery.

14. Patient with atrial fibrillation and coronary artery disease

Scope of the problem and randomized clinical trial evidence

The combination of AF and coronary artery disease (CAD) is not only a common and complex clinical setting to deal with regarding anticoagulation and antiplatelet therapy, it is also associated with significantly higher morbidity and mortality.[300,301] The practice of adding aspirin or a $P2Y_{12}$ inhibitor to a (N)OAC is referred to as 'dual therapy', while adding both aspirin and a $P2Y_{12}$ inhibitor to a (N)OAC is called 'triple therapy'. Dual antiplatelet therapy is referred to as 'DAPT'. Stacking antithrombotic agents, i.e. by adding one or two antiplatelet(s) to NOACs, inevitably increases the risk of bleeding significantly,[170,171,302,303] leading to a clear need to avoid long-term triple therapy in daily clinical practice.[304–306]

The current understanding is that DAPT is necessary to prevent stent thrombosis but not sufficient for stroke prevention,[307] and vice versa, that (N)OAC are essential for stroke prevention but on their own not suitable for preventing new coronary events, especially in the acute/subacute setting.[3] A combination of at least one antiplatelet agent in addition to (N)OAC is recommended for up to 12 months after an ACS event and/or stenting procedure according to the most recent ESC guidelines on AF,[3] ST-elevation myocardial infarction (STEMI),[33] and the use of antiplatelet agents.[32]

To date, there are a handful of prospective trials addressing the issue of oral anticoagulation after PCI, including two RCTs comparing NOACs to VKA, in a variety of combinations with antiplatelet agents.[141,308] In essence, these trials focus on bleeding as the primary endpoint, and are underpowered to address relatively rare ischaemic/thromboembolic events including stroke, re-infarction and stent thrombosis. A meta-analysis combining WOEST, PIONEER AF-PCI, and RE-DUAL PCI suggests that the likelihood of an excess of thromboembolic events during dual therapy vs. triple therapy is low.[309] The two ongoing NOAC in AF trials, AUGUSTUS (NCT02415400) and ENTRUST-AF PCI (NCT02866175)[310] will add further information on how and how long (if at all) triple anticoagulation should be administered.

Randomized clinical trial evidence for non-vitamin K antagonist oral anticoagulants post-percutaneous coronary intervention

In PIONEER AF-PCI, two different rivaroxaban regimens were compared with 'standard' triple therapy with VKA and DAPT in 2124 AF patients undergoing PCI: a low-dose of rivaroxaban 15 mg (10 mg in patients with CrCl 30–50 mL/min) with a $P2Y_{12}$ inhibitor and a very low dose of rivaroxaban 2.5 mg twice daily combined with aspirin and a $P2Y_{12}$ inhibitor.[311] The trial design was complex: One year fixed treatment of 15 mg rivaroxaban plus $P2Y_{12}$ inhibitor was compared to triple anticoagulation with very-low dose rivaroxaban (2×2.5 mg) or VKA. The $P2Y_{12}$ inhibitor was clopidogrel in the vast majority of patients, and DAPT durations of 1, 6, and 12 months were pre-specified for the latter two arms. PIONEER AF-PCI showed that both rivaroxaban arms reduced the risk of clinically significant bleeding complications at 1 year when compared with standard triple therapy with a VKA targeted to an INR between 2 and 3 and with

varying DAPT durations.[308] While there were numerically similar rates of cardiovascular death, myocardial infarction, or stroke in all three arms, the trial was underpowered for efficacy. However, neither of the rivaroxaban doses in PIONEER AF-PCI (15 mg/10 mg OD or 2.5 mg BID) have been investigated for stroke prevention in AF [with the exception of the 15 mg dose in a relatively underpowered trial conducted in an exclusively Japanese population with normal renal function (J-ROCKET)].[156]

In RE-DUAL PCI, the safety of two doses of dabigatran (110 or 150 mg BID) in combination with clopidogrel or ticagrelor (i.e. dual therapy, without aspirin) were compared with standard triple therapy (for 1 or 3 months depending on the type of stent) with VKA, aspirin, and either clopidogrel or ticagrelor in 2725 patients with AF undergoing PCI.[141] The composite of major or clinical relevant non-major bleeding events and major bleeding events alone were significantly reduced in the 110- and 150-mg dabigatran dual therapy arms compared to the standard VKA triple therapy arm. This trial was also underpowered for individual efficacy endpoints; however, it was powered to show non-inferiority of the combined dual-therapy arms vs. the triple therapy in a composite efficacy endpoint of death, thromboembolic events and unplanned revascularization. Stent thrombosis was observed in 15 (1.5%) patients in the 110-mg dual therapy group vs. 8 (0.8%) patients in the triple-therapy group ($P = 0.15$) and in 7 (0.9%) patients in the 150-mg dual-therapy group.[141] Both dabigatran doses in RE-DUAL PCI have been shown non-inferior (110 mg) or superior (150 mg) to VKA for stroke prevention in AF.[28]

Key 'scientific' data on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and acute coronary syndrome, percutaneous coronary intervention, or stable coronary artery disease

What is known:

(1) Adding aspirin and/or a $P2Y_{12}$ inhibitor to oral anticoagulants substantially increases bleeding risk across different clinical scenarios and should thus be avoided in AF patients without clear indication for antiplatelet therapy, including CAD patients beyond 12 months after an ACS.[170,300,312] However, in general the bleeding risk seems to be lower with a NOAC plus antiplatelet combination than with a VKA plus antiplatelet combination.[170,302,313]

(2) ESC guidelines clearly state that the length of DAPT does not depend (anymore) on the type of stent (i.e. DES or BMS) but on the clinical presentation of the patient.[3,32] As contemporary DES are more efficient and as safe (or safer) as BMS regarding the risk for stent thrombosis, it does not make sense to opt for a BMS as a strategy to reduce the duration of $P2Y_{12}$ inhibitor therapy in patients on a NOAC. The use of a contemporary DES will also minimize the risk of avoidable repeat interventions due to restenosis thereby reducing the need for additional periods of dual or triple therapy.

(3) Clinical trials with contemporary DES suggest that (very) short dual antiplatelet regimens (i.e. 1 month after elective stenting or 6 months in case of ACS) are safe and efficacious in patients perceived to have a high bleeding risk and/or the elderly.[314,315] Patients receiving (N)OAC in combination with dual antiplatelet agents are considered to be at high bleeding risk.

(4) Rivaroxaban 15 mg or dabigatran 110/150 mg BID in dual therapy with $P2Y_{12}$ inhibitor, mainly clopidogrel (but without aspirin) is safer in terms of bleeding risk than triple therapy with VKA, clopidogrel, and low-dose aspirin (PIONEER AF-PCI / RE-DUAL PCI).[141,308]

(5) Rivaroxaban 2.5 mg BID in triple therapy with aspirin and clopidogrel is safer in terms of bleeding risk than triple therapy with dose-adjusted VKA, clopidogrel, and low-dose aspirin.

(6) 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 $P2Y_{12}$ inhibitor; new-generation drug-eluting stents (DES) to minimize the duration of dual/triple therapy; and a radial approach for interventional procedures (reducing at least the risk of access site bleeding).[33,316]

(7) Prolonged antiplatelet therapy beyond 1 year after ACS or DES implantation has been suggested in non-(N)OAC treated patients based on large-scale RCTs.[317–319] 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. In the PEGASUS TIMI 54 trial, patients were randomized 1–3 years after an myocardial infarction to aspirin plus ticagrelor or aspirin alone, and followed for a median of 33 months. Since patients in need of long-term OAC therapy were excluded from these studies, the results are of less relevance for treatment of AF patients.

What is unknown

(1) It is unknown whether the doses of rivaroxaban used in PIONEER AF-PCI (i.e. 2.5 mg BID or 15 mg OD) are sufficient for stroke prevention, at least compared with standard dose-adjusted VKA or compared with the 20 mg OD rivaroxaban dose in patients with a normal renal clearance.[29]

(2) It remains unknown whether dual therapy strategies combining a NOAC with clopidogrel are safer in terms of bleeding risk than a dual therapy with a VKA and clopidogrel. This is currently being addressed in the AUGUSTUS study with apixaban.

(3) It remains unknown whether dual therapy (i.e. rivaroxaban 15 mg OD or dabigatran 110/150 mg BID in combination with a $P2Y_{12}$ inhibitor) sufficiently protects against stent thrombosis or myocardial infarction, due to underpowered clinical trials.[141,308]

(4) It remains unknown whether dual therapy with NOAC and aspirin could be an alternative to NOAC and a $P2Y_{12}$ inhibitor, as there is no randomized study evaluating aspirin vs. a $P2Y_{12}$ inhibitor as part of dual therapy with NOAC or VKA.

(5) There were insufficient numbers of patients on ticagrelor or prasugrel in both PIONEER AF-PCI and RE-DUAL PCI to conclusively assess the safety of combining these more powerful $P2Y_{12}$ inhibitors in dual or triple therapy regimens.

(6) In VKA-treated patients, a PCI seems safe without bridging and without additional periprocedural heparin.[320] It is unknown if this applies also to NOACs, since most 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 pre-procedural dabigatran provides insufficient anticoagulation during PCI.[321]

A similar study with rivaroxaban, however, showed suppressed coagulation activation after elective PCI, without increased bleeding.[322] The safety of performing a PCI in patients on a NOAC, with or without additional periprocedural intravenous anticoagulation still needs to be prospectively studied in larger clinical trials.

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

Whereas guidelines recommend maintaining 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 non-ST-elevation ACS where early coronary angiogram is anticipated, as has been done during the pivotal NOAC vs. VKA AF trials. NOACs should be continued in non-invasively-managed ACS patients. Performing a PCI (scheduled or not) under NOAC is different than under VKA for many reasons: last dose and adherence needs to be carefully scrutinized; uncertainty about the extent of anticoagulation in the absence of mainstream/point of care tests, and hence uncertainty about stacking of additional periprocedural anticoagulants; variability in renal function (especially when unknown in an acute setting); singular anti-factor II or Xa blockade vs. multifactor antagonism with VKA, etc. Temporary discontinuation of the short-acting NOACs allows safe initiation of antiplatelet therapy and standard local anticoagulation practices periprocedurally.

In the 2016 ESC AF guideline and 2017 DAPT focused update, the use of ticagrelor or prasugrel as part of a triple therapy regimen is discouraged (Class III, level of evidence C), but no comments are made on dual therapy with combination of ticagrelor or prasugrel and a NOAC as possible alternative for triple therapy with aspirin, clopidogrel and a NOAC.[3,32] It leaves the opportunity to use one of these newer $P2Y_{12}$ inhibitors with a (N)OAC under certain circumstances such as perceived high thrombotic risk, ACS, or prior stent thrombosis. In a subset of the RE-DUAL PCI study the use of ticagrelor appeared safe and effective in the setting of dual therapy (Oldgren *et al.*, presented at AHA 2017). Triple anticoagulation with any of the new $P2Y_{12}$ inhibitors, on the other hand, is clearly discouraged beyond the first day(s) post-PCI. A signal for a relevant role of 'clopidogrel resistance' has so far not surfaced clinically in the large outcome trials but experience in earlier DAPT studies may provide a rationale for further studies on the use of newer $P2Y_{12}$ inhibitors in the setting of dual anticoagulation.

In-hospital management

A general flow diagram indicating possible scenarios is provided in *Figure 10*.

Elective coronary intervention (stable coronary artery disease)

Contemporary DES are preferred to shorten exposure to dual or triple therapy after the procedure (see below) but also to avoid the need for repeat interventions. There is no reason anymore to opt for a BMS as a strategy to reduce DAPT duration.[32,314] Sole balloon angioplasty or bypass surgery should be considered as an alternative in patients in need for chronic anticoagulation due to the reduced 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 an increased bleeding and thromboembolic risk compared with restarting the NOAC.

NOAC therapy should be discontinued before patients are taken to the cath lab and the procedure be performed at least (12–)24 h after last intake (see **chapter 12**). Periprocedural anticoagulation should be used per local practice. Unfractionated heparin (70 IU/kg) or bivalirudin rather than enoxaparin is preferred.[323] Unfractionated heparin should be administered to target ACT or aPTT levels per standard clinical practice. Bivalirudin may be an alternative because of its very short therapeutic half-life.

Acute coronary syndrome

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 $P2Y_{12}$ inhibitor. Since clopidogrel as well as the newer $P2Y_{12}$ inhibitors take considerable time to achieve their maximal antiplatelet effect in unstable patients, $P2Y_{12}$ inhibition without aspirin cannot be recommended in the acute setting. In frail patients at high bleeding risk, aspirin only might be a safer initial therapy awaiting invasive management, when indicated.

ST-elevation myocardial infarction. In case of a STEMI, primary PCI via a radial approach is strongly recommended over fibrinolysis.[324] It is recommended to use additional parenteral anticoagulation (i.e. UFH, enoxaparin, or bivalirudin, but not fondaparinux), regardless of the timing of the last dose of NOAC. Unless used for bail-out situations, routine glycoprotein IIb/IIIa inhibitors should be avoided.

If fibrinolysis is the only available reperfusion therapy, it may be considered if the NOAC-treated patient presents with normal dTT, ECT, aPTT (for dabigatran), PT (for FXa inhibitors), and importantly, plasma levels below the reference range (*Table 9*). 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 awaiting the waning of its effect (12 h or longer after last intake; **chapter 12**), fondaparinux or enoxaparin can be initiated. The use of upstream glycoprotein IIb/IIIa inhibitors should be avoided in this setting. Unfractionated heparin or bivalirudin is only recommended in bail-out situations, awaiting an intervention (Class IIb C).[325] To reduce the risk of access site bleeding, a radial approach is preferred.[324]

In more urgent situations, the same approach as in primary PCI STEMI patients should be followed, as described above.

Post-procedural resumption of anticoagulation

In stabilized patients (i.e. no recurrent ischaemia or need for other invasive treatments), anticoagulation can be restarted as soon as parenteral anticoagulation has been stopped. There are no data to recommend switching to VKA (which may even be associated with higher bleeding and thromboembolic risks, especially in VKA-naive patients in whom the correct VKA dose is unknown). The same applies for AF patients after coronary bypass grafting.

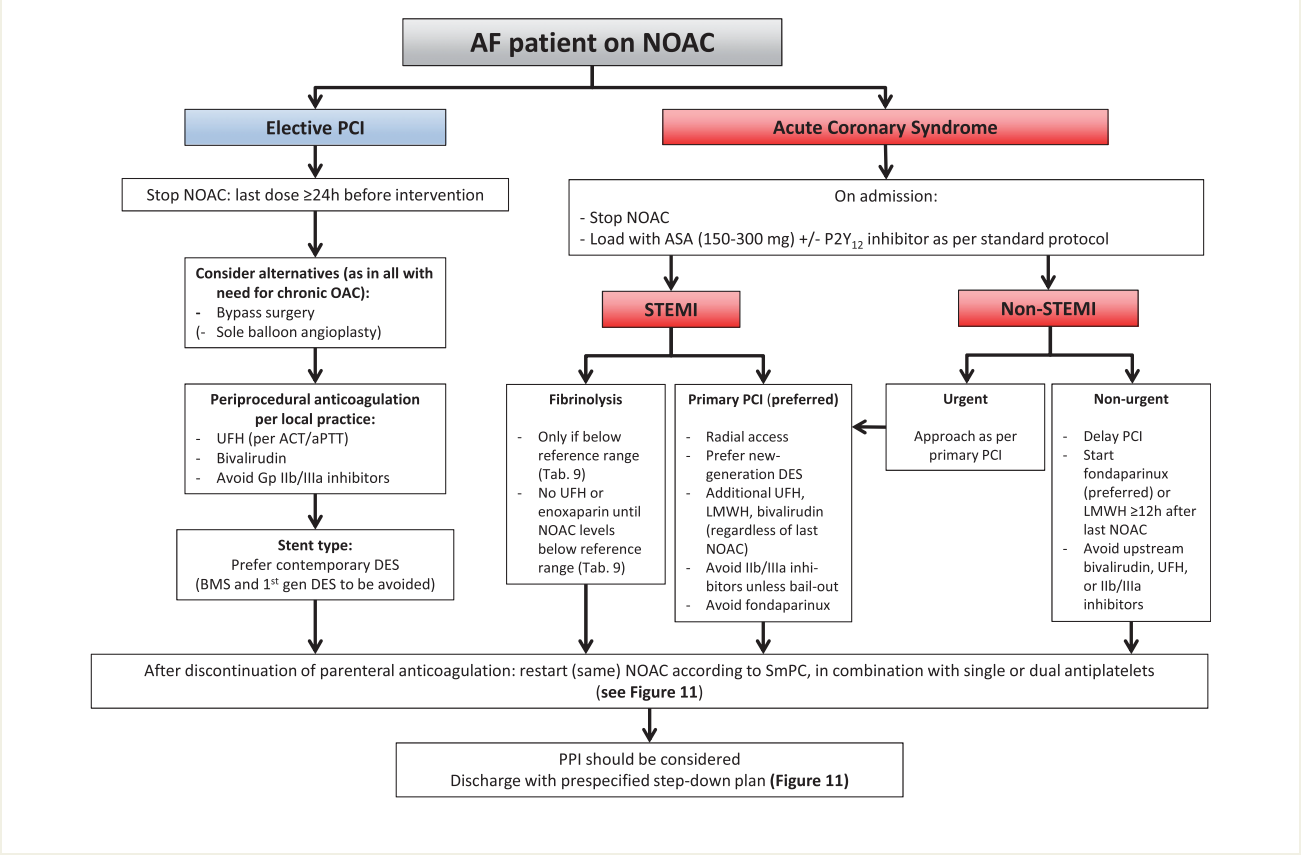

Figure 10 Acute management of elective percutaneous coronary intervention or acute coronary syndrome in atrial fibrillation patients treated with non-vitamin K antagonist oral anticoagulant.

The initial combination of antiplatelet agent(s) and NOAC as well as the subsequent duration of aspirin or $P2Y_{12}$ inhibitor treatment need to be individualized, based on a careful assessment of ischaemic vs. bleeding risk (*Figure 11*). Based on PIONEER AF-PCI and RE-DUAL PCI, triple treatment should be kept as short as possible (see chronic phase below). An alternative is to opt for dual therapy with only a NOAC and a $P2Y_{12}$ inhibitor within 1–7 days after the acute phase.

While awaiting the results of trials with apixaban and edoxaban the 150 mg dabigatran dual therapy appears to be the preferred choice over triple therapy for the majority of patients based on both the results from RE-LY[28] and RE-DUAL PCI[141]; dual therapy using 110 mg dabigatran or rivaroxaban 15 mg (10 mg in renal insufficiency) appears as a viable alternative for patients with estimated high bleeding risk—provided that dabigatran or rivaroxaban *per se* appear as a good choice for this individual patient based on age (see **chapter 18.1**), comorbidities (e.g. renal insufficiency; see **chapter 6**), interactions (see **chapter 5**), and others.

Management from discharge to 1 year post-acute coronary syndrome/percutaneous coronary intervention

Combining one or two antiplatelet agents with chronic anticoagulation (NOAC or VKA) significantly increases bleeding risk, regardless of the large varieties of possible combinations.[141,170,300,302,308,326] Despite two recent studies on dual or triple therapy with NOAC (and two more underway), there is no one combination fitting every patient. The type and level of anticoagulation as well as one or two antiplatelet agents and its duration need to be highly individualized, based on atherothrombotic risk, cardioembolic risk, and bleeding risk.[3,32,33] It is highly recommended to formally assess stroke and ischaemic event risk using validated tools such as the CHA_2DS_2-VASc and GRACE scores.[32] Estimating the bleeding risk should lead to efforts to correct or reduce reversible bleeding risk factors.[3] 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. Proton pump inhibitors should be encouraged in all patients with a combination of antiplatelets and anticoagulants, particularly in the setting of triple anticoagulation.

In patients at high ischaemic risk (e.g. after an ACS), a default time of triple therapy of 1 month up to 6 months is proposed, thereafter stepping down to dual therapy (with NOAC and either aspirin or clopidogrel) until 1 year.[32] Triple therapy beyond 6 months after PCI is not recommended, and (much) shorter regimens will likely suffice for most patients. Factors that weigh in to shorten triple therapy with earlier switch to dual therapy are an estimated low atherothrombotic

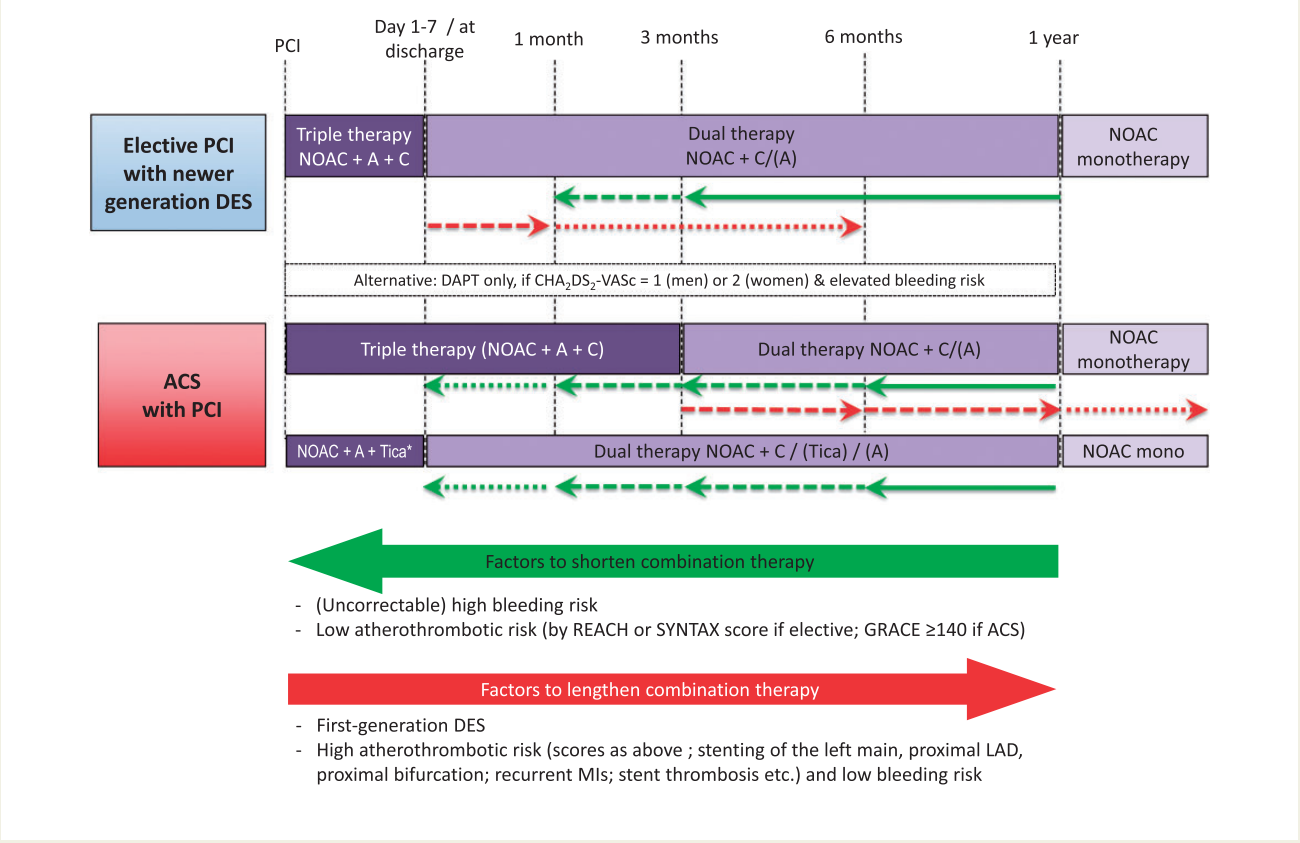

Figure 11 Long-term treatment of patients on non-vitamin K antagonist oral anticoagulant therapy after elective percutaneous coronary intervention or acute coronary syndrome. There are innumerable possible variations on this global theme, as discussed in the text. Patient characteristics and institutional practices should be taken into account to *individualize the approach* to each and every single patient. This figure wants to create a 'backbone' as guidance for such tailored approaches. A: aspirin 75–100 mg OD; C: clopidogrel 75 mg OD; Tica: Ticagrelor 90 mg BID. *If triple therapy needs to be continued after discharge clopidogrel is preferred over ticagrelor (due to lack of data).

risk or a high (uncorrectable) bleeding risk. Conversely, procedural and/or anatomical factors may drive longer triple therapy regimens. Beyond those patients at very high ischaemic risk, early dual therapy may well become the default strategy for most patients based on PIONEER AF-PCI and RE-DUAL PCI (while awaiting results from AUGUSTUS and ENTRUST-AF PCI).[32,310]

In a small subset of patients with a low stroke risk (CHA_2DS_2-VASc of 0–1 in males or 1–2 in females, i.e. only ACS) and elevated bleeding risk, one could opt to treat with DAPT only, without anticoagulants, from the onset.[307]

Chronic coronary artery disease setting (≥1 year post-acute coronary syndrome/percutaneous coronary intervention)

The 2017 ESC DAPT and 2016 AF guidelines recommend discontinuing any antiplatelet agent at 12 months after a PCI or ACS episode (see following paragraphs) and to only consider keeping one antiplatelet plus a (N)OAC beyond 12 months in patients at very high risk of coronary events.[3,32] Switching to NOAC monotherapy at an earlier stage (e.g. at 6 months) could represent an alternative for patients at low ischaemic- and high bleeding risk after a PCI for stable angina.

Independent of the chosen anticoagulation regimen and timing, the patient needs to be discharged with a pre-specified planned downgrade schedule of antithrombotic/antiplatelet agents to reduce the longer-term risk of bleeding while protecting against coronary events. Such a schedule should be prominently delineated in the discharge letter, and reviewed at every following patient visit.

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

Current ACS guidelines recommend DAPT for up to 1 year after the acute event in patients without indication for OAC, while high-risk patients might require an even longer DAPT duration.[318,319] They do, however, also allow for shorter DAPT durations (3–6 months) in high bleeding risk ACS patients.[32,33,327] If AF develops during the first year after an ACS and there is an indication for thromboembolic prevention with anticoagulation, (N)OAC should be started and the need for continuing DAPT carefully weighed against the increased bleeding risk. Following a scheme as outlined above (Management from discharge to 1 year post-ACS/PCI) appears reasonable in this setting.

Scenario 3: a stable coronary artery disease patient (acute coronary syndrome ≥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 plus aspirin may not be more protective but associated with excess bleeding, anticoagulation only without additional antiplatelet agents is considered sufficient for most AF patients with stable CAD.[32,316,328]

In the four Phase III NOAC AF trials, about one third of the patients had CAD and 15–20% of patients had a prior MI.[28–31] No interaction in terms of efficacy 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 older patients treated with dabigatran or VKA, which did not reveal any increased risk for MI.[79,329] Since direct comparative data are lacking, there is no strong argument for choosing one NOAC over another in this setting based purely on the existence of stable coronary artery disease.

15. Avoiding confusion with non-vitamin K antagonist oral anticoagulant dosing across indications

In order to replicate the positive findings of the RCTs, using the correct dosing is critical, especially since all NOACs are also studied in other indications. With four NOACs available in different dosages for different indications and with different dose reduction criteria, identification of the correct dose has become more complicated and is one of the key challenges in the daily use and individualization of treatment.

Table 13 gives an overview of the currently available NOACs and their doses in the different populations and indications, including the relevant dose reduction criteria for each NOAC and indication.

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

Based on current ESC guidelines,[3] in patients with AF of ≥48 h (or unknown) duration undergoing electrical or pharmacological cardioversion, effective oral anticoagulation needs to be established for at least 3 weeks prior to cardioversion or transesophageal echocardiography (TOE) 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.[3,348] Different scenarios have to be distinguished: electrical cardioversion in a patient who is on chronic treatment with a NOAC and now requires cardioversion for a new bout of AF, and cardioversion in a patient newly diagnosed with AF and naïve to anticoagulation (*Figure 12*).

Cardioverting an atrial fibrillation patient treated for ≥3 weeks with non-vitamin K antagonist oral anticoagulant

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) thromboembolic risk as under warfarin.[28–30] Later prospective trials with rivaroxaban (X-VeRT),[349] edoxaban (ENSURE-AF),[350] and apixaban (EMANATE, Ezekowitz *et al.*, presented at ESC 2017) have confirmed the low peri-cardioversion stroke risk in patients treated with a NOAC for ≥3 weeks compared with warfarin. These trials did not include sufficient patient numbers to demonstrate statistically sound non-inferiority. In congregate, however, these data indicated that a cardioversion without TOE seems reasonably safe under regular and continued NOAC intake, provided that adequate anticoagulation has been installed for 3 weeks before cardioversion.[3] As there is no coagulation assay available for any NOAC that provides information on effective anticoagulation over the past 3 weeks, the patient needs to be inquired about adherence over the last weeks and his/her answer documented in their file. If in doubt about adherence, a TOE should be performed prior to cardioversion under a NOAC. Importantly, 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 thromboembolic 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, with the risk of thrombus correlating with the $CHADS_2$ score (thrombus incidence ≤0.3% in $CHADS_2$ 0–1 patients, thrombus incidence 0.5% in $CHADS_2$ ≥2 patients).[351–353]

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 who is not on NOAC, the X-VeRT,[349] ENSURE-AF,[350] and EMANATE (presented at ESC 2017)[354] studies with rivaroxaban, edoxaban, and apixaban, respectively, offered important data since they included 57%, 27%, and 100% of OAC-naïve patients, respectively. The cardioversion strategy was either early (with TOE) or without TOE (delayed strategy, i.e. with 3–8 weeks anticoagulation before cardioversion). OAC-naïve patients tended to have slightly higher thromboembolic event rates (which was not statistically significant). Overall, there was no difference in ischaemic or bleeding events between NOAC and VKA groups (except for lower ischaemic events with apixaban in the EMANATE trial), nor between early and delayed groups, although neither of the trials were powered for non-inferiority. In EMANATE, about half of the patients received an initial loading dose of 10 mg (followed by 5 mg BID); also these patients did not show a higher

Table 13 NOACs and approved/studied doses across indications

Stroke prevention in atrial fibrillation (SPAF)		
	Standard dose	**Comments/dose reduction**
Apixaban[30]	2 × 5 mg	2 × 2.5 mg if two out of three: weight ≤60 kg, age ≥80 years, serum creatinine ≥133 µmol/(1.5 mg/dL) [*or* if CrCl 15–29 mL/min]
Dabigatran[28]	2 × 150 mg / 2 × 110 mg	No pre-specified dose-reduction criteria[a]
Edoxaban[31]	1 × 60 mg	1 × 30 mg if: weight ≤60 kg, CrCl ≤50 mL/min, concomitant therapy with strong P-Gp inhibitor (see **chapter 5**)
Rivaroxaban[29]	1 × 20 mg	1 × 15 mg if CrCl ≤50 mL/min
Treatment of DVT/PE		
	Initial therapy	**Remainder of treatment phase**
Apixaban[330]	2 × 10 mg, 7 days	2 × 5 mg, no dose reduction
Dabigatran[331]	Heparin/LMWH	No pre-specified dose-reduction criteria[b]
Edoxaban[332]	Heparin/LMWH	1 × 60 mg, same dose reduction as for SPAF (see above)
Rivaroxaban[333,334]	2 × 15 mg, 21 days	1 × 20 mg, no dose reduction[c]
Long-term prevention of recurrent DVT/PE (i.e. after 6 months)		
	Standard dose	**Comments/dose reduction**
Apixaban[335]	2 × 2.5 mg	
Dabigatran[336]	2 × 150 mg	No pre-specified dose-reduction criteria[d]
Edoxaban	not specifically studied	
Rivaroxaban[337]	1 × 10 mg	e
VTE prevention post-major orthopaedic surgery		
	Standard dose	**Comments/dose reduction**
Apixaban[338]	2 × 2.5 mg	
Dabigatran[339,340]	1 × 220 mg	f
Edoxaban[341,342]	1 × 30 mg	Not approved in Europe (only studied in Asia)
Rivaroxaban[343–346]	1 × 10 mg	
Stroke prevention post-PCI (with concomitant atrial fibrillation)[g]		
	Standard dose	**Comments/dose reduction**
Apixaban	To be determined (pending results of AUGUSTUS trial)	
Dabigatran[141]	150 mg BID or 110 mg BID	+Clopidogrel or Ticagrelor; no dose reduction
Edoxaban	To be determined (pending results of ENTRUST-AF PCI trial)[310]	
Rivaroxaban[308]	15 mg OD (+Clopidogrel)	Dose reduction to 10 mg OD if CrCl 30–49 mL/min

Secondary prevention of atherothrombotic events post-ACS (without AF)		
	Standard dose	**Comments/dose reduction**
Rivaroxaban[171]	2.5 mg BID	In addition to Aspirin ± $P2Y_{12}$ inhibitor
Secondary prevention of atherothrombotic events in stable CAD (without AF)[h]		
	Standard dose	**Comments/dose reduction**
Rivaroxaban[347]	2.5 mg BID	In addition to Aspirin[h]

ACS, acute coronary syndrome; CAD, coronary artery disease.
[a]SmPC: 2 × 110 mg if age ≥80 years, concomitant verapamil, increased risk of GI bleeding.
[b]SmPC: 2 × 110 mg if age ≥80 years, concomitant verapamil, increased risk of GI bleeding (based on PK/PD analyses; not studied in this setting).
[c]SmPc: 15 mg if risk of bleeding outweighs risk for recurrent DVT and PE (based on PK/PD analyses; not studied in this setting).
[d]SmPC: 2 × 110 mg if age ≥80 years, concomitant verapamil (both based on PK/PD analyses; not studied in this setting).
[e]SmPc: 1 × 20 mg in patients. At high risk of recurrence.
[f]SmPc: 1 × 150 mg if CrCl 30–50 mL/min; concomitant verapamil, amiodarone, quinidine; age >75 years.
[g]As outlined in detail in **chapter 14**, both PIONEER AF-PCI as well as RE-DUAL PCI were powered for safety and were underpowered to determine non-inferiority for individual efficacy endpoints.
[h]As studied in COMPASS; approval of this indication and regimen is pending.

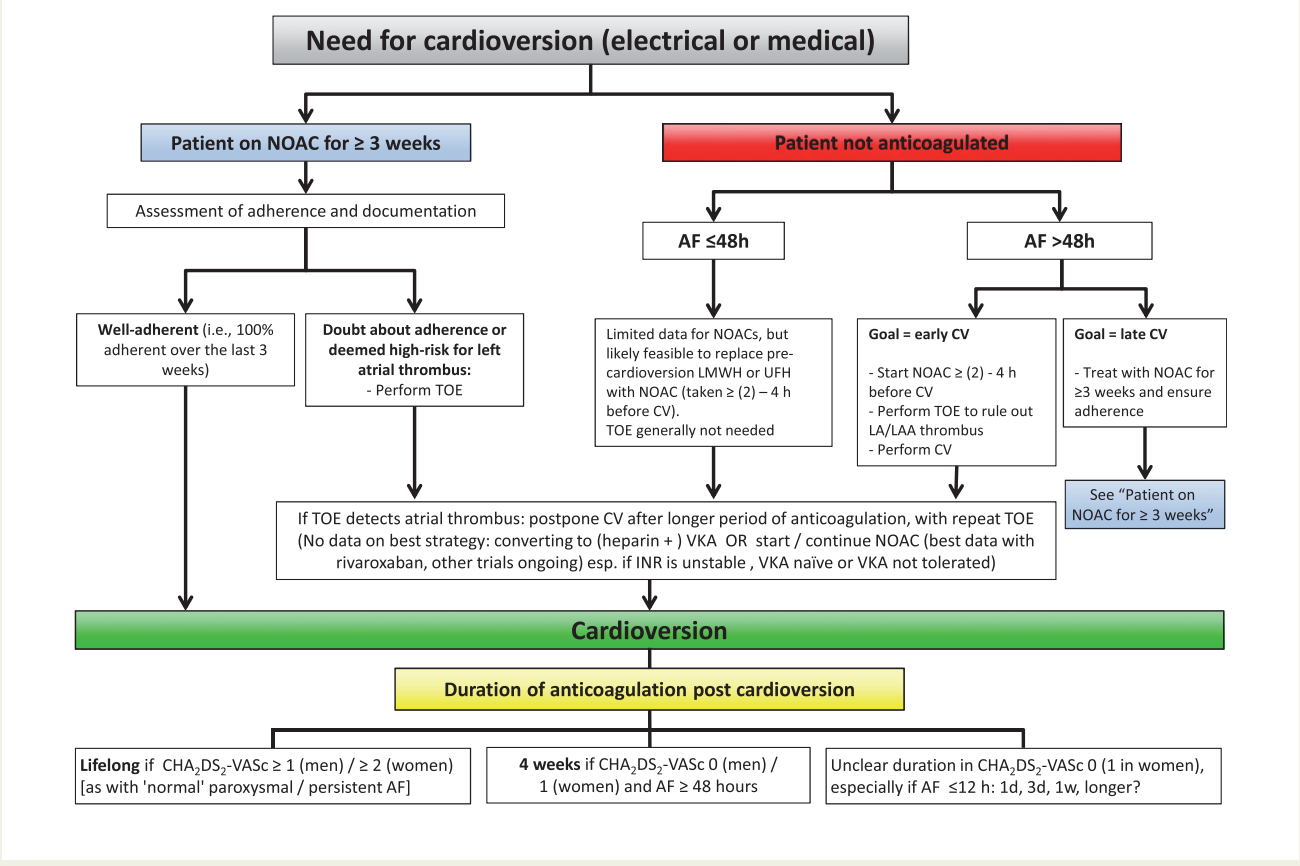

Figure 12 Cardioversion work-flow in atrial fibrillation patients treated with NOACs, depending on the duration of the arrhythmia and prior anticoagulation. TOE, transoesophageal echocardiography.

bleeding tendency. The 10 mg loading dose is not part of the official labelling (which may change in the near future). Taken together, a strategy with at least a single NOAC dose ≥4 h before cardioversion (≥2 h after apixaban loading dose) appears safe and effective in patients with AF of ≥48 h duration, provided that a TOE is performed prior to cardioversion. The alternative is starting anticoagulation with a NOAC for at least 3 weeks followed by cardioversion (without TOE unless high risk patient or deemed non-adherent).

Cardioverting atrial fibrillation of ≤48 h in an anticoagulation-naive patient

Even in patients with recent onset AF of ≤48 h, different observational studies have shown a lower thromboembolic incidence rate with vs. without anticoagulation, especially in those with a CHA_2DS_2-VASc ≥2 and AF duration ≥12 h.[355,356] Neither X-VeRT nor ENSURE-AF provided information on whether intake of at least one dose of NOAC is a feasible strategy in patients with AF of ≤48 h duration, who are currently often cardioverted after a single dose of LMWH (with continuation of anticoagulation for ≥4 weeks). Some of such patients were included in EMANATE, but publication of the final results is still pending and subgroup results are unknown.

In the absence of data, adherence to current institutional practice with heparin/LMWH with or without TOE may be prudent in such patients. Given the consistent efficacy and safety of NOACs in patients with AF ≥48 h combined with the similar pharmaco-dynamic and -kinetic properties of NOACs and LMWH, the use of a single dose of NOAC (2)–4 h before cardioversion to replace LMWH may be justified in patients with AF <48 h, without a TOE. Nevertheless in high risk patients (i.e. CHA_2DS_2-VASc ≥4) or those in whom there is any doubt about the onset of AF, a TOE strategy or a strategy with longer term anticoagulation (at least for 3 weeks before cardioversion) is recommended. It needs to be kept in mind that the 48 h cut-off is not binary and cardioversion in the setting of even shorter durations of AF have been associated with an increased risk of stroke, e.g. cardioversion after 12–48 h vs. <12 h).[356,357]

Duration of anticoagulation post-cardioversion

The long-term management of patients post-cardioversion depends on the individual patient's CHA_2DS_2-VASc score. Men and women with a CHA_2DS_2-VASc ≥2 and ≥3, respectively, require long-term anticoagulation independent of the 'success' of cardioversion according to current guidelines.[3] This is also true for AF with a clear 'trigger' including pulmonary embolism, sepsis, or major surgery, since the trigger does not negate underlying structural or vascular factors associated with increased thromboembolic risk. For AF of >48 h duration and a low CHA_2DS_2-VASc score (0 in men, 1 in women) anticoagulation needs to be continued for 4 weeks post-cardioversion. In contrast, it is currently unknown how long (if at all) the latter patients should be anticoagulated if AF is of shorter duration (especially when <12 h), since AF and/or cardioversion may contribute to atrial mechanical and/or endothelial dysfunction for hours to days.[357]

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 have not shown a different thrombus incidence in patients treated with NOAC or VKA.[349,358–360] There are no comprehensive hard clinical endpoint data on the best strategy how to treat a left atrial thrombus with either form of anticoagulant. Previously, standard therapy consisted of VKA therapy with rigorous follow-up and INR monitoring until resolution of the thrombus (with heparin bridging if necessary). Recently, the prospective X-TRA study indicated a thrombus resolution rate of 41.5% (22/53 patients) with standard dose rivaroxaban (20 mg/d)[361] – comparable to the retrospective CLOT-AF registry in which left atrial thrombus resolution was observed in 60/96 patients (62.5%) in heparin/warfarin treated patients.[361] Similarly, in the EMANATE trial, thrombus resolution rate was similar in patients treated with apixaban (52%, 12/23) as with conventional therapy (56%, 10/18; Ezekowitz *et al.*,[8] presented at ESC 2017). Individual case reports are equally available for the other NOACs; the RELATED AF study (with dabigatran; NCT02256683) is still ongoing. In congregate, these data indicate that using NOACs for left atrial thrombus resolution may be an option (best data available for rivaroxaban and apixaban), particularly in patients where a VKA is not well tolerated or adequate INR control cannot be obtained.

17. Atrial fibrillation patients presenting with acute stroke while on non-vitamin K antagonist oral anticoagulants

According to controlled clinical trials, the incidence of ischaemic stroke remains 1–2% per year in patients with AF despite anticoagulant treatment. Adherence to medication needs to be assessed in case of stroke in NOAC treated AF patients. The measurement of anticoagulant plasma level at the time of hospital admission may help to optimize secondary stroke prevention.[362] In addition, alternative causes of stroke should be assessed in any AF patient.

Management the acute phase of stroke in NOAC treated AF patients

Patients with acute ischaemic stroke

According to current guidelines and official labelling, thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) is approved within 4.5 h of onset of stroke symptoms but should not be administered in patients on full anticoagulation (e.g. INR ≥1.7 in VKA treated patients) (*Figure 13*).[363] Thrombolytic therapy cannot be given within 24 h after the last intake of a NOAC due to their plasma half-lives (*Table 6*), which may even be prolonged in renal insufficiency (see **chapter 6**), the elderly (see **chapter 18**) and other situations. The case is different for dabigatran due to the availability of the rapid acting specific reversal agent, idarucizumab (see **chapter 11**). After reversal and assessment of coagulation status, intravenous thrombolysis within 4.5 h of onset of moderate to severe stroke seems feasible and safe according to case series.[364,365] In the absence of randomized studies demonstrating the overall efficacy and safety of this approach, balancing the anticipated benefit of this approach vs. its risks is of paramount importance. It remains to be demonstrated whether the same approach will be safe and effective also for Xa-inhibitors once andexanet alpha becomes available.

Published case series suggest that rt-PA may also be safe in patients with low plasma concentrations of NOACs.[366,367] Despite recent advances reliable and sensitive rapid (point-of-care) tests for the individual NOACs are not widely available yet.[362,368,369] However, the use of rt-PA may be considered in selected patients on a NOAC in

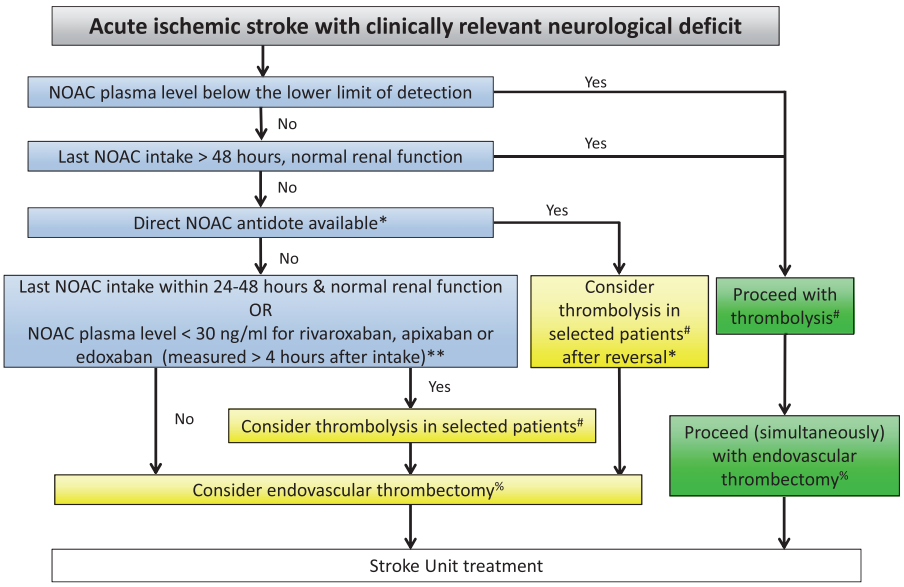

Figure 13 Acute management of acute ischaemic stroke in a patient on non-vitamin K antagonist oral anticoagulant. *Currently only available for dabigatran (idarucizumab). #Perform systemic thrombolysis only if there are no (other) contraindications for intravenous application of recombinant tissue plasminogen activator according to its label. %Perform endovascular thrombectomy only if there is a target vessel occlusion and procedure is indicated and feasible according to present evidence. **According to expert consensus.[370]

cases in which a reliable and NOAC specific coagulation assessment (see **chapter 7**) is available without long delay and demonstrating a concentration <30 ng/mL for rivaroxaban, apixaban, or edoxaban (if measured more than 4 h after drug administration), a reference value which is based on expert consensus only.[370] Since the efficacy and safety of this strategy needs to be further evaluated in clinical studies, we urge for the implementation of easy-to-use point-of-care testing for the emergency setting. In contrast, the use of thrombolysis in situations with uncertainty about the anticoagulation status (e.g. in AF patients with aphasia, unknown time of last NOAC dose, and lack of availability of rapid assessment of plasma levels) cannot be recommended.

There is a proven benefit of endovascular thrombectomy up to 7.3 h after stroke onset in selected non-anticoagulated patients with a distal occlusion of the internal carotid artery or the proximal middle cerebral artery.[371] Interestingly, endovascular thrombectomy also seems to be beneficial in highly selected stroke patients with a distal occlusion of the internal carotid artery or the proximal middle cerebral artery and favourable perfusion mismatch (according to the DEFUSE or DAWN study) within 6 to up to 24 h of last seen normal.[372,373] The European Stroke Organization recommendations now mention the use of endovascular thrombectomy as 'first-line treatment' in patients with contraindication for intravenous thrombolysis, while the AHA's guidelines provide no specific recommendation in this regard.[363,374] Although the trials underlying these recommendations either excluded or contained just a few patients on VKA or NOAC, the small amount of data available suggests that endovascular thrombectomy may be safe also in these individuals. Of note, the potential impact of present anticoagulation on reperfusion-related bleeding risk has to be taken into account and a comparably high rate of asymptomatic haemorrhagic transformation was observed in a prospective registry including 28 NOAC patients undergoing mechanical recanalization.[375] Further prospective data are urgently needed.

Patients with acute intracranial bleeding

About two thirds of all NOAC-related intracranial bleedings (ICBs) are intracerebral and about one third of all ICBs are subdural bleedings.[376,377] According to a meta-analysis of retro- as well as prospective studies, patients with intracerebral bleeds on NOAC (without using idarucizumab as a specific reversal agent of dabigatran) had the same poor prognosis as patients on VKA,[378] while a more recent and much larger retrospective analysis of the Get With the Guidelines-Stroke program found a more favourable outcome with NOACs compared with VKA.[379] A neurologist/stroke physician should examine all patients presenting with ICB on a NOAC, and neurosurgical consult should be solicited.

Recommendations for the treatment of ICB under oral anticoagulants are published, but the available level of evidence is low for NOAC-related ICB. In analogy to patients with acute ICB being treated with warfarin, discontinuation of the drug, urgent blood pressure management and rapid correction of the coagulation status (see also **chapter 11**) is needed to limit haematoma enlargement in patients under NOAC.[376,380,381] Whether the use of PCC is helpful

in NOAC-related ICB is a matter of debate since a retrospective multicentre analysis did not prove a significant benefit on haematoma enlargement.[382] For dabigatran related ICB reversal is possible via infusion of idarucizumab (see **chapter 11**). According to a reported case series,[365] haematoma growth was observed in two out of twelve ICB patients treated with dabigatran receiving idarucizumab on hospital admission. Despite present recommendations, the efficacy of this reversal strategy is unclear and needs to be further evaluated in clinical studies.

Management in the post-acute phase

Atrial fibrillation patients post-ischaemic stroke

There is no evidence from RCTs to prefer one NOAC over the other or to switch from one NOAC to another in patients with a history of ischaemic stroke under NOAC therapy (*Figure 14*). Appropriate dosing as well as patient specific issues need to be assessed.[41,93,202] Substantial study data regarding timing of reinstitution of oral anticoagulation by using a NOAC after transient ischaemic attack (TIA) or stroke in AF patients are missing,[383] as Phase III trials excluded patients within 7–30 days after stroke.

Therefore, present recommendations are based on consensus opinion, and NOACs should be (re-) initiated in analogy to clinical practice with VKAs. Recommendations on (re-) starting of oral anticoagulation after ischaemic stroke must outweigh (recurrent) stroke risk vs. secondary haemorrhagic transformation (*Figure 14*).[3,383] As stated in the current ESC guidelines,[3] oral anticoagulation using a NOAC may be continued (according to prescription and label) or started one day after a transient ischaemic attack (TIA) and exclusion of ICB by imaging. If stroke size is not expected to substantially increase the risk of secondary haemorrhagic transformation in patients with mild stroke, oral anticoagulation may be initiated ≥3 days after an ischaemic stroke. In patients with moderate stroke, anticoagulation may be started ≥6–8 days and in patients with severe stroke at ≥12–14 days, after excluding secondary haemorrhagic transformation by repeating brain imaging [using computed tomography (CT) or magnetic resonance imaging (MRI)].[383–385]

Due to the rapid onset of action of NOACs as well as an associated risk of bleeding, 'bridging' with heparin (LMWH or UFH) is not recommended. Moreover, a meta-analysis revealed that administration of parental anticoagulants within 7–14 days after ischaemic stroke is associated with a significant increase in symptomatic ICB.[386]

Atrial fibrillation patients with ischaemic stroke and concomitant atherosclerosis

Besides a (well-tolerated) statin therapy, temporally limited addition of aspirin to a NOAC may be considered in selected patients if underlying large-vessel disease is suspected and bleeding risk is considered to be comparably low. However, evidence for both approaches is lacking and further studies are required. Patients with AF and known carotid atherosclerosis with an asymptomatic stenosis of the internal carotid artery should be treated with a statin and an oral anticoagulant, without the need for additional antiplatelet therapy, similar to the situation in stable coronary heart disease (see **chapter 14**). Acute stroke patients with AF and 'symptomatic' high-grade carotid stenosis should preferably undergo carotid endarterectomy,[387] as carotid stenting would result in the need for dual antiplatelet therapy in addition to anticoagulation therapy with a subsequently higher risk of major bleeding. In patients undergoing endarterectomy, aspirin is recommended prior to and for some days after surgery. Aspirin should be stopped after (re-) starting oral anticoagulation.

Patients post intracranial bleeding

Apart from its immediate prognosis, an ICB in the setting of AF is also associated with later ischaemic stroke and mortality, partly due to the cessation of anticoagulation after ICB (*Figure 15*).[388–390] Evidence-based guidelines regarding the use of NOACs in AF patients after ICB are not available. A history of a spontaneous ICB constitutes a contraindication against anticoagulation according to labelling of VKAs and NOACs, unless the cause of the bleeding (like uncontrolled hypertension, aneurysm or arteriovenous malformation, or medical 'triple' therapy) has been reversed.[3] A recent meta-analysis of observational studies demonstrates that restarting VKA (but not antiplatelet agents) is associated with a significantly lower rate of ischaemic stroke without significantly increasing the risk of recurrent ICB.[389] However, publication bias as well as selection bias have to be taken into account. In the absence of RCTs, a case-by-case consideration is needed whether or not to reintroduce anticoagulation of any type in patients who have experienced an anticoagulation-related ICB (*Figure 15*).[3] Adequate blood pressure control is of paramount importance in all patients post ICB.[380] Left atrial appendage occlusion may be considered as potential substitute for long-term anticoagulation in AF patients post-ICB.[3] However, this strategy requires a period of antiplatelet treatment post-deployment, which also carries a risk of ICB. The safety and effectiveness of shorter duration antiplatelet therapy (or foregoing anticoagulation altogether) is not known. Overall, RCT evidence for LAA occlusion after OAC-related ICB under OAC is missing, which is why, ideally, treatment should occur in the framework of a randomized trial to contribute to evidence.

Patients post intracerebral bleeding

In analogy to the management of VKA-related intracerebral bleeding, administration of NOACs may be restarted 4–8 weeks after intracerebral bleeding if the individual risk of cardioembolic stroke is estimated to be high and the risk of recurrent ICB is estimated to be lower.[391] In practice, however, the same risk factors (including old age, hypertension, and previous stroke) are predictive for ischaemic stroke as well as recurrent intracerebral bleeding.[381]

Arguments for not resuming or initiating anticoagulation in intracerebral bleeding patients with AF should be assessed on an individual basis (*Figure 15*).[3,380] Patients with (probable) cerebral amyloid angiopathy have a very high risk of recurrent ICB and should not be anticoagulated.[390] Whether long-term anticoagulation should be avoided after a lobar bleed, as currently recommended by the AHA guidelines, is a matter of debate, since a recent meta-analysis of three retrospective studies indicate decreased mortality and favourable functional outcome after resumption of oral anticoagulation after intracerebral bleeding, irrespective of haematoma localization.[391]

Patients post subarachnoid haemorrhage

There is little evidence to guide the resumption of OAC treatment in patients with AF following subarachnoid haemorrhage. A thorough

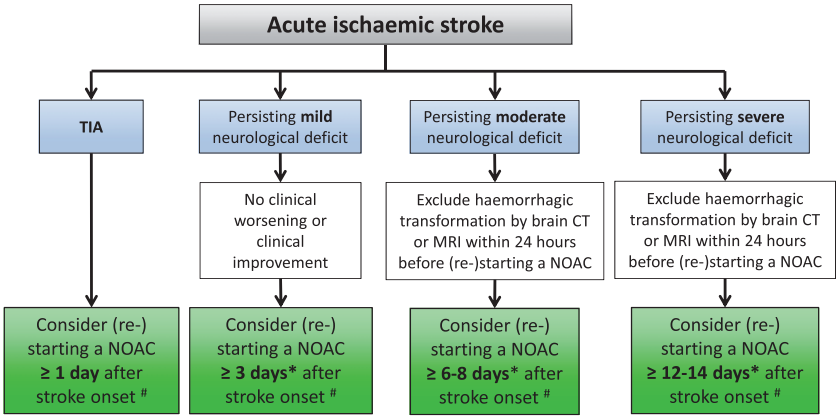

Figure 14 (Re-) initiation of anticoagulation after transient ischaemic attack/stroke. (Re-) start only in the absence of contraindications and if stroke size is not expected to substantially increase the risk of secondary haemorrhagic transformation. *Consider shorter delays to (re-) start a non-vitamin K antagonist oral anticoagulant if there is a very high risk of stroke recurrence (e.g. left atrial appendage thrombus) and no haemorrhagic transformation on follow-up brain imaging (using computed tomography or magnetic resonance imaging). Consider longer delays to (re-)start a non-vitamin K antagonist oral anticoagulant according to the recommendations made in the European Society of Cardiology Atrial Fibrillation Guidelines 2016. #Without proven evidence; consider inclusion of patient in an ongoing trial.

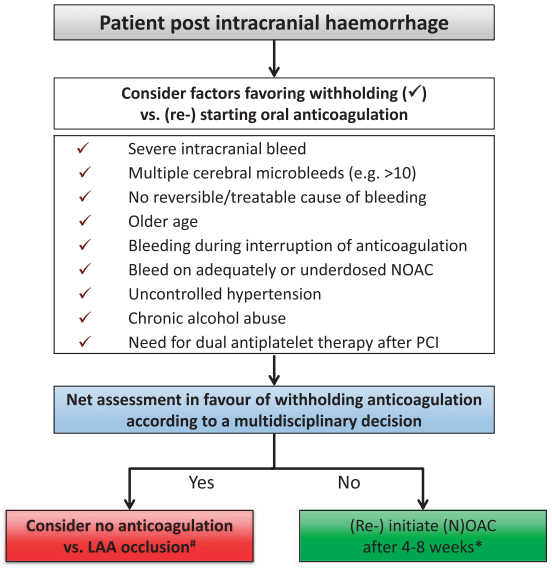

Figure 15 (Re-) initiation of anticoagulation post intracranial bleeding. #Without evidence; ideally include the patient in an ongoing trial. *Brain imaging (CT/MRI) should be considered before (re-)initiation of (non)-vitamin K antagonist oral anticoagulant.

angiographic evaluation and treatment of underlying aneurysm or arteriovenous malformation is needed. Moreover, neurological/neurosurgical evaluation regarding future risk of re-bleeding is key to balance the risk vs. benefit of OAC resumption in such cases. When subarachnoid haemorrhage occurs in AF patients taking a NOAC in the absence of a remediable aetiology it seems prudent not to re-initiate OAC treatment. Despite the absence of data, LAA closure should be considered, ideally in the framework of a randomized trial.

Patients post epidural or subdural haematoma

Although there are no specific data, it appears to be safe to start or reinitiate anticoagulation about 4 weeks after (surgical removal of) traumatic epidural or subdural haematoma, if ongoing (chronic) alcohol abuse or a substantial risk of falling is not present (see **chapter 18**). Adequately dosed NOAC or no anticoagulation at the time of non-traumatic epidural or subdural haematoma does not support (re-) initiation of oral anticoagulation.[3] According to clinical presentation and haematoma extension, brain imaging (using CT or MRI) is recommended before (re-) starting OAC.

18. NOACs in special situations

18.1. Non-vitamin K antagonist oral anticoagulants in the frail and older patients

The ≥75-year-old patient

The incidence of AF rises steadily with each decade.[392,393] Stroke prevention in older AF patients is important as stroke risk rises dramatically with age.[394] However, OAC remains underutilized in older age groups.[395] Older people with AF do better on OAC than not and on NOACs rather than VKA.[396–398]

All trials of NOAC treatment in AF included significant populations of older people (defined as ≥75 years) ranging from 31% to 43% in the individual trials, comprising over 27 000 older patients in whom

NOACs have been studied. Meta-analyses of NOAC trial data suggest no interaction of age for safety and efficacy.[246] Importantly, the higher absolute risk resulted in a larger absolute risk reduction by using NOACs instead of VKA in these older patients, resulting in a lower number needed to treat compared to younger patients.[399] Older patients had more bleeding but the overall pattern of bleeding observed (reduced intracranial and increased GI bleeding) showed no difference between NOACs and VKA.[246] While ICB remains lower with all NOACS compared with VKA, individual trial results showed heterogeneity on the interaction between age and bleeding outcomes. There was a significant interaction between age and increased extracranial major bleeding with both doses of dabigatran.[155] Conversely, no significant age interaction on rates of extracranial major bleeding was seen with apixaban, edoxaban, or rivaroxaban compared with overall trial results.[399–401] Importantly, certain comorbidities (renal insufficiency in particular, see **chapter 6**) are more common in the older patient, and the individual choice of the NOAC needs to take this into consideration. One interesting study investigating low-dose edoxaban in the management of elderly Japanese patients with atrial fibrillation who are ineligible for standard oral anticoagulant therapies (ELDERCARE-AF study) is currently ongoing.[402]

Frailty and falls

Frailty and pre-frail states are common with age and raise specific considerations with regard to the risk-benefit ratio of OAC. Frailty is commonly defined as a rules-based distinct phenotype or by clinical judgement of deficits in function in a frailty scale (see *Table 14*).[403–405]

Among others, frailty is a risk for rapid deterioration of renal function (see **chapter 6**) and risk of falling. Community dwelling individuals over 65 years have a 1–2% risk of falling per year; only 5% of falls, however, result in fracture and hospitalization.[406] Falls and risk of subdural haemorrhage in particular are often considered by physicians as a contraindication to OAC.[407] While in states of *severe* frailty with poor physical functioning and limited life expectancy there may be limited benefit to OAC, a Markov decision analytic model has demonstrated that with VKA a patient would have to fall 295 times in order for the risk of a subdural haematoma to outweigh the benefit of anticoagulation.[408] Given the even lower risk of subdural bleeding compared with VKA, this 'number needed to fall' would be even higher with the use of NOACs.

The risk of falling can be estimated using simple or more sophisticated tools (*Table 15*). The effect of NOACs vs VKA in patients at risk of falling was specifically analysed in two NOAC trials (prospectively defined in ENGAGE-AF TIMI 48, retrospectively in ARISTOTLE).[52,409] The treatment effect of the respective NOAC was consistent in patients at increased vs. not at increased risk of falling. However, the larger absolute risk of events of patients at increased risk of falling resulted in a larger absolute risk reduction vs. VKA and, consequently, a lower number needed to treat compared to those not at an increased risk of falling.

In summary, frailty *per se* should not be an exclusion criterion to anticoagulate since frail and older patients are at an increased risk of stroke and have been shown to benefit from OAC. The benefit of NOACs over VKA has best been demonstrated for edoxaban and apixaban in this patient population. To improve things further, all falling patients on OAC should be referred to a falls service for multidisciplinary assessment of diagnosis, risk and to address remediable pathology and/or prescribe interventions (e.g. exercise programs; home environmental assessment etc.) that reduce risk of further falls.[411–413]

Dementia and anticoagulation

Dementia is common in older age groups. A stroke is a very significant event for patients with dementia with a greater risk of cognitive and functional decline, loss of independence and institutionalization compared to non-dementia patients.[414] Indeed, atrial fibrillation is itself a risk factor for dementia and there is encouraging evidence that use of OAC may reduce the risk of dementia in AF patients.[415,416]

Dementia does pose unique considerations, however, when considering anticoagulation and in particular around patient capacity in decision making, choice of treatment and managing drug adherence safely. Importantly dementia should not be a viewed as a general contraindication to anticoagulation, especially if well managed from a logistical point of view (see below). All patients with dementia should have a careful assessment of their ability to understand and make a treatment decision regarding OAC in AF, with indicative risks of stroke and bleeding provided. Where capacity is lacking, it may be reasonable for the physician to recommend treatment on the basis of the 'best medical interest' principle, ideally including next of kin assent.

Adherence to OAC intake is a significant consideration in dementia. Once daily medications, weekly tablet boxes, reminders or blister packing may be helpful. Paradoxically, the fact that others take care of providing medication to dementia patients may guarantee higher adherence. The possible advantages of electronic monitoring, or even telemonitoring, in this population should further be explored.[51]

18.2. Obesity and low body weight

Obesity

The WHO defines overweight and obesity as a body mass index (BMI) of greater than 25 and 30 kg/m^2, respectively. The incidence of obesity has tripled since 1975. In 2016, 650 million adults (13.1% worldwide population) were obese.[417] Among many other things, obesity also increases the risk of atrial fibrillation and recurrences of atrial fibrillation after successful ablation.[418–420]. As such, weight loss is an integral part in the multidisciplinary treatment of patients with AF and obesity.[421]

Obesity affects the pharmacokinetics of drugs, including the volume of distribution (of lipophilic drugs in particular) as well as drug clearance. Indeed, renal blood flow and CrCl have been shown to be increased in obesity and could increase elimination of OACs.[422] A number of studies of VKA have indicated that obese patients require greater doses and longer lead-in periods for achieving therapeutic INR values.[423]

Studies of dabigatran reported no effect of weight on pharmacokinetic variables although analysis in older healthy individuals did not include very obese patients.[159,166,182] Pharmacokinetic data on both rivaroxaban and apixaban initially reported weight-dependent changes on volume distribution and half-life across a range of weights; however, these were felt unlikely to be clinically significant.[185,424,425] Data with edoxaban suggests low body weight may be a factor in

Table 14 The 'Canadian Study of Health and Aging' (CHSA) Clinical Frailty Scale

From http://www.csha.ca and Ref.[404]

(1) Very fit – People who are robust, active, energetic, and motivated. These people commonly exercise regularly. They are among the fittest for their age.

(2) Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

(3) Managing well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

(4) Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being 'slowed up', and/or being tired during the day.

(5) Mildly frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

(6) Moderately frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

(7) Severely frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).

(8) Very severely frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

(9) Terminally ill – Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

IADL, instrumental activities of daily living.

reduced clearance of the drug,[426] and a converse situation would seem plausible.

Concerns have been expressed about the reliability of the anticoagulant effect of NOACS in obese patients.[427,428] Weight was not an exclusion criterion in any of the NOAC trials in AF or VTE. However, case reports of treatment failure with low serum levels of dabigatran have been reported in cases of severe obesity (BMI ≥40 kg/m^2).[429,430]

Apixaban demonstrated no difference in efficacy and safety in patients <60 kg vs. >60 kg,[30] but patients with a BMI ≥30 kg/m^2 had a trend towards a better outcome compared to the remainder of the study (independent of treatment).[431] This was in contrast to the reduced bleeding seen in the obese patient group in the AMPLIFY study of apixaban in the treatment of VTE.[330] Similarly in ROCKET-AF, obese patients (BMI ≥35 kg/m^2) had a reduced stroke risk compared with the remainder of the cohort, and there was no interaction for the efficacy and safety of rivaroxaban vs. warfarin depending on BMI.[432] ENGAGE-AF did not (yet) report a sub-analysis of efficacy and safety with edoxaban according to weight criteria.[31] Clinical trial data from use of edoxaban in acute VTE, included 611 (14.1%) patients >100 kg and sub analysis by weight showed no difference in safety or efficacy.[332]

Because of limited data in extreme obesity, the use of VKA in patients with a BMI ≥40 kg/m^{2}or weight >120 kg should be considered (in line with recommendations from the International Society on Thrombosis and Haemostasis).[427] In rare case when a NOAC is needed in such circumstances, specific measurements of drug trough levels should be considered. This, however, should only be done under the guidance of a haematologist and in the knowledge that hard clinical outcome data do not exist for such an approach.

Low body weight

There is no unifying definition of low body weight and future criteria may need to be race specific as Asian populations tend to be smaller and leaner. Low body weight may increase exposure to any NOAC and as such increase the risk of bleeding.[433] Importantly, patients with low body weight frequently present with other conditions and co-morbidities which may increase the risk of stroke as well as bleeding, including old age, frailty, cancer, and renal insufficiency. Of note, renal function may be overestimated in underweight patients due to their reduced muscle mass (especially when calculated with the MDRD formula; see **chapter 6**). As such, special care is needed when anticoagulating these patients.

Body weight ≤60 kg was a dose-reduction criterion for apixaban (if also age ≥80 years and/or creatinine ≥1.5 mg/dL, see **chapter 15**) as well as for edoxaban. For these drugs, efficacy and safety compared to warfarin was consistent in the (few) underweight patients when compared with the remainder of the study cohort.[30,31] As such, both drugs may be a preferred choice for patients <60 kg.

Dabigatran was studied *post hoc* in patients with low body weight (<50 kg) with consistent efficacy and safety compared with the remainder of the study cohort.[28] However, observational studies have suggested that low BMI (<23.9 kg/m^2) can be an independent predictor of bleeding events with dabigatran.[434] In addition, frequently co-existing renal insufficiency may make dabigatran a less preferably option for the underweight patients. Also rivaroxaban showed similar efficacy and safety in an exploratory analysis of lower body weight, but only patients <70 kg were compared with those >70 kg.[29] No outcome data are available for patients with <60 kg or <50 kg in patients on the full AF dose of rivaroxaban.

Table 15 Examples of falls risk tools

(A) High risk of falls (from ENGAGE-AF TIMI 48)[52]
Presence of one or more of • Prior history of falls • Lower extremity weakness • Poor balance • Cognitive impairment • Orthostatic hypotension • Use of psychotropic drugs • Severe arthritis • Dizziness

(B) Probability falls assessment[410]	
1 point for each 'Yes'	
Previous falls	Yes/No
Medications	
>4	Yes/No
Psychotropics	Yes/No
Low visual acuity	Yes/No
Diminished sensation	Yes/No
Near tandem stand 10 s	Yes/No
Alternate step test 10 s	Yes/No
Sit to stand 12 s	Yes/No

Score	0–1	2–3	4–5	6+
Probability of fall per year	7%	13%	27%	49%

Severely underweight patients (<50 kg) were clearly underrepresented in the large outcome trials. As such, even for NOACs that were dose-reduced based on body weight (apixaban and edoxaban), data are limited for these patients. Of note, bleeding may also be increased with VKA therapy in underweight patients.[431] If therapy with a NOAC is warranted in these individuals, measurement of trough levels may be considered to check for accumulation of the drug.[435] However, no evidence-based recommendations can be given regarding (further) dose reduction in such cases.

18.3. Women of reproductive age

All OAC use should be considered with caution in women of childbearing age and an appropriate test to rule out pregnancy and contraceptive counselling advice arranged before initiation of any agent. Abnormal uterine bleeding (AUB; formerly called *menorrhagia*), occurs in 9–14% of the general female population of reproductive age,[436] which may be exacerbated by oral anticoagulants.[437]

In a recent case series of NOAC use in the treatment of acute VTE in women of reproductive age, rivaroxaban was associated with prolonged (>8 days) menstrual bleeding (27% vs. 8.3%, $P = 0.017$), increased need for menorrhagia-related medical or surgical intervention (25% vs. 7.7%, $P = 0.032$), and more adaptations of anticoagulant therapy (15% vs. 1.9%, $P = 0.031$) compared with VKA.[438] A similar trend towards increased AUB with rivaroxaban compared to enoxaparin has also been reported.[439] Registry data report a 32% incidence of AUB in women of reproductive age ($n = 178$) on factor Xa inhibitor.[440] Most cases were managed successfully with change of hormonal or anticoagulation therapy, including temporary discontinuation or cessation of factor Xa inhibitor medication. Some authors have expressed concern about the lack of robust data for NOAC use in this population with AF.[441] In any case, women should be counselled about the risk of increased menstrual bleeding while on NOAC and monitored carefully especially during the first cycles after NOAC initiation.[442]

All cases of AUB on OAC need to have gynaecological assessment for underlying structural problems and possibility of local hormonal treatments and/or surgical procedure to reduce risk of recurrence of AUB. Importantly, NOACs are contraindicated in pregnancy as well as during breastfeeding.

18.4. Non-vitamin K antagonist oral anticoagulants in Athletes

AF is the most common arrhythmia in athletes and endurance athletes are known to be more prone to AF.[443–446] Additional risk factors for stroke may be uncommon in this population; however, older individuals are increasingly engaged in competitive and/or vigorous sports activities.[447]

If the CHA_2DS_2-VASc score is ≥1 in men and ≥2 in women, the use of anticoagulation may be warranted in such settings according to current guidelines.[3] Traditional advice to athletes on OAC for VTE has been to avoid contact sports while on treatment and there is little published evidence on the use of NOACs in AF in such populations. The use of a OD agent may be preferable with intake in the evening to avoid high levels of the drugs during the actual exercise, but no outcome data are available to support this. All athletes presenting with AF should have a full cardiological assessment.

18.5. Epilepsy

A risk of seizures has been reported in >5% of overall post-stroke patients.[448,449] Following an unprovoked seizure after stroke, the risk of subsequent unprovoked seizures is about 65% within 10 years.[450]

OAC poses a special risk for patients with epilepsy due to the risk of injury during a seizure (with or without falling). Most seizures in older people or post-stroke patients are focal in onset. However, patients who do suffer rare generalized atonic seizures are particularly vulnerable to head trauma while tongue biting is a risk in the tonic component of generalized seizures.

Anticoagulation is affected by antiepileptic drugs via various potential interactions (*Table 5*).[147] A number of antiepileptic drugs can in addition cause thrombocytopenia or platelet dysfunction.[147] The significance of these drug–drug interactions is still largely unknown with only occasional case reports available. In

some situations of severe, relevant interactions NOACs may not be the preferred choice.

19. Anticoagulation in atrial fibrillation patients with a malignancy

The scope of the problem

Cancers are not infrequent in older patients, similar to AF. One study found a prevalence of 2.4% of pre-existing AF and 1.8% new AF among cancer patients.[451] Cancer and cancer therapy may in turn precipitate AF, while both age and malignancy are independent risk factors for thrombosis and bleeding.

The greater incidence and prevalence of AF in patients with malignancy may result from the presence of comorbid conditions (e.g. hypertension, heart failure), a direct tumour effect (including dehydration, altered sympathetic tone due to anxiety or pain, systemic inflammation, etc.) or as a complication of cancer therapy (e.g. after lung cancer surgery or as a side effect of specific targeted therapies such as tyrosine kinase inhibitor ibrutinib).[452–455] The increasing survival of cancer patients may additionally increase the incidence of AF among patients with active and past malignancies.

The risk of VTE is increased in the presence of cancer through a host of possible mechanisms.[456] Brain, pancreatic, ovarian, lung, or haematological malignancies, as well as many cancer treatments (e.g. cisplatin, gemcitabine, 5-fluorouracil, erythropoietin, granulocyte colony stimulating factors) are associated with particularly increased thromboembolic risk.[457]

Conversely, cancers may cause infiltrative liver failure resulting in thrombocytopenia or coagulopathy and increased risk of bleeding. Tumours may erode into blood vessels directly, and many GI and solid tumours such as intracranial tumours, renal cell carcinoma, or metastatic melanoma are very vascular and prone to bleeding. Haematologic malignancies may cause coagulation defects thus increasing the risk of bleeding further. In addition, every form of cancer therapy, be it surgery, radiation, or chemotherapy, may induce bleeding through local wounds (surgery), tissue damage (radiation), or systemic antiproliferative effects reducing platelet count and function (e.g. chemotherapy, some forms of irradiation).

Anticoagulant therapy in atrial fibrillation patients with malignancy

So far, the only published RCT specifically targeting cancer patients stems from the HOKUSAI-VTE Cancer trial comparing edoxaban with LMWH in patients with VTE (but not AF).[458] Edoxaban proved to be non-inferior regarding the primary endpoint of recurrent VTE and major bleeding; while recurrent VTE trended to be lower with edoxaban, major bleeding was higher (driven by an increased risk of upper GI bleeding in patients with gastrointestinal cancer). In line with these findings, several meta-analyses of the small subgroup of cancer patients in VTE trials reported similar or better efficacy of NOACs in comparison to VKA or LMWH for VTE prevention, although major bleeding rates were higher.[459,460] Most of these cancer patients may have been clinically stable, in contrast to those requiring active therapy or in a palliative setting.

Table 16 Atrial fibrillation and malignancy

Interdisciplinary teamwork
(1) Estimate individual patient risk profile • AF-related risk factors (CHA_2DS_2-VASc, bleeding risk) • Cancer-related risk factors (type, liver metastases, coagulopathy, renal/hepatic function etc. • Treatment-related risk factors (thrombocytopenia, surgery, radiation, central lines etc.)
(2) Choose anticoagulant • Current standard of care: VKA/(LMWH)[a] • NOACs: Available data scarce, but encouraging • Consider patient preference (VKA vs. NOAC)
(3) Protect the patient • Gastric protection (PPI/H2 blockers) • Beware of drug–drug interactions (*Table 4*) • Dose reduction/treatment interruption (if platelets <50k, renal dysfunction, bleeding, . . .)
Beware • Risk of thromboembolism ↑ • Risk of bleeding ↑

[a]If oral therapy is not possible reversion to LMWH is reasonable.

Moreover, in how far these findings apply to AF patients with cancer requires further data. In cancer patients who develop incident AF, VKAs, or LMWH have been traditionally preferred over NOACs, based on greater clinical experience with these drugs, possibility for closer monitoring and availability of 'reversal' options. However, evidence for stroke prevention with LMWH in AF is lacking and LMWH is contraindicated in secondary prevention in the setting of acute stroke.[386] Active malignancy was an exclusion criterion in most NOAC AF trials, and although there were a few patients with cancer in the Phase III AF trials, the absence of information on the type and stage of cancer precluded any relevant subgroup analysis. An exploratory analysis of AF patients with active cancer ($n = 157$) or a history of malignancy ($n = 1079$) in the ARISTOTLE trial showed consistently superior efficacy and safety of apixaban vs. warfarin in patients with and without cancer.[461] A large registry using prescription based analysis for AF patients on VKA or NOAC with and without cancer recently reported equivalence for bleeding and thromboembolic risk and cancer status, although the rates of both were lower in the NOAC population.[462] However, much is still unknown about drug–drug interactions between NOACs and specific chemotherapeutic agents, urging further caution (*Table 4*).[144]

Overall, antithrombotic therapy in patients with AF suffering from a malignancy needs a dedicated interdisciplinary team approach (*Table 16*).[463] Especially, when myelosuppressive chemotherapy or radiation therapy is planned, temporary dose reduction or cessation of NOAC therapy needs to be evaluated, taking into account full blood counts including platelets, renal/liver function, and physical signs of bleeding. Gastric protection with PPI or H2 blockers should be considered in all such patients.

20. Optimizing dose adjustments of vitamin-K antagonists

In spite of the preferred use of NOACs for stroke prevention in eligible patients with AF,[3] some situations still require the use of VKA, including patients with mechanical heart valves as well as those with AF in the setting of rheumatic mitral stenosis. As such, mastering VKA therapy and dosing to keep patients in the therapeutic range remains an important skillset.

Beyond the standard target INR of 2.0–3.0 much of the optimal management of VKA therapy in AF is experience - rather than evidence-based. As such, various algorithms exist for the management of different VKA[464,465] and experience in the past decades has led to different clinical routines (e.g. anticoagulation clinics, self-measurement via point-of-care devices etc.). One aspect, however, is key to success in VKA treated patients: Maintenance of a high time in therapeutic range (TTR) has been shown to reduce the risk of ischaemic and bleeding events and should be the primary goal in the treatment of these patients independent of the type management approach. Conversely, a change in the approach to these patients needs to be considered if a low TTR is consistently observed.

Table 17 Maintenance Warfarin dosing for out-of-therapeutic-range international normalized ratio

INR	Dose adjustment per week
≤1.5	↑ by 15%/week
1.6–1.9	↑ by 10%/week
2–2.9	Unchanged
3–3.9	↓ by 10%/week
4–4.9	Hold 1 dose, then restart with dose ↓ by 10%/week
≥5	Hold until INR is 2–3, then restart with dose ↓ by 15%/week

Suggested dose adjustment in case of out-of-therapeutic-range INR.[472] Importantly, dosing is optimized not using daily dose adjustments but adjustments based on the weekly intake in warfarin.

Dosing during initiation of therapy

Automated dosing calculators are available that help in the determination of the 'optimal' starting regimen (e.g. http://www.warfarindosing.org). One randomized trial comparing a 10 mg and 5-mg Warfarin Initiation Nomograms for the outpatient treatment of acute VTE suggested the 10 mg scheme to be superior with patients reaching a therapeutic INR faster.[466] However, a meta-analysis found no evidence of superiority of either starting regimen.[467] Moreover, the situation is different in patients with AF as they are generally older and more frail than VTE patients. Furthermore, AF patients are usually not initiated in the setting of an acute thrombotic event. Indeed, various factors may play in favour of using a low (or even lower, i.e. 2 mg qd) starting dose, including older age, frailty, and renal insufficiency. As such, no strong recommendation can be made for routinely using either strategy, and individualizing the approach based on patient characteristics is recommended. In view of the lack of evidence supporting genotype-based dosing the latter is not recommended on a general basis.[465,468]

In many parts of Europe, anticoagulation with phenprocoumon is frequently started with a loading dose in order to shorten the time to therapeutic INR levels owing to the long half-life of the drug,[469] whereas the situation for warfarin and acenocoumarol is less clear.[470] In order to prevent a possible transient prothrombotic effect due to a reduction of the equally vitamin K dependent, anticoagulant protein C (and S), the first phase of anticoagulation (particularly with phenprocoumon) is frequently paralleled by a parenteral anticoagulant, but evidence for the superiority of routinely using this approach is missing.

Dosing during maintenance therapy

Interpatient variability of optimal warfarin dose is enormous. Even in (formerly) 'stable' patients, intercurrent illness, change in dietary habits, changes in co-medication etc. may have a substantial impact on INR values. Despite the large variation of warfarin dosing habits amongst different centres, data have emerged indicating the usefulness of using dosing algorithms to optimize VKA dosing and, ultimately, the time in therapeutic range (TTR).[471–473] One such algorithm is presented in *Table 17*, derived from the warfarin arm of the RE-LY trial. Importantly from a conceptual point of view dosing is optimized not using daily dose adjustments but adjustments based on the weekly intake in warfarin. Obtaining INR measurements at least every 4 weeks and at least weekly in case of out-of-range values is an important prerequisite. A similar dosing scheme may be used for phenprocoumon given its even longer half-life, whereas for acenocoumarol more short-term based adjustment may be feasible given its shorter half-life.

In patients with repeated out-of-range INR values, supplemental measures may be required including (re-)educating patients on the risk and benefits of VKA intake, the importance of strict adherence as well as food- and drug–drug interactions etc. Receiving care at a dedicated anticoagulation clinic[474,475] as well as self-monitoring and self-management[476] has been shown to improve INR control. However, patient selection is a critical component, particularly for the latter, and not every patient may be suitable.

In summary, every effort needs to be made in VKA treated patients to optimize the individual patient's TTR. At the same time, however, it needs to be kept in mind that even being within the therapeutic range does not protect from bleeding events. Recent studies indicate that although the risk of ICB increases at an INR >3 (and clearly >4–5), the vast majority of events in absolute numbers occurs at a therapeutic INR level.[377] Keeping the patient in the therapeutic range (2.0–3.0) hence primarily confers relative, but not absolute efficacy and safety.

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