2021 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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Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs) are considered by atrial fibrillation (AF) guidelines world-wide as the preferred choice of anticoagulants to prevent stroke in patients with atrial fibrillation [1-4] The term NOAC has been used for many years, is used by the current ESC AF guidelines,[1] and is widely recognized. Therefore, even though some authors refer to these drugs as 'direct oral anticoagulants' (DOACs),[5] we prefer to continue to use the term 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.

NOACs have an improved efficacy / safety ratio and a predictable anticoagulant effect without the need for routine coagulation monitoring.[6, 7] However, the proper use of NOACs requires a carefully considered approach to many practical aspects. Each of the available NOACs is accompanied by the instructions for its proper use in many clinical situations (summary of product characteristics (SmPCs); patient cards; information leaflets for patients and physicians), but these are often slightly different (from drug to drug and from country to country), and physician education tools sometimes create confusion rather than clarity. 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. 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; [8] a first update was published in 2015;[9] and a fully revised new version in 2018.[10] The EHRA Practical Guide's purpose is to provide support for *safe and effective use of NOACs in daily practice*, thereby supplementing ESC and other international guidelines mainly focusing on the *scientific evidence* for treatment of patients with AF with anticoagulation in general and of NOACs in particular.[1-4]

A writing group formulated practical answers to 16 clinical scenarios, based on updated information. During the conception and writing of the 2021 Practical Guide, a public call was made to all EHRA members as well as to the Heads of the National Cardiac Societies to submit their suggestions additions, corrections, modifications, etc. to the 2018 version of the Guide, and these have been incorporated wherever possible and appropriate. We thank all participants for their input, which has further improved this Guide. As in the previous iterations, 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 European SmPCs. However, the final responsibility of this document resided entirely with the EHRA writing group. In some instances, the authors opted to advise options that do not fully align with all SmPCs, with the goal of providing more uniform and simple practical advice (e.g., on the start of NOACs after cessation of VKA; on advice after a missed or forgotten dose; on perioperative management and others). Obviously, local regulations and healthcare providers' freedoms for prescription may vary and final responsibility of use lies with the prescribing healthcare professional.
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 the current revision further improves the practical tool that EHRA envisioned. The authors realize that there will always be grey areas, unaddressed questions, gaps in knowledge, and hence areas of uncertainty and debate. Therefore, readers can continue to address their suggestions for change or improvement to the website or via EHRANOACguide2021@escardio.org.

1. NOAC eligibility and dosing

NOAC eligibility

NOACs are approved for stroke prevention in "non-valvular" AF. Most summary of product characteristics (SmPCs) base eligibility on the $CHADS_2$ score as it was commonly used in the phase III randomized clinical trials (RCTs). Given the consistent efficacy and safety, the indication for NOAC therapy has subsequently been broadened to patients qualifying for anticoagulation according to the CHA_2DS_2-VASc score,[1] with some regional differences (e.g., Canada, Japan).

In order to avoid confusion, the use of the term “non-valvular” is strongly discouraged in the ESC guidelines on the management of patients with AF, and reference is made to the specific underlying valvular heart disease.[1, 11, 12] 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 RCTs on which their regulatory approval was based. When it is used, the term “non-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),[1, 12, 13] which were exclusion criteria for all phase III NOAC vs. warfarin trials in AF. However, there is no RCT indicating that NOACs are less efficacious in patients with rheumatic mitral stenosis, and no rational base on which to hypothesize a differential response to NOACs vs. VKA.[14] Indeed, the lack of eligibility only stems from exclusion of these patients from the pivotal RCTs. The INVICTUS-program investigating the use of VKA, Rivaroxaban or Aspirin in patients with rheumatic heart disease is currently ongoing (NCT02832531). Until these and other trials are completed, such patients should be treated with VKA as a standard of care. However, if therapy with VKA is truly impossible (e.g., no means of monitoring, no stable INR even when using self-monitoring and -management etc.) use of a NOAC may be an option which physicians could carefully evaluate, also in view of the lack of other studied, safe and effective alternatives, after informed consent of the patient regarding the off-label use in this situation.

In contrast, for AF in the context of mechanical heart valves, particularly in the setting of mechanical mitral valve replacement, NOAC therapy should be discouraged unless new evidence reverses existing data that NOACs may be inferior to VKA for stroke prevention.[15, 16] Patients with degenerative valvular heart disease were variously included in the phase III trials, and NOACs demonstrated 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 'Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation' (ROCKET-AF) trial).[12, 17-22] NOACs may therefore be used in patients with AF and most forms of valvular heart disease (Table 1).[1, 12, 23]

Oral anticoagulation in patients with AF and biological valves or after valve repair constitute a grey area, even though these patients were included in some of the landmark NOAC trials.[12, 17, 19, 20] In the 'Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation' (RIVER) trial rivaroxaban was non-inferior to warfarin regarding the mean time until the combined endpoint of death, major cardiovascular events, or major bleeding at 12 months in 1005 patients with atrial fibrillation or flutter and a bioprosthetic mitral valve.[24] Similarly, edoxaban was non-inferior in 220 patients included in the 'Efficacy and Safety of edoxabaN in Patients After Heart Valve Repair or Bioprosthetic vaLve Replacement' (ENAVLE) trial (presented at ACC 2020). NOACs hence appear as a valid option for the management of concomitant AF especially after the immediate 8-12 weeks after surgery.

For patients after trans-catheter aortic valve implantation (TAVI), who have an indication for anticoagulation (e.g., AF), a small RCT of 157 patients comparing OAC alone with a combination of OAC plus clopidogrel, indicated a benefit from OAC alone in terms of reduced bleeding without compromising ischaemic events.[25] A possibly even greater advantage was seen with the use of NOACs in this study (vs. VKA), but the study was underpowered to address this question. Observational data similarly found a lower rate of early thromboembolic- and bleeding events (as well as all-cause death in a more recent analysis) with NOACs vs. VKA after TAVI but residual confounding is likely.[26, 27] Dedicated trials are ongoing looking at the specific efficacy and safety of NOACs in this setting (e.g., 'Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis' (ATLANTIS),[28] 'EdoxabaN Versus standard of care and theIr effectS on clinical outcomes in pAtients havinG undergonE Transcatheter Aortic Valve Implantation–Atrial Fibrillation' (ENVISAGE-TAVI)).[29] It is important to remember that while OAC (including NOAC) monotherapy may be considered after TAVI in patients with AF, OAC is currently not indicated in patients without an established indication for OAC in such patients.[30]

In both obstructive and non-obstructive hypertrophic cardiomyopathy (HCM), AF is associated with a high rate of thromboembolism.[31, 32] Despite the absence of dedicated RCTs, increasing evidence from observational studies indicates that NOACs may be safe and effective in this condition.[33-36] Indeed,

there does not seem to be a mechanistic rationale why NOACs should be inferior to warfarin in hypertrophic cardiomyopathy. On the contrary, AF in HCM shares many similarities of HFpEF related AF, for which NOACs are non-inferior to VKA.[37-39] 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 hypertrophic cardiomyopathy may be eligible for NOAC therapy.

NOACs are contraindicated in pregnancy, and reliable contraceptive measures need to be in place in women of child-bearing age before starting NOAC therapy (see Online Supplement). Paediatric patients have been excluded from the pivotal stroke prevention RCTs and AF with need for OAC is rare in this population. NOAC therapy should be discouraged in children but can be considered in fully grown adolescents with body weight > 50kg. Of note, body-weight adjusted treatment with rivaroxaban has proven safe and effective for children with acute venous thromboembolism compared to standard anticoagulants over 3 months;[40] also dose-adjusted treatment with Dabigatran revealed a favorable safety profile for secondary prevention of venous thromboembolism in children 3 months - 18 years.[41]

Patients with "non-valvular" AF and antiphospholipid syndrome should be treated with VKA rather than NOACs, as a higher rate of thromboembolic events and major bleeding was observed with rivaroxaban vs. warfarin in these patients.[42]

Dosing

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. Table 2 gives an overview of currently available NOACs and their doses in the different indications, including the relevant dose-reduction criteria.

Even in settings with optimal patient education (see Chapter 2) dosing errors are common in daily practice, and patients need to be informed on what to do in such cases. In order to provide a more uniform and simple practical advice, the writing group acknowledges that some of the below advice does not fully align with all European SmPCs.

Missed dose

A forgotten dose may be taken until half of the dosing interval has passed. Hence, for NOACs with a twice-daily (BID) dosing regimen (i.e. every 12 h), a forgotten full dose can be taken up until 6 h after the scheduled intake. For NOACs with a once-daily (QD) dosing regimen, a forgotten dose can be taken up until 12 h after the scheduled intake. After these time points, the dose should be skipped, and the next scheduled dose should be taken.

Double dose

For NOACs with a BID dosing regimen, the next planned dose (i.e. after 12 h) may be skipped, with the regular BID dosing regimen restarted 24 h after the double dose intake.
For NOACs with a QD 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 continue with the regular dose regimen, i.e. starting with the next dose at the 12 h interval.
For NOACs with a QD dosing regimen, when thromboembolic risk is high (CHA_2DS_2-VASc ≥3), it may generally be advisable to take another tablet 6-8 hours after the original (uncertain) intake and then continue the planned dose regimen. In case the thromboembolic risk is low (CHA_2DS_2-VASc ≤2) we advise to wait until the next scheduled dose.

2. Practical considerations for initiation and follow-up

Choice of anticoagulant therapy and initiation

Indication for anticoagulation and choice between VKA and NOAC

- After the indication for OAC is established, NOACs are preferred over VKAs in all NOAC-eligible AF patients (see Chapter 1).[1, 2]
- When starting a NOAC, knowledge of current kidney and liver function is required as all NOACs are eliminated to some extent via the kidneys, and renal function affects NOAC dosing. Importantly, kidney function should be assessed using the Cockcroft-Gault formula as it was used in the four pivotal phase III trial (see Chapter 4 for details). Indeed, use of other formulas including 'Modification of Diet in Renal Disease' (MDRD) and 'Chronic Kidney Disease - Epidemiology Collaboration' (CKD-EPI) may overestimate kidney function particularly in older patients and in those with low body weights.[43]
- It is wise to also obtain a baseline haematological profile for reference during future follow-up.
- Bleeding risk, as estimated using the HAS-BLED score, is not in itself a reason to deny OAC to AF patients at risk of stroke or reduce the dose of the NOAC. Instead, particularly patients at high bleeding risk (eg HAS-BLED ≥3) should have their modifiable bleeding risk factors identified and addressed,[1, 44] and should be scheduled for an earlier and more frequent clinical follow-up.[45]
- Similarly, frailty, cognitive decline and risk of falling should not generally be a reason not to anticoagulate patients. Care needs to be taken to minimize the risk of falling and to ensure optimal compliance and adherence. This topic is dealt with in detail in chapter 12.

Choosing the type and dose of NOACs

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 (Chapter 1). Local factors, such as regulatory approval, formulary restrictions, and the cost of therapy, may influence NOAC availability in specific healthcare settings.

All NOACs have been tested in large randomized prospective trials and have shown efficacy and safety of the respective agents. Testing of different doses, however, was carried out differently. In the 'Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation' (ARISTOTLE) trial (using apixaban) and ROCKET-AF (using rivaroxaban) trials, patients received a standard dose which was reduced in the presence of predefined patient characteristics.[46, 47] In contrast, in 'Randomized Evaluation of Long-Term Anticoagulation Therapy' (RE-LY) trial (with dabigatran) and 'Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation - Thrombolysis in Myocardial Infarction 48' (ENGAGE AF-TIMI 48) trial (with edoxaban) both a lower and a higher dose were tested in fully powered patient cohorts (*without* further dose reduction for dabigatran, and *with* further dose reduction for edoxaban in certain patients).[48, 49] **Dose reduction of NOACs is primarily recommended according to the published and approved dose reduction** criteria (Chapter 1).[1] Whenever possible, the tested and approved dose of NOACs should be used to provide optimal benefit for the patient.

There is a wealth of published data to confirm that in daily clinical practice - i.e., outside the controlled clinical trial setting - NOACs are at least as safe and efficacious as warfarin.[50-55] However, some patterns have emerged from large observational studies indicating a higher than anticipated off-label dosing of NOACs.[51, 56-68] This is related to the fact that healthcare providers mostly worry about the risk of bleeding (as an iatrogenic event), whereas the risk of a stroke is often viewed as a possible "natural course of the disease". However, various large trials and observational series indicate that high-risk patients derive a particularly pronounced benefit from anticoagulation.[47, 49, 53, 69-71] Involving the patient into the decision process and discussing together the options of anticoagulation ("shared decision making") is key in order to adequately assess patients' needs, as for patients - in contrast to physicians – the risk of stroke usually outweighs the risk of a bleed. [72-74]

In addition, it is important to consider co-medications, some of which may be contraindicated or result in unfavourable drug-drug interactions (Chapter 3). Also, patient age and frailty (Chapter 12), weight (Chapter 13), renal function (Chapter 4), and other comorbidities influence the choice. Proton pump inhibitors (PPIs) may be considered to reduce the risk for gastrointestinal (GI) bleeding and accompanying hospitalizations, especially in those with a history of GI bleeding or ulcer and patients requiring concomitant use of (dual) antiplatelet therapy.[75-80] This gastroprotective effect was especially demonstrated in patients receiving antiplatelet or VKA therapy[81-83], while data on the preventive effects in NOAC treated patients are limited.[79] Decision aids are available to guide clinicians about which NOAC may be best suited for a specific target group.[84-87]

Practical considerations regarding adherence and persistence

Practical considerations to assure adherence and persistence with NOAC therapy are summarized in Figure 1 and discussed in the Online Supplement. Figure 2 shows the EHRA NOAC card (details see Online Supplement), Figure 3 shows the structured follow-up scheme of NOAC treated patients.

Organization of follow-up and continued care

The organization of follow-up and continued care is summarized in Figure 3 and Table 3, and is discussed in detail in the Online Supplement.

Switching between anticoagulant regimens

Practical advice on how to switch between anticoagulant regimens is summarized in Figure 4 and discussed in detail in the Online Supplement.

Special considerations for NOAC use during the 'coronavirus disease of 2019' (COVID-19) pandemic

In addition to the general preference of NOACs over VKA for stroke prevention in AF due to efficacy and safety,[1, 6] NOAC therapy comes with some potentially important practical advantages over VKA-based anticoagulation during the COVID-19 pandemic, including the lack of necessity for frequent clinic / office visits for INR monitoring. Community teams for at home INR controls may equally be limited during these periods. As a result, both the individual's risk for contracting the virus as well as the workload on the healthcare system would be reduced.

Nevertheless, NOAC therapy also comes with its inherent challenges necessitating a well-planned and executed follow-up scheme (Figure 3) to optimize efficacy and safety of the drugs (see above). Conversely, any "file and forget" NOAC use needs to be avoided also during a high-tide pandemic situation. Unfortunately, this is particularly true for high-risk AF patients - who almost inevitably would also potentially be high-risk COVID-19 patients in case of exposure and infection, likely primarily due to concomitant risk factors and comorbidities.[88-90] Careful and wise decision making regarding the type of NOAC, dose and follow-up scheme is essential. Importantly, since plasma level assessment of NOACs or coagulation tests are not needed, large parts of the regular follow-up routine may be performed via telemonitoring, including assessment of any thromboembolic or bleeding events, side effects, adherence, clinical factors precipitating a relevant decline in renal function (e.g., dehydration, intercurrent illnesses, NSAID use, …) etc. By doing so, in-person consultation may be reduced to a minimum and only be scheduled if physical examination and / or blood sampling (renal function, haemoglobin etc.) is required. Nevertheless, clear communication, ideally in writing (e.g., with E-mail follow-up) is key in order to avoid misunderstandings in these frequently older patients not accustomed to this way of consultation.
If patients on NOACs are infected with COVID-19 and particularly in case of severe infection requiring hospitalization, increasing evidence indicates a benefit for continuing anticoagulation to stave off COVID-19 complications.[91] However, clinical deterioration (particularly of renal function) as well as administration of concomitant medication (see Chapter 3) needs to be carefully observed and therapy adjusted accordingly. Assessment via a multidisciplinary expert team including cardiologist, intensive care specialists, haematologists, neurologist etc. and, if in doubt, conversion to low-molecular or unfractionated heparin is advisable. Further specific guidance can be found in the "ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic".[92]

Covid-19 vaccines are usually administered by intramuscular (i.m.) injection. In patients on NOACs it is advisable to follow the scheme for "minor risk" interventions as outlined in chapter 8 (as well as in the Online Supplement):

- Leave out the morning dose of the NOAC prior to i.m. injection
- Use a fine-gauge needle for injection
- Apply firm pressure for 2-5 minutes after the injection
- In QD NOACs: Take the left-out morning dose 3 hours after the injection (esp. in case of high stroke risk and QD NOAC)

- In BID NOACs: Re-start NOAC with the next scheduled dose.

3. Pharmacokinetics and drug-drug interactions of NOACs

Treatment with VKAs requires careful consideration of multiple food- and drug-drug interactions. Despite fewer interactions with NOACs, physicians need to consider the pharmacokinetic interactions of accompanying drugs and comorbidities when prescribing NOACs. This section aims to provide a simple, non-exhaustive guide to deal with such situations. However, every patient may require more specific consideration, especially when a combination of interfering factors is present. The considerations on drug-drug interactions given in this chapter are based on extensive research using Stockleys Drug Interactions (https://about.medicinescomplete.com/publication/stockleys-drug-interactions/), UpToDate (https://www.uptodate.com/home/drugs-drug-interaction), the Phil database (https://phil.apb.be/nl-BE/product/2756153) as well as numerous published studies, reviews and case reports. Knowledge regarding interactions (with effect on plasma levels and/or on clinical effects of NOAC drugs) is expanding, so that new information is likely going to modify existing advice.

The absorption, distribution, metabolism, and excretion of the different NOACs are summarized in Table 4 and Figure 5.[9] An important interaction mechanism for most NOACs consists of significant gastrointestinal re-secretion over a P-glycoprotein (P-gp) transporter after absorption in the gut. P-gp is also involved in active renal secretion of NOACs.[93] Competitive inhibition of the P-gp pathway will result in *increased* plasma levels, which needs to be considered since many drugs used in AF patients are P-gp inhibitors (e.g., verapamil, dronedarone, amiodarone, ranolazine, and quinidine). CYP3A4-type cytochrome P450-dependent elimination is relevantly involved in the hepatic clearance of rivaroxaban and apixaban.[94] Strong cytochrome P (CYP) 3A4 inhibition or induction may affect plasma concentrations, and should be evaluated in context (see Table 5-9 and color coding, discussed below). Non-metabolic clearance of apixaban is diverse (including excretion of the unchanged compound by > 50%).[95] In general, NOAC use is not advisable in combination with drugs that are strong inhibitors of both P-gp and/or CYP3A4. Conversely, strong inducers of P-gp and / or CYP3A4 (such as rifampicin, carbamazepine, etc.) will markedly *reduce* NOAC plasma levels; concomitant use with NOACs 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 RCTs and resulted in documented efficacy and safety of the respective agents. 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 1, Table 2). Whenever possible, the tested and approved dosing regimen of NOACs should be used.**[1]

However, there may be a clinical rationale for using a lower dose of a NOAC in patients with a particularly high bleeding risk and/or when a higher plasma level of the drug can be anticipated based on a combination of factors even if the label-recommended criteria for dose reduction are not fulfilled.[1, 96-99] Prospective clinical trial data only exist for 'lower doses' of dabigatran (110 mg BID) and edoxaban (lower dose edoxaban regimen: 30/15 mg QD; but not approved for stroke prevention). For edoxaban 30/15 mg QD a 41% higher ischaemic stroke risk compared to 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 haemorrhagic stroke, major bleeding, cardiovascular- and all-cause mortality was observed compared with warfarin.[49, 98] This was confirmed in a recent direct comparison of the lower-dose edoxaban regimen (30mg / 15mg) and higher-dose edoxaban regimen (60mg / 30mg).[100] For dabigatran 110 mg BID, a similar stroke risk and significantly reduced major bleeding vs. warfarin was observed.[48] These data represent the only available RCT-based evidence of a 'lower dose' of a NOAC for stroke prevention in AF on hard clinical endpoints.[48, 49] In contrast, no 'lower dose' arm was included (only 'dose reduction') in ROCKET-AF (for rivaroxaban) or ARISTOTLE (for apixaban) and as such, no clinical outcome data are available for the use of these reduced doses outside the tested dose reduction algorithms. The 'Japanese ROCKET' (J-ROCKET) study demonstrated a safety profile of 15 mg QD rivaroxaban as standard dose for stroke prevention in AF in Japanese patients as compared to VKA but was not powered for efficacy outcomes.[101] In the ELDERCARE-AF trial, Japanese patients ≥80 years of age deemed unsuitable for anticoagulation receiving a very low and unapproved dose of 15mg QD edoxaban showed a 4.4%/year absolute risk reduction in stroke / systemic embolism as compared to placebo, at the cost of a non-significant 1.5%/year absolute increase in the risk of major bleeding.[102] Whether these findings translate to non-Japanese populations remains to be determined.

The use of plasma level measurements for NOAC dose-adjustment or in the setting of 'off label' lower dose prescription (see Chapter 5) 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 sub-optimal stroke prevention.[103] 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 6).[104] 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 (Chapter 5).
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 5 gives an overview of the effect of various frequently used agents on NOAC plasma levels; Table 6 focusses on common cancer drugs (see also Chapter 15), Table 7 on antiepileptic drugs (see also Chapter 14) and table 8 on common herbal products. There are several major limitations particularly regarding the assessment of NOACs - herbal drug interactions including the possibility of several hypothetical pharmacokinetic and pharmacodynamic pathways, unknown mechanisms of interaction, and the inherent variation in composition. As such, firm advice regarding the safety of use is difficult to give. Particularly in patients with additional risk factors, plasma level measurements may be considered (including its inherent limitations, as discussed above).

Taking into consideration these factors as well as the setup and results from the large randomized NOAC outcome trials the algorithm shown in Figure 6 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 Tables 5-9).

Food intake, antacids, and nasogastric tube administration

Rivaroxaban for stroke prevention in AF (20mg / 15mg QD) needs to be taken with food since the area under the curve (AUC) of the plasma concentration increases by 39% to a very high bioavailability of almost 100%.[105] There is no relevant food interaction with the other NOACs. The concomitant use of PPIs and H_2-blockers leads to a reduction in the bioavailability of dabigatran, but without effect on clinical efficacy.[106, 107] There is also no relevant antacid interaction for the other NOACs.[105, 108, 109] 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.[110-113] In contrast, dabigatran capsules must not be opened as this results in a substantial increase in drug bioavailability (+75% per SmPC).

Interactions of specific drug classes and considerations for polypharmacy are discussed in the Online Supplement.

Pharmacodynamic interactions

Apart from the pharmacokinetic interactions, co-administration of NOACs with other anticoagulants, platelet inhibitors (e.g., aspirin, clopidogrel, ticlopidine, prasugrel, ticagrelor; see also Chapter 9), and NSAIDs increases the risk of bleeding.[114-116] 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 prevent bleeding (see Chapter 9).

4. NOACs in patients with chronic kidney disease or advanced liver disease

Atrial fibrillation and chronic kidney disease

AF and chronic kidney disease (CKD) are not only frequent comorbidities but also strongly interacting diseases: AF facilitates the development and progression of CKD, and, vice versa, the prevalence and incidence of AF increase with decreasing renal function.[117-120] Patients with AF and CKD have a markedly increased morbidity and mortality especially due to their excessive risk for both thromboembolic and severe bleeding events, making risk stratification and treatment challenging.[121, 122] This is of particular relevance since all four available NOACs are in part eliminated by the kidneys: dabigatran has the greatest extent of renal elimination (80%), while 50%, 35% and 27% of edoxaban, rivaroxaban, and apixaban, respectively, are cleared via the kidneys.

Further details regarding the available data on NOACs in patients with CKD are discussed in detail in the Online Supplement. Basic information on the diagnosis/staging of CKD and assessment of renal function is provided in Table 10. Practical considerations for the use of NOACs based on renal function are summarized in Figure 7.

Oral anticoagulant therapy in patients with severe CKD (CrCl of 15-29 mL/min)

There are no randomized clinical trial data on the use of warfarin for thromboprophylaxis in AF patients with severe CKD or on dialysis, and all landmark trials with NOACs essentially excluded patients with a CrCl of <30mL/min (apart from few patients on apixaban with CrCl 25-30 mL/min).[123] In the US (but not in Europe), a low dose dabigatran 75 mg BID has been approved for patients with severe CKD (a CrCl of 15-29 mL/min), based on pharmacokinetic (PK) simulations. 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 a reduced dose regimen (Figure 7). Observational data indicate a favourable efficacy and safety profile of all three FXa inhibitors compared to VKA in patients with severe renal dysfunction but these data need to be interpreted with caution based on the inherent high likelihood of substantial residual confounding.[124-126] The 2020 ESC guidelines recommend the use of factor Xa inhibitors "with caution" and at reduced doses for patients with CrCl 15-29 ml/min.[1]

Apixaban is least renally cleared (27%) and its dose is reduced by 50% under rather stringent conditions; furthermore, the rate of major bleeding with apixaban is reduced more (vs. warfarin) in patients with impaired renal function.[123, 127] Edoxaban is more 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 (35%) and is reduced less (by 25%) under similar conditions as edoxaban. In view of the individual NOAC pharmacokinetics (27% renal clearance for apixaban), dose-reduction criteria (50% reduction for apixaban and edoxaban), and available evidence from RCTs, the use of either apixaban or edoxaban may be preferable in these patients, but direct head-to-head comparisons are missing. Given the important limitation of observational studies[128] further randomized RCT-based data are urgently required for these difficult to treat patients.

Oral anticoagulant therapy in patients with end-stage CKD (CrCl of <15 mL/min and/or dialysis)

Numerous observational studies have reported conflicting results for the use of both VKA and NOACs in patients with end-stage renal disease regarding effectiveness and bleeding without a clear signal for a benefit of OAC.[129-132] A propensity score matched analysis of 4,537 Medicare patients as well as a meta-analysis of 16 studies with 71,877 dialysis-dependent patients with AF (about 3,000 with NOACs) did not demonstrate a benefit regarding the risk for stroke and thromboembolism but instead found a markedly increased incidence of bleeding complications in patients with OAC compared to those without.[133, 134]

The use of VKA in end-stage CKD may in some cases result in calciphylaxis, a painful and often lethal condition caused by calcification and occlusion of cutaneous arteries and arterioles.[135] Moreover, there is also an ongoing controversy about the clinical relevance of aggravated calcifications of the large vessels as well as those of the kidney itself under VKA.

The efficacy and safety of NOACs in patients with end-stage renal dysfunction and on dialysis is unclear and subject to ongoing studies. Plasma levels while on treatment with apixaban 2.5 mg BID[136] (as well as with 5mg, Pokorney et al, presented at ESC 2020), edoxaban 15 mg QD[137] and rivaroxaban 10mg QD[138] or 15mg[139] were found to be similar to patients with the full dose and normal renal function. Initial registry data had indicated a higher incidence of hospitalization or death from bleeding in dialysis-dependent patients with dabigatran or rivaroxaban as compared to VKA.[140] More recent analyses indicated more similar thromboembolic- and bleeding rates with apixaban and rivaroxaban vs. VKA; however, residual confounding is likely to be substantial in these analyses precluding any definitive answer regarding efficacy and safety of NOACs in these patients.[124, 141-143] Furthermore, two

randomized controlled trials have been initiated comparing apixaban vs. VKA ('RENal Hemodialysis Patients ALlocated Apixaban Versus Warfarin in Atrial Fibrillation' (RENAL-AF) in the US (NCT02942407), and 'A Safety Study Assessing Oral Anticoagulation With Apixaban Versus Vitamin-K Antagonists in Patients With Atrial Fibrillation (AF) and End-Stage Kidney Disease (ESKD) on Chronic Hemodialysis Treatment' (AXADIA) in Germany (NCT02933697)[144]). Both studies lacked a third treatment arm without any OAC and both suffered from severe recruitment problems. RENAL-AF has been stopped prematurely after including 154 patients and reported similar rates of major and clinically relevant non-major bleeds as well as a (numerical) doubling of cardiovascular deaths with apixaban vs. warfarin (presented at AHA 2019). Of note, a large proportion of warfarin patients were outside the therapeutic range (TTR 44%) and about 50% of apixaban patients received 5 mg BID. A third, smaller trial (NCT03987711) comparing warfarin, apixaban, and no anticoagulation is currently ongoing. Despite the lack of data for NOACs (or OAC in general) in dialysis-dependent patients, their usage seems to be increasing.[145]

In summary, given the lack of strong evidence the decision to anticoagulate and (if so) whether to use a NOAC or VKA in patients with end-stage renal failure or on dialysis requires a high degree of individualization. Measurements of NOAC plasma levels (Chapter 5), although intuitively appealing for this situation, has equally never been prospectively investigated for hard clinical endpoints, and should hence be reserved to highly specialized centres. Patients need to be informed of the lack of data as well as the "off label" character of whichever strategy or drug is chosen, including the uncertain benefit and the increased risk of complications. Ideally, such patients should be included in ongoing trials to improve the evidence base for this difficult to treat patient population.[121, 146] Of note, there are also no RCT data for the use of alternative stroke prevention strategies such as LAA occluder implantation for these individuals.

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 concerning possible drug-drug interactions between the NOAC and concomitant immunosuppressive therapies (see Chapter 3).

NOACs in liver disease

Practical considerations for the use of NOACs in liver disease are discussed in the Online Supplement and are summarized in Figure 8.

5. NOAC plasma level measurements: Technical approach, indications, pitfalls

Assessment of the anticoagulant effect of NOACs

The use of NOAC in daily clinical practice does not require monitoring of coagulation since all four phase III RCTs comparing NOACs to VKAs have been conducted without dose adjustments based on plasma level measurements.[46-49] However, assessment of the anticoagulant effect of NOACs may be desirable in certain, rare situations (see below).

NOAC anticoagulant activity can be measured via specific coagulation assays developed for the quantification of NOAC plasma levels.[147-149] Most routine coagulometers are capable of measuring NOAC plasma levels within ≤30 minutes. Institutions should strongly consider 24/7 availability of these tests for emergency situations. In contrast, point-of-care tests are being developed and are entering clinical practice, but are not yet widely available.[150, 151]

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. Even though levels in clinical trials were measured using High Performance Liquid Chromatography / Mass Spectrometry (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. These determinations have been demonstrated to be comparable to HPLC/MS.[152-154] It is advisable to primarily use plasma concentrations rather than anti-FXa activity or dTT to gauge the level of anticoagulation in NOAC-treated patients to minimize inter- and intra-laboratory variability as well as other potential methodological limitations.[155, 156] An overview of the expected peak and trough levels in patients on NOACs can be found in Table 11. 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 2-3 hours (+/- 1 hour) after intake for each of these drugs (Table 4).

Impact of NOACs on other coagulation assays

Routine coagulation tests (prothrombin time (PT), activated prothrombin time (aPTT), activated clotting time (ACT)) generally do not provide an accurate assessment of NOAC anticoagulant effects and cannot be used to accurately gauge anticoagulant activity (Table 11) or provide information on adherence to treatment. However, a normal aPTT excludes supratherapeutic levels in dabigatran-treated patients. The effect of apixaban, edoxaban, and rivaroxaban on the PT is highly dependent on the PT reagent that is used. Therefore, a normal PT does not necessarily exclude therapeutic levels of rivaroxaban, edoxaban and particularly apixaban.[148, 156, 157] Point-of-Care INR devices developed to monitor VKAs do not accurately reflect the anticoagulant status of NOAC treated patients.
There is not enough information to consider the use of thromboelastography (TEG) or rotational thromboelastometry (ROTEM) for adequately assessing NOAC activity, as they lose sensitivity at trough levels of the NOACs.[156] Urine tests may be useful for detecting exposure to NOACs but levels do not correlate well with plasma concentrations.[156, 158]

Impact of NOACs on thrombophilia testing

NOACs interfere with thrombophilia tests and the measurement of coagulation factors.[159] Therefore, leaving a time window of at least 24 h is reasonable between the last intake of a NOAC and blood sampling to confidently assess coagulation parameters.[147] This time window may need to be even longer for lupus anticoagulant measurements (≥48 h) or in the presence of factors potentially prolonging the anticoagulant effect such as chronic kidney disease. In patients in whom interruption of anticoagulation is not feasible, *ex vivo* neutralization of the NOAC activity in plasma samples is possible in specialized hemostasis labs. This may allow for correct interpretation of thrombophilia tests, but requires good collaboration with the hemostasis lab and appropriate clinical information.[160, 161]

Potential indications for NOAC plasma level measurements

No studies have investigated if measurement of drug levels and dose adjustment based on laboratory coagulation parameters, e.g., by dose reduction in case of higher than expected levels or by dose increase in case of lower than expected levels, improve the overall benefit of NOACs during long-term treatment. As such, routine monitoring of plasma levels and subsequent dose adaptation is generally discouraged.

However, laboratory assessment of drug exposure and anticoagulant effect may help clinicians in emergencies such as bleeding (Chapter 6), urgent (Chapter 7) or certain elective procedures (Chapter 8), suspected overdose, and acute stroke (Chapter 11). Also, in special situations during long-term care such as multiple possible drug-drug interactions (Chapter 3), extremes of bodyweight (Chapter 13) or severely impaired renal function (Chapter 4) plasma level measurements may aid in the clinical decision making. This, however, should only be done under the guidance of a coagulation expert and in the knowledge that prospective randomized clinical outcome data still do not exist to support such a strategy (only observational data).[104, 162-164] Also patients need to be informed of and consent to this "off-label" approach.

6. Management of bleeding under NOAC therapy

General Aspects

The phase III NOAC studies have consistently shown that NOACs cause less intracranial and less life-threatening bleeds than warfarin, despite the absence of specific reversal agents in these trials. Not only was there a similar or even a reduced bleeding incidence, but patients experiencing a major (particularly extracranial) bleed under NOACs were also shown to have a more favourable outcome than for bleeding under VKA treatment.[165-169] This is underlined by the reduction in all-cause mortality as well as life-threatening / fatal bleeds which was observed with NOACs vs. warfarin.[6, 46, 49, 165, 170]

Nevertheless, as more patients are being treated with NOACs, the absolute number of NOAC-related bleeding events increases. Importantly, any bleed is an opportunity to review the correct choice and dosing of the NOAC (see Chapter 1) and to evaluate modifiable bleeding risk factors including sub-optimally treated hypertension, labile INR (if on VKA) or erratic dosing, excessive alcohol intake and concomitant antiplatelet therapy, NSAIDs, glucocorticoids etc.[1]

To optimally manage NOAC-treated patients who present with a bleed we strongly suggest developing a hospital-wide policy in an interdisciplinary manner among cardiologists, hemostasis experts, emergency physicians / intensive care specialists, surgeons, and others. This protocol should describe the availability, timing, and indications of specific coagulation tests as well as the availability and use 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.). In addition, a regular interdisciplinary review and discussion of patients experiencing severe bleeding complications (as well as strokes) is encouraged in order to share different subspecialty experiences as well as patient perception of such events and subsequent preferences.

Strategies to manage bleeding complications in patients treated with NOACs rely on a precise analysis of the clinical situation (Figure 9).

1) The type of bleeding: nuisance / minor, major non-life threatening, or life-threatening.

- Based on clinical judgement - including location, extents, patient's age, comorbidities, …

- Potentially supported by 'official' bleeding definitions (e.g., TIMI,[171] ISTH,[172] GUSTO[173] or others)

2) The patient and his / her treatment, including:

- The exact time of last NOAC intake
- Prescribed dosing regimen
- Renal function
- Other factors influencing plasma concentrations (e.g., hepatic function, co-medications etc.)
- Other factors influencing hemostasis (e.g., concomitant use of antiplatelet drugs).

3) The patient's thromboembolic risk

- Particularly when considering the use of prothrombotic agents, and regarding the necessity of (early) re-initiation of anticoagulant therapy

Both routine coagulation tests and assays that specifically measure NOAC plasma levels are important adjuncts in the assessment of NOAC related bleeds (see Chapter 5).[174] Normal results of dTT / ecarin clotting time (for dabigatran) or anti-Xa activity (for anti-FXa treated patients) exclude relevant levels of the respective anticoagulants. Importantly, 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 and consumption coagulopathy. Conversely, it needs to be kept in mind that restoration of coagulation alone does not necessarily result in improved clinical outcome (e.g., in the context of intracranial hemorrhage).[175, 176]

Practical advice for the management of **nuisance / minor bleeding** and **non-life-threatening major bleeding** is summarized in Figure 9 and discussed in the Online Supplement.

Life-threatening bleeding or bleeding into a critical site

Patients with a life threatening bleed or bleeding into a critical site[172, 174, 177, 178] while treated with NOACs may benefit from its reversal in addition to the standard measures outlined above. Although laboratory values (including a full coagulation panel) should be taken prior to any reversal measures in order to guide further treatment during the course, immediate actions are guided by clinical

assessment without waiting for the results of laboratory measurements. Conversely and importantly, normalization of coagulation in itself is not necessarily sufficient to stop a bleed but may allow for more invasive interventions to control the bleeding source. Furthermore, even after direct reversal, significant NOAC concentrations may reappear in some patients and contribute to recurrent or continued bleeding (particularly after andexanet alpha due to its shorter half-life, less after idarucizumab administration),[179, 180] underlining the necessity for continued clinical and laboratory monitoring.

Idarucizumab

Idarucizumab is a humanized antibody fragment that specifically binds dabigatran. In the 'Reversal Effects of Idarucizumab in Patients on Active Dabigatran' (RE-VERSE-AD) study the drug was successfully used in patients on dabigatran presenting with major or life-threatening bleeding, or with the necessity of emergency surgery.[181] This was confirmed in the observational RE-VECTO registry.[182] Idarucizumab completely reversed the anticoagulant activity of dabigatran within minutes in almost all patients[181] and is hence considered first-line therapy in such situations. A total of 5g idarucizumab is administered intravenously in two ready-to-use doses of 2.5g i.v., administered as two consecutive infusions over 5 to 10 minutes each or as a bolus injection.[183] Continued clinical and laboratory monitoring is strongly advised, since a 5g dose of idarucizumab may not completely neutralize an exceptionally high level of dabigatran (e.g., in case of overdose or chronic kidney disease). Also, low levels of dabigatran may reappear after 12 to 24 hours.
After 24 hours, dabigatran can be re-started if clinically indicated and feasible, with normal kinetics.
Other anticoagulants, including heparins, are not affected by idarucizumab.
If idarucizumab is not available, dialysis may be used to partially eliminate dabigatran from the circulation.[184] However, starting and performing dialysis in a patient with a severe (potentially life-threatening) bleed may be challenging and may only be advisable if idarucizumab is not readily available.

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

Andexanet alfa is a recombinant, inactive human FXa analogue that non-specifically binds FXa inhibitors thereby preventing all FXa inhibitors (including low-molecular weight- and unfractionated heparins) from inhibiting FXa. In the 'Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors 4' (ANNEXA-4) study, andexanet alpha was successfully used in major or life-

threatening bleeding; in contrast to RE-VERSE-AD the trial did not include patients undergoing emergency surgery.[185] The drug comes as a lyophilized powder which needs to be reconstituted before use. It is administered as a bolus over 15-30 minutes, followed by a 2-hour infusion depending on the NOAC and on the timing since last intake (Figure 10). In the EU Andexanet alpha is only approved for the reversal of life-threatening or uncontrollable bleeding in patients taking apixaban or rivaroxaban. In view of the very similar mode of action it can be assumed that it will have a similar effect in patients on edoxaban. Since anticoagulant activity may re-appear after cessation of the infusion 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.[186, 187] Indeed, any NOAC-antagonizing effect of a procoagulant 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 prothrombin complex concentrate (PCC) and activated PCC (aPCC) for the normalization of coagulation parameters under NOAC treatment as a surrogate for haemostatic support.[188-194] As indicated above, data from the large phase III trials demonstrated that outcomes of bleeds under NOACs were similar (if not better) than in the VKA arm (with diverse bleeding treatments applied, including PCC / aPCC).[165-167] The efficacy on clinical outcomes of PCCs or aPCCs in patients taking NOACs who are actively bleeding has not been firmly established in a randomized clinical trial. However, several observational studies in patients with major bleedings 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 hemostasis.[195-199] Its usefulness in intracranial hemorrhage, on the other hand, is uncertain (see Chapter 11).[200] The administration of PCCs or aPCCs can hence be considered in a patient with a life-threatening bleed if immediate haemostatic support is required, especially in situations where a specific reversal agent is not available or too costly.[201] The choice between PCC and aPCC may depend on their availability and the experience of the treatment center. As indicated, 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 (90µg/kg) given the absence of any outcome data and the latter's pronounced pro-coagulant effect.[202, 203] Fresh frozen plasma (FFP)

is no longer considered a useful reversal strategy, primarily due to the plasma abundance of NOACs which will inhibit newly administered coagulation factors upon administration of FFP and the resulting large volume of FFP that would need to be administered to have any impact on coagulation.[203] Vitamin K and protamine administration have no role in the management of a bleeding under NOACs; these may only be useful in the management of bleeding under NOACs when vitamin K deficiency is suspected or in case of concomitant treatment with heparins, respectively.

(Re-)initiating 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 bleeds, particularly life-threatening bleeding episodes, require a careful re-assessment of the risks and benefits of re-initiating anticoagulation. In most cases of bleeds due to secondary (e.g., bleeding post-trauma) and / or reversible causes (e.g., genito-urinary bleeding due to cancer) anticoagulation can be resumed once the cause of the bleeding has been eliminated. As exemplified for gastro-intestinal bleeds many additional factors need to be taken into consideration (Figure 11). Conversely, for severe and life-threatening bleeds 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,[1] but RCT-based evidence for LAA occlusion after bleeding under OAC is currently missing.
The approach after intracranial (intracerebral, subarachnoidal, subdural or epidural) bleeding is outlined in Chapter 11.

Measures to consider in case of a (suspected) overdose without bleeding or a clotting test 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, but also intercurrent events such as an acute decline in renal function (especially with dabigatran) or

administration of drugs with known drug-drug interactions (see Chapter 3) may increase NOAC plasma concentrations to supratherapeutic levels. In terms of management, it is important to distinguish between an overdose with resultant bleeding and without. In case of a suspected overdose, assessment of NOAC plasma levels can help to determine its degree and possible bleeding risk (Table 11). Given the relatively short plasma half-life of 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 supra-therapeutic doses of ≥50 mg rivaroxaban.[204] There are no data in this respect for the other FXa inhibitors or dabigatran.

In the case of recent acute ingestion of an overdose (especially when ≤2 h ago), the use of activated charcoal to reduce absorption may be considered for any NOAC (with a standard dosing scheme for adults of 30 – 50 g) although clinical data on its effectiveness are lacking.[165, 205, 206]

If a more aggressive normalization of plasma levels is deemed necessary, or rapid normalization is not expected (e.g., severely impaired renal function) the steps outlined in patients with an active bleed may need to be considered (Figure 9). Only in exceptional cases administration of coagulation factors (PCC, aPCC) awaiting clearance of the drugs should be considered; 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.

7. Patients requiring an urgent surgical intervention

If an emergency intervention is required, any NOAC should be discontinued immediately. Considerations for the specific management depends on the level or urgency (acute emergency, urgent or expedite)[207] as summarized in Figure 12 and discussed in the Online Supplement.

In all such situations, particularly prior to the application of any haemostatic agent, a full panel of coagulation assays (including PT, aPTT, anti-FXa or, dTT/ECA etc.) should be obtained to assess the patient's coagulation status. Even if in an emergency situation the indication for application of reversal- and / or pro-haemostatic agents is governed by the patient's clinical presentation, results of these initial tests may have important implications for further treatment during the ensuing hours. Furthermore, assessment of NOAC plasma levels may be of great help in interpreting the patient's anticoagulant status as well as the waning of any NOAC effect (see Chapter 5).

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

General considerations

About one quarter of anticoagulated patients requires temporary cessation for a planned intervention within two years.[187] 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 advised to check this guide's schemes against the relevant recommendations of their country / healthcare setting and professional societies. Ever since its introduction, the EHRA practical guide intended to provide a unified approach which is as simplified as possible to allow for its broad implementation. Data from the PAUSE trial and drug-specific registries have meanwhile added to the evidence that such an approach may be safe and effective across many clinical scenarios, but also that additional individualization based on patient characteristics could further improve safety.[208, 209]

While invasive surgical interventions require temporary discontinuation of NOACs, many less invasive procedures carry a relatively low bleeding risk and may be performed under minimally- or uninterrupted NOAC therapy (Table 12, Figures 13-15). However, patient characteristics (including age, stroke risk, history of bleeding complications, concomitant medication, kidney function etc.) as well as surgical factors need to be taken into account to determine when to discontinue and restart a NOAC (Figure 13). As such, the "default" NOAC interruption periods provided in Figures 14 and 15 may require adaptation based on the individual benefit/risk ratio. It is strongly advisable to develop and implement institutional guidelines and hospital-wide policies concerning perioperative anticoagulation management in different surgical settings, which are widely communicated and readily available. 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 the intervention as well as the date and time of last NOAC intake.

Laboratory testing before surgery or invasive procedures

Specific coagulation measurements (see Chapter 5) prior to surgery or invasive procedures provide a direct assessment of the residual drug concentration[210] and have been proposed in high-risk interventions or interventions in which even some bleeding may have severe consequences. Although theoretically reasonable, HCPs as well as patients need to be aware that adapting the duration of interruption based on residual NOAC levels is without prospectively validated evidence concerning its clinical impact, including the determination of 'safe' NOAC levels for different types of procedures. In the 'Perioperative Anticoagulant Use for Surgery Evaluation' (PAUSE) trial, patients undergoing low-risk procedures had a higher likelihood of mildly (≥ 30 ng/ml) or moderately (≥ 50 ng/ml) elevated NOAC levels due to shorter NOAC interruption times.[211] For high-risk procedures, creatinine clearance < 50mL / min, standard (vs. reduced) NOAC dose, body weight < 70 kg and female sex were associated with elevated NOAC levels. In the prospective multicenter 'COncentration of RIvaroxaban, Dabigatran and Apixaban' (CORIDA) study creatinine clearance < 50mL / min and use of certain antiarrhythmic drugs (amiodarone, verapamil, diltiazem) were associated with elevated perioperative plasma levels.[162] However, elevated NOAC levels were not independently predictive of an increased likelihood of bleeding in either PAUSE or CORIDA.[162, 211] Hence, although assessment of residual NOAC levels may be considered in certain selected patients, particularly before undergoing high risk interventions, a 'time-based' interruption as outlined above generally appears safe for the majority of patients and procedures.[208, 209] Of note, if NOACs are interrupted for >72 hours the likelihood of any residual NOAC level appears very low[162, 211] precluding the necessity of NOAC level assessment outside scenarios with very high risk of drug accumulation (e.g., severely reduced renal function).

Interruption times based on bleeding risk classifications

Suggested interruptions times based on bleeding risk classifications (Table 12) are discussed in the Online Supplement and are summarized in Figures 14 & 15.

Bridging

Pre-operative bridging with low-molecular weight (LMWH) or unfractionated heparin (UFH) is not recommended in NOAC-treated patients since the predictable waning of the anticoagulation effect allows for properly timed short-term cessation of NOAC therapy before surgery. For patients on VKA, bridging with heparin/LMWH was associated with a significantly higher risk of major bleeding during cessation of oral anticoagulation but did not reduce thromboembolic events.[212] Similarly for NOACs, bridging is associated with an increased bleeding risk.[187, 213-215]

Based on prior experience with VKA, the very few very high-risk situations in which bridging may be discussed include urgent surgery with a high bleeding risk in patients with a recent (≤ 3 months) thromboembolic event (including stroke, systemic embolism or venous thrombosis / pulmonary embolism) or who suffered an event during previous adequate interruption of NOAC therapy.[216] In these instances, in addition to 'timed' NOAC interruption, switching to unfractionated heparin or low dose dabigatran - both with the possibility of rapid reversal - around the operation may be evaluated based on a multidisciplinary team decision. Further research on the optimal management in such high-risk patients is required as they were frequently excluded from or under-represented in the available trials addressing perioperative management of NOAC-treated patients; as such, randomized trial data regarding their management is lacking.

In patients with chronic coronary artery disease treatment with NOAC monotherapy is safe and effective and considered standard therapy in the long-term management (see Chapter 9).[1] However, particularly patients with a high coronary risk may be at risk for peri-operative cardiovascular events during NOAC interruption due to the absence of any antithrombotic therapy.[217, 218] In the 'Perioperative Ischemic Evaluation 2' (POISE-2) trial, peri-operative aspirin use did not reduce the risk of myocardial infarction or death but increased the risk of major bleeding in 10,010 patients at risk for vascular complications (one third with a history of vascular disease).[219] However, whether these results translate to patients at very high risk of coronary events during perioperative interruption of NOAC therapy remains unclear. A strategy with initiation of aspirin therapy pre-operatively, performance of the operation under continued aspirin (with suspended NOAC), and re-initiation of NOAC therapy post-operatively (with discontinuation of aspirin therapy) may be evaluated and based on a multidisciplinary team decision. Again, further studies are required to help guide the perioperative management in these high-risk situations.

Restarting NOAC therapy after an invasive procedure

After a procedure with immediate and complete hemostasis, NOACs can generally be resumed 6 – 8 h after the end of the intervention. However, in some surgical interventions resuming full dose anticoagulation within the first 48 - 72 h after the procedure may carry a bleeding risk which outweighs the risk of AF-related embolism. In such cases, postoperative thromboprophylaxis using LMWH in prophylactic dose 6 - 8 h after surgery and delay of therapeutic anticoagulation by deferring restart of the NOAC ≥ 48 - 72 h can be considered. Similarly, in patients in whom oral drug intake is not possible (e.g., in the case of artificial ventilation, post-op nausea and vomiting, ileus etc.) heparin administration should be considered. In contrast, there are no data on the safety and efficacy of the post-operative use of a reduced dose of the NOACs (such as used for the prevention of venous thromboembolism after hip/knee replacement) in patients with AF undergoing a surgical procedure.

Special considerations for selected procedures

Special considerations for selected procedures are discussed in the Online Supplement.

Special considerations for atrial fibrillation ablation procedures

Left atrial catheter ablation is an intervention with a risk of major groin bleedings as well as serious bleeding secondary to transseptal puncture and manipulation / ablation in the left atrium (although the incidence of these complications has been decreasing, particularly in experienced centers).[220] On the flipside, the intervention directly increases the risk of thromboembolic complications.[220, 221] Recent international consensus statements and guidelines recommend performing left atrial catheter ablation under uninterrupted anticoagulant treatment with VKA (target INR 2.0-2.5 if on VKAs),[1, 220] since such a strategy was associated with less thromboembolic events and less bleeding.[222] The efficacy and safety of uninterrupted NOAC vs. VKA therapy for AF ablation have been examined in dedicated randomized clinical trials for apixaban,[223] dabigatran[224], edoxaban[225], and rivaroxaban.[226] The last dose of once-daily based NOACs were recommended (rivaroxaban) or mandated (edoxaban)

to be administered in the evening before the procedure whereas twice-daily dosed NOACs (apixaban, dabigatran) were administered in the morning of the procedure.[227] While substantial variations in the event rate in the VKA arm of these trials were observed, major bleedings were lower with NOACs without an increase in thromboembolic complications.[225] A recent meta-analysis of 29 studies comprising over 12'000 patients confirmed a lower rate of bleeding events with NOACs vs. VKA at a similar (low) rate of thromboembolic complications.[228] Taken together, uninterrupted NOAC therapy can be considered safe and effective in AF ablation and should likely be the preferred mode of anticoagulation for patients undergoing this procedure.

An institutional protocol for NOAC patients undergoing AF ablation should be developed to ensure a uniform approach. To mimic the trial situation as closely as possible, switching NOAC intake to the evening well in advance (e.g., 1 week) of the intervention may be reasonable for the once-daily based NOACs edoxaban and rivaroxaban.[225, 226] Whether opting to administer the last NOAC dose shortly before the procedure (i.e. 'truly uninterrupted') for BID dosed NOACs or to go for a short cessation period (last NOAC dose on the evening before the procedure), may depend on a number of factors including renal function, a routine practice of heparin administration prior to (first) transseptal puncture, and administration of protamine prior to sheath removal.[9, 220, 229] Indeed, in particular in the latter case, patients may be exposed to low anticoagulant levels following the procedure if the morning dose is withheld.[227] RCT-based evidence comparing 'truly'- and minimally interrupted NOAC strategies, however, is not available. In the RE-CIRCUIT trial, the 5 major bleeding events in the dabigatran arm all occurred in patients with ≤ 4 hours (n=2) or 4-8 hours (n=3) since last intake of dabigatran. Moreover, 19.6% of patients had their last intake of the drug >8 hours prior to the procedure resulting in a similar duration of interruption as in QD NOACs with last intake on the evening before the procedure. Skipping the morning dose on the day of the ablation may hence be a valid option in BID-dosed NOACs.

Routine exclusion of LA/LAA thrombus prior to AF ablation is recommended according to current expert consensus statements and guidelines also in NOAC treated patients, especially in patients presenting for the procedure without anticoagulation.[1, 10, 230]
During the ablation, intravenous heparin should be administered to achieve an activated clotting time (ACT) of 300 – 350 seconds.[231] It has been noted that the total need for heparin and the time to target ACT was higher in some NOAC- (particularly FXa-inhibitor-) treated patients.[226, 232, 233] Indeed,

dabigatran readily prolongs ACT measurements whereas the effect of FXa inhibitors are variable depending on the assay used.[234] The clinical implications of this, however, are currently unclear. It may hence be reasonable to use the same target ACT levels for heparin titration in NOAC-treated patients as in patients on (uninterrupted) VKA.

NOAC intake can be resumed 3 - 5 hours after sheath removal if adequate hemostasis is established and pericardial effusion has been ruled out.[229]

Special considerations for cardiac surgery procedures

Cessation and re-initiation of NOACs around cardiac surgery

Elective cardiac surgery in patients on NOACs fall into the “red” category of procedures with high risk (i.e., with a risk of frequent and / or high impact bleeding), as indicated in Table 12 and Figures 14 & 15. Hence, a standard interruption time of 48 hours applies, also according to the European Association for Cardio-Thoracic Surgery (EACTS) Guidelines,[235] but longer interruption times of 72-96 hours may be considered in patients at risk of NOAC accumulation (e.g., older patients, chronic kidney disease etc.). Of note, if NOACs are interrupted for >72 hours the likelihood of any residual NOAC level appears very low,[162, 211] precluding consideration of NOAC level assessment outside scenarios with very high risk of drug accumulation (e.g., severely reduced renal function). Importantly, and as for most other situations, pre-operative bridging with low-molecular weight heparin is not advised for elective patients on NOACs.

In patients on NOACs who need to urgently undergo cardiac surgery, i.e., without the possibility to interrupt treatment for the above-indicated intervals, assessment of NOAC plasma levels may be helpful for risk stratification (see Figure 12). EACTS guidelines suggest plasma levels < 30 ng/ml as cut-off values below which operations may "safely" be performed, but prospective outcome data are lacking.[235] If higher values are measured and further waiting is impossible, reversal of dabigatran using idarucizumab may represent a valid treatment option.[181] It is currently unclear if reversal of FXa inhibitors using andexanet alpha is similarly safe and effective in such situations, particularly given its potential pro-thrombogenic effect as well as its non-specific inhibitory effect on other FXa inhibitors including unfractionated heparin (which may require the use of direct thrombin inhibitor such as argatroban or bivalirudin during cardiopulmonary bypass).[236] In view of these limitations, combined with the limited availability and high cost of andexanet alpha, FXa inhibitor "reversal" using PCC or

aPCC may be advisable, also carefully weighing its indication against its potential prothrombotic effect, until further data for andexanet alpha become available in the context of cardiac surgery procedures.[235, 237]

Following cardiac surgery, the optimal time point for NOAC (re-)initiation depends on a number of factors, including adequate hemostasis as well as any additional interventions (planned and unplanned). Prophylactic unfractionated heparin or low-molecular weight heparin is advisable in the initial postoperative period due to its rapid onset and offset as well as its reversibility, followed by therapeutic heparin 12-48h post-op, as discussed in Section 8.[235] Once adequate hemostasis has been confirmed and no further interventions are planned, UFH or LMWH may be transitioned to a NOAC in eligible patients (Table 1 & 4; excluding, importantly, patients after mechanical valve replacement as well as patients after bioprosthetic valve implantation or valve repair as discussed below).

NOAC management around interventions following cardiac surgery (including chest tube insertion, removal of temporary epicardial pacing wires)

There are no strong data to advice on how to best deal with interventions performed or planned to be performed shortly after cardiac surgery, including removal of temporary epicardial pacemaker wires. In most scenarios, a similar scheme as for "low bleeding risk" interventions can be applied (Table 12, Figures 14&15), i.e., with a 24h interruption of NOAC therapy. However, a host of other factors may influence the duration of NOAC interruption including thrombocytopenia, additional antiplatelet therapy, co-medications, deterioration of chronic kidney disease etc. It may hence be advisable to not initiate NOAC therapy following cardiac surgery prior to temporary pacing wire removal or when any other intervention (drainage of pleural effusion etc.) is still anticipated.

NOAC use in post-operative AF

Post-operative AF is common following cardiac surgery, with incidences reported as high as 20-50%.[1, 238] The 2020 ESC guidelines (developed in collaboration with the EACTS) indicate that long-term OAC therapy may be considered in patients at risk for stroke with (newly developed) postoperative AF after cardiac surgery (Class IIb, level of evidence B), since both the short- and long-term risk of stroke may be substantially elevated in such patients.[1, 239] The timing of OAC / NOAC initiation follows the general principles after cardiac surgery as outlined above.

NOAC use in patients with AF after bioprosthetic valve implantation or valve repair

Traditionally, VKA have been the anticoagulants of choice during the first 1-3 months after bioprosthetic valve implantation or valve repair in patients with AF.[235] As discussed in Chapter 1, NOACs appear as a valid option after this period given data from the pivotal phase III studies as well as the dedicated RIVER trial. [12, 17, 19, 20, 24] Results of the latter imply that patients may be treated with a NOAC even earlier after biological valve replacement, but the number of patients randomized <3 months post-op was small (n = 95, on rivaroxaban). Further confirmatory data, also with other NOACs, are needed.

Practical aspects on the use of NOACs after TAVI implantation are covered in chapter 1 (see also Table 1).

NOACs after coronary artery bypass grafting (CABG)

In patients without AF, dual antiplatelet therapy (DAPT) is frequently administered to patients following CABG, as it has been associated with improved vein graft patency and reduced mortality (although the level of evidence especially for the latter is weak).[240-242] In patients with concomitant AF, the combination of a single antiplatelet agent (aspiring or clopidogrel) with a NOAC appears reasonable but - in contrast to patients after PCI / ACS (Chapter 9) - randomized trial evidence is not available. The combination of dual antiplatelet therapy with a NOAC seems undesirable due to its inherent bleeding risk, but again, no prospective evidence is available. The timing of post-operative initiation of NOAC therapy follows the same principles as indicated above. One year post-CABG, NOACs may be continued as monotherapy, similar to patients with chronic coronary syndrome.[243]

NOACs after surgical AF treatment ± LAA occlusion / exclusion

According to the 2020 ESC / EACTS AF guidelines, long-term OAC therapy is recommended in patients after AF surgery and appendage closure based on the patient's thromboembolic risk as assessed by the CHA_2DS_2-VASc score and not on the "success" of the procedure (no RCT data).[1] Post-operative initiation of NOAC therapy follows the general principles after cardiac surgery as outlined above.

9. Patients with atrial fibrillation and coronary artery disease

The combination of AF and coronary artery disease (CAD) is not only a common clinical scenario, it is also a complex setting to combine anticoagulation and antiplatelet therapy. According to the 2020 ESC guidelines AF patients with relevant CAD have at least a CHA_2DS_2-VASc score of 1 (and mostly higher due to the presence of other cardiovascular risk factors) and hence an indication for OAC. The convention is that a period of dual antiplatelet therapy (DAPT, i.e aspirin and a $P2Y_{12}$ inhibitor) is necessary to prevent stent thrombosis or recurrent events after an acute coronary syndrome (ACS) and/or stenting for CAD - but that this is not sufficient for stroke prevention. Conversely, NOACs are essential for stroke prevention but on their own insufficient for preventing new coronary events in the immediate phase after ACS or stenting. The choice of antithrombotic drug combinations therefore represents a clinical conundrum: too little and risk a coronary event and/or stroke, too much and risk a bleeding event.

Triple vs. dual therapy

NOACs vs. VKA in dual vs. triple therapy

Four dedicated prospective RCTs have addressed the issue of using a NOAC or VKA in a variety of combinations with antiplatelet agents to reduce bleeding events after PCI and/or an acute coronary syndrome in patients with AF.[244-247] In essence, these trials focused on bleeding as the primary endpoint, with coronary events and stroke as important secondary outcomes. On aggregate, these studies showed that dual therapy with a NOAC plus a $P2Y_{12}$ inhibitor reduced bleeding risk compared to triple therapy with VKA, aspirin and a $P2Y_{12}$ inhibitor (mostly clopidogrel). The bleeding risk reduction appeared to be driven by both receiving a NOAC instead of VKA as well as by omitting aspirin,[244] and this benefit was also observed in medically managed ACS/PCI patients with AF.[244, 248]

NOAC-based dual therapy also seems to be safe in terms of coronary ischemic risk although the evidence is less strong as such events were relatively rare in all four studies which (as a result) were underpowered for thrombotic events analyses.[244-247] While a recent network meta-analysis indicated that, on aggregate, a NOAC plus a $P2Y_{12}$ inhibitor reduces bleeding risk without significantly increasing coronary thrombotic risk compared to any other regimen that includes dual antiplatelet

therapy,[249] several other meta-analyses including the four NOAC RCTs indicate that there might be a small but statistically significant increase in the risk of coronary (but not stroke) events when omitting aspirin.[250-253]

Duration of triple therapy after ACS / PCI

According to the current 2020 ESC guidelines on AF as well as on NSTE-ACS, a short course of triple therapy is recommended for up to one week in all patients with AF undergoing PCI.[1, 254] In medically-managed NST-ACS patients, combination of a NOAC with only a single antiplatelet agent (preferably clopidogrel) is recommended from the event onwards.[254] However, the time frame of inclusion for the four aforementioned NOAC RCTs ranged from several hours after percutaneous coronary intervention (PCI) up to > 10 days. As such, a selection bias towards lower-risk patients cannot be excluded; furthermore, a variable course of triple therapy may have been given to a substantial number of patients subsequently randomized to NOAC-based dual therapy. Finally, although bleeding events were consistently reduced across the 4 NOAC trials by NOAC-based dual therapy this did not translate into a reduction in all-cause mortality (as compared to VKA-based dual vs. triple therapy). Therefore, a low threshold for prolonging triple therapy with DAPT and a NOAC up to 30 days may be advisable in patients with a high atherothrombotic risk, including those after a complex PCI or with a history of stent thrombosis. In contrast, continuation of triple therapy beyond 30 days rarely seems warranted.[255]

The choice of anticoagulant as well as the duration of triple (and dual) therapy hence needs to be personalized based on atherothrombotic-, cardioembolic- and bleeding risk.[75] It is highly recommended to formally assess stroke and cardiac ischemic event risk using validated tools such as the CHA_2DS_2-VASc and Global Registry of Acute Coronary Events (GRACE) scores.[1, 75] Estimating the bleeding risk should lead to efforts to correct or reduce reversible bleeding risk factors. Proton pump inhibitors should be encouraged in all patients with a combination of antiplatelets and anticoagulants.

NOAC dosing in the context of dual / triple therapy

It is unknown whether rivaroxaban 15mg QD (dose reduced to 10mg QD in patients with moderately reduced renal function) as used in the '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' (PIONEER) trial is sufficient for stroke prevention in patients with ACS and / or undergoing PCI as the trial (like the other 3 NOAC trials) was underpowered for individual efficacy outcomes.[246] In contrast, approved stroke-preventive doses of NOACs were tested for apixaban (5 mg bid), dabigatran (110/150 mg bid), and edoxaban (60 mg QD) in the respective dual vs triple therapy trials; in all three trials doses were reduced according to the respective standard criteria.[244, 245, 247] NOAC dosing therefore should follow the general published and approved criteria with dose reduction be performed according to the individual NOAC's dose reduction criteria.[1]
Adding a very low dose of rivaroxaban (2.5 mg BID) decreased ischemic events including stent thrombosis as compared to DAPT alone in ACS patients without AF (albeit with an increase in bleeding).[115] The same dose was used in the NOAC "triple" therapy arm in the PIONEER study;[246] its protective effect against AF-related stroke, however, remains undetermined making this strategy unsuitable for AF patients after an ACS/PCI.

Choice of P2Y12 inhibitor

In the 2020 ESC AF guidelines, the use of ticagrelor or prasugrel as part of a triple therapy regimen is discouraged.[1] Ticagrelor increases bleeding risk in patients on dual therapy when compared to clopidogrel.;[256] Although only few patients have been included with a P2Y12-inhibitor other than clopidogrel into the above-mentioned RCTs, the benefit in terms of reduced bleeding risk with NOAC-based dual therapy compared to VKA-based triple therapy, however, appears to be maintained regardless of the type of $P2Y_{12}$ inhibitor.[256] In post-ACS patients at high coronary thrombotic risk and low bleeding risk in whom otherwise a VKA- or NOAC- based triple therapy would be warranted, dual therapy with a NOAC plus ticagrelor could be considered instead. Further data, including dedicated RCTs, are warranted in this area. Indeed, up to 40% of patients on clopidogrel may reach insufficient platelet inhibition.[257] It is unknown whether measuring the antiplatelet response to clopidogrel when considering omitting aspirin, and adapting the strategy (e.g., switching to ticagrelor or re-introducing aspirin) will will result in a net benefit in this setting.

Treatment of patients with chronic coronary syndrome (CCS)

Until recently there were only indirect data from the pivotal phase 3 NOAC trials as well as some observational data on whether it might be safe to transition to NOAC monotherapy in patients with chronic coronary syndrome (CCS).[258] The Japanese multi-center, open-label AFIRE trial demonstrated

that continuing rivaroxaban 15 mg QD monotherapy beyond one year after a revascularization procedure in AF patients not only decreased the risk of ISTH bleeding (primary safety outcome) but also demonstrated non-inferiority for the primary composite end point of cardiovascular events (stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization) or death from any cause compared with the combination of rivaroxaban and antiplatelet therapy.[259] Indeed, the trial was stopped prematurely due to an increased mortality in the combination therapy arm.[259] Although it is formally unclear if these results translate to other NOACs, other doses, and other populations, these data suggest that most AF patients with a (remote) history of CAD should be transitioned to NOAC monotherapy without an antiplatelet agent as recommended in current ESC AF guidelines (Figure 17).[1]

Creation of local standard operating procedures is strongly advised for the management of patients with AF and ACS or CCS, based on the available evidence, recent ESC AF- and Non- ST-Elevation Acute Coronary Syndrome (NSTE-ACS) Guidelines.[1, 254]

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

Performing a PCI (scheduled or not) under NOAC is different than under VKA for several reasons, and various aspects and uncertainties need to be taken into consideration, including:

- timepoint of the last dose, adherence, and renal function
- variability in renal function in an acute setting
- uncertainty about the extent of anticoagulation in the absence of established tests, and hence
- uncertainty about stacking of additional periprocedural anticoagulants
- singular factor II or Xa blockade vs. multifactor antagonism, etc.

Temporary discontinuation of the short-acting NOACs may allow for safe initiation of antiplatelet therapy and standard local anticoagulation practices peri-procedurally (Figure 18). In contrast, NOACs should be continued in non-invasively managed ACS patients.

New-generation drug-eluting stents (DES) are preferred to shorten exposure to dual or triple therapy after the procedure but also to avoid the need for repeat interventions. Sole balloon angioplasty or bypass surgery should always be considered as an alternative in patients in need for chronic anticoagulation since they can reduce the need for long-term dual or triple therapy. There is no longer a reason to opt for a bare metal stent (BMS) as a strategy to reduce DAPT duration.[260-262] The specific discussion of the possible scenarios (elective PCI, NSTE-ACS, STEMI) is provided in the Online Supplement and summarized in Figure 18.

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

ACS guidelines recommended DAPT for up to 1 year after the acute event in patients without indication for OAC, and high-risk patients might require an even longer DAPT duration.[263, 264] In high bleeding-risk ACS patients, however, current ESC guidelines allow for shorter DAPT durations (3-6 months).[75, 76, 265] If AF develops during the first year after an ACS and there is an indication for anticoagulation, a NOAC should be started and the need for continuing DAPT should be carefully weighed against the increased bleeding risk. Beyond one month after the event, aspirin can be stopped in the majority of such patients as discussed above.

Scenario 3: a chronic coronary syndrome patient (acute coronary syndrome ≥ 1 year ago) develops atrial fibrillation

Patients with a chronic coronary syndrome developing AF should receive anticoagulation, depending on their CHA_2DS_2-VASc score (which per definition will be ≥1). A NOAC without any antiplatelet agent appears to be the preferred strategy for these patients as discussed above, based on the results of the four landmark NOAC trials (which included up to 15-20% of patients with a prior MI) and the 'Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease' (AFIRE) trial.[10, 259] An additional antiplatelet agent should only be considered in individual patients with a very high ischemic- and low bleeding risk.

Treatment of left ventricular thrombus after myocardial infarction in patients with atrial fibrillation

In the absence of randomized studies, it remains uncertain whether a NOAC is effective in the treatment of left ventricular thrombi complicating a large infarction. One observational study suggests that NOACs were associated with a higher incidence of thromboembolic events compared to VKA in (mostly non-AF) patients with a left ventricular thrombus, while others showed a similar rate of thrombus resolution.[266] [267-269] Although residual confounding can never be excluded in these settings, VKA should be viewed as standard of care for the treatment of patients with LV thrombus until more data are available. Only in very special situations (e.g., no VKA monitoring possible, no stable INR despite maximal efforts, etc.) NOACs may be evaluated after clear communication and consent from the patient about the lack of data and the off-label situation.

10. Cardioversion in a NOAC-treated patient

Based on current ESC guidelines,[1] 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 a pre-cardioversion transesophageal echocardiography (TEE) needs to rule out left atrial thrombi, irrespective of CHA_2DS_2-VASc score.[1, 2, 227] 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 19).

Considerations regarding the practical management of patients cardioverted after ≥3 weeks of NOAC treatment, as well as of patients with >48h or ≤48h AF without NOAC therapy are summarized in the Online Supplement.

Duration of anticoagulation post cardioversion

Oral anticoagulation post cardioversion should be continued as per the recommendations provided in the ESC AF guidelines.[1] 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, have a class I recommendation for long-term anticoagulation independent of the "success" of cardioversion.[1] 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 hours 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 hours). Indeed, these patients may in addition have shorter, self-limiting (i.e., "self-cardioverting") episodes of AF for which the optimal anticoagulation strategy is currently unclear. Given the overall low risk of thromboembolism in these patients, longer and particularly life-long anticoagulation generally does not seem to be mandated.[227] Current AF

guidelines indicated the possibility to drop post-cardioversion anticoagulation in patients with a definite duration of AF ≤ 24 h and a very low stroke risk (CHA_2DS_2-VASc of 0 in men or 1 in women).[1]

Management of a patient with documented left atrial appendage thrombus

Patients in whom TEE identifies a left atrial thrombus should not undergo cardioversion. There are no (and likely never will be any) adequately powered prospective endpoint trials to investigate the best anticoagulation strategy (NOAC vs. VKA) in this scenario. Previously, standard therapy consisted of VKA therapy (with heparin bridging if necessary) with rigorous follow-up and INR monitoring until resolution of the thrombus. One prospective study indicated a thrombus resolution rate of 41.5% (22 of 53 patients) with standard dose rivaroxaban (20 mg/d)[270] – comparable to a retrospective registry in which left atrial thrombus resolution was observed in 60 of 96 patients (62.5%) in heparin/warfarin treated patients.[270] A small study showed also complete thrombus resolution incidence with dabigatran 150 mg BID in 17 of 19 patients (89.5%) versus 17 of 22 patients (77.3%) on warfarin.[271] Another prospective study with dabigatran (NCT02256683) finished inclusion but study outcomes have not been reported yet. In the 'Eliquis evaluated in acute cardioversion compared to usual treatments for anticoagulation in subjects with NVAF' (EMANATE) trial, thrombus resolution rate was similar in patients treated with apixaban (52%, 12/23) as with LMWH/VKA (56%, 10/18).[272] This is supported by observational evidence indicating a similar degree of thrombus resolution using a NOAC vs. a LMWH/VKA based regimen.[227, 273-275] Together, these data indicate that using NOACs for left atrial thrombus resolution may be an option (most data available for apixaban and rivaroxaban), particularly in patients where a VKA is not well tolerated or adequate INR control cannot be obtained.

If a thrombus persists during follow-up despite confirmed good adherence to the NOAC regimen an individualized management strategy is required. This may include switching to a different type of NOAC (direct thrombin inhibitor to FXa-inhibitor or vice versa) or INR-tailored VKA-therapy. Some centers have reported LAA closure in patients with a persistent thrombus.[276] Finally, long-standing thrombi may become organized and fixed, allowing cardioversion if regaining sinus rhythm is considered to be of substantial benefit for the patient outweighing any residual thromboembolic risks. All of the aforementioned strategies are lacking strong evidence and further studies are clearly required in this field.

11. AF patients presenting with acute stroke while on NOACs

The incidence of ischaemic stroke is 1-2% per year in AF patients treated with a NOAC. Stroke may occur despite good adherence to drug treatment but NOAC plasma concentration may correlate both with stroke severity (as is the case with INR in patients on VKA) and large vessel occlusion.[277] Case series and observational studies reveal an adequate NOAC dose at ischaemic stroke-onset is mainly associated with milder severity and more favourable outcome compared to non-anticoagulated stroke patients with AF.[278, 279]

Intracerebral bleeding (ICB) accounts for 8-15% of stroke in Europe and the US. 15-25% of all ICBs are related to OAC.[280, 281] RCTs indicate an ICB incidence of 0.13-0.37% per year in AF patients on NOAC treatment, while the incidence of intracranial haemorrhage (ICH; also including subarachnoid, epidural and subdural haemorrhage) is 0.23-0.55% per year.[47, 170, 282-284] A retrospective analysis of the US "Get With the Guidelines-Stroke" and a national Japanese database found a more favourable outcome with NOACs compared to VKA, contrasting previous studies reporting similar outcomes and a mortality rate of 25-40% after NOAC-related ICB.[285, 286] All stroke patients on NOAC treatment require immediate neurologist / stroke physician input to decide on the best therapeutic approach.

Management of NOAC treated AF patients in the acute phase of stroke

The management of AF patients on NOACs in the acute phase of ischemic stroke is summarized in Figure 20 as well as in the Online Supplement. The management of AF patients on NOACs in the acute phase of an intracranial bleeding is discussed in the Online Supplement.

Management in the post-acute phase of stroke patients with AF

AF patients post ischaemic stroke or transient ischaemic attack (TIA)

Alternative (and treatable) causes of stroke have to be assessed in every AF patient.[279, 287] No RCT evidence exists favoring one NOAC over another or to switch one NOAC to another in patients with transient ischaemic attack (TIA) or ischaemic stroke *on* NOAC therapy. Treatment needs to be

individualized with appropriate dosing and assessment of patient specific co-morbidities and co-medication (Chapter 1). Measurement of NOAC plasma levels at the time of hospital admission may help assess adherence at least at the time of stroke.

Since stroke-related disruption of the blood-brain-barrier increases the risk of secondary hemorrhagic transformation, timing of (re-)starting oral anticoagulation must balance the risk of recurrent ischaemic stroke vs. risk of parenchymal bleeding. Data from large RCTs are missing, as phase III trials of NOACs excluded patients within 7-30 days after stroke and within 3-6 months after severe stroke.[280] As RCTs are ongoing, current recommendations are based on consensus opinion,[11, 288] observational studies[289-291] and an individual patient data analysis of prospective cohort studies.[292] The 2020 ESC guidelines on the management of AF state that OAC "should be (re-)initiated as soon as considered possible from the neurological perspective (in most cases within the first 2 weeks)".[1] The 2019 AHA/ASA guidelines conclude that “for most patients with an [acute ischaemic stroke] in the setting of AF, it is reasonable to initiate oral anticoagulation between 4 and 14 days after the onset of neurological symptoms”.[288] A recent European Stroke Organisation (ESO) expert consensus concluded that “recommendations about the optimal time for initiating anticoagulation in patients with AIS” could not be made.[280]

At present, several randomized trials (e.g., ELAN (NCT03148457), OPTIMAS (NCT03759938), TIMING (NCT02961348), START (NCT03021928), AREST (NCT02283294)) focusing on early vs. late (re-)starting of a NOAC after acute ischaemic stroke are underway with results expected in 2021/22.[290] In the interim practical guidance is required for this common clinical dilemma. As first specified in the 2015 EHRA Practical Guide, oral anticoagulation using a NOAC may be continued (according to prescription and label) or started the next day in TIA patients after exclusion of ICB/secondary hemorrhagic transformation by imaging, and considering the size of imaging-documented acute ischaemic brain lesion.[9, 11] If infarct size is not expected to substantially increase the risk of hemorrhagic transformation in patients with mild stroke, oral anticoagulation may be initiated >3 days after AIS (Figure 21). 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 hemorrhagic transformation by repeating brain imaging (using computer tomography (CT) or magnetic resonance imaging (MRI)). As indicated before, these time frames and actions represent expert opinion-driven practical advice until more evidence becomes available. A multidisciplinary team approach appears mandatory in these challenging situations.

A patient-centered decision to (re-)start oral anticoagulation should also consider if left atrial (appendage) thrombus is present or if there is evidence of cerebral amyloid angiopathy. However although MRI-detected cerebral microbleeds (CMB) are independently associated with increased risk of symptomatic ICH, they are also associated with risk of recurrent AIS, and the burden of CMB related to ICB remains to be defined.[280, 292-294] Presence of CMB alone should not per se dictate the decision against anticoagulation.

Due to the rapid onset of action of NOACs as well as an associated risk of bleeding, “bridging” with heparin before (re-)starting a NOAC or treatment with LMWH as an anticoagulant is not recommended.[280] If initiation of OAC is delayed in patients with AIS, aspirin should be administered before initiation according to expert opinion.[280] In case of OAC intake peri-onset of stroke, treatment with aspirin should be postponed according to the NOAC half-life and kidney function or should be based on the results of (specific) coagulation tests. Antiplatelets used for secondary stroke prevention in AF patient after AIS should be stopped at the time of (re-) starting a NOAC unless a clear indication exists for concomitant use (e.g recent coronary- or carotid stenting).

NOAC use at hospital discharged in AF stroke patients was associated with more days spent at home and a lower rate of major adverse cardiovascular events compared to VKA according to a large multicenter cohort study including stroke survivors.[295] Of note, appropriate dosing of NOACs and patient adherence is essential to ensure optimal secondary stroke prevention.[62, 278, 295]

AF patients with ischaemic stroke and concomitant atherosclerosis

Addition of antiplatelets to a NOAC for a specified period may be necessary or considered in selected AIS patients with AF, if stroke is most probably caused by large-vessel disease (i.e. “symptomatic” (intracranial) stenosis), or the patient has recently undergone a stenting procedure, and bleeding risk is considered to be low. However, evidence for this approach is lacking and further studies are required.[296] AF patients with AIS due to "symptomatic" high-grade carotid stenosis should preferably undergo carotid endarterectomy (CEA), as carotid stenting necessitates (dual) antiplatelet therapy in addition to OAC with a subsequently higher risk of bleeding.[296] In AF patients undergoing CEA, aspirin is recommended prior to and for some days after surgery but ordinarily should be stopped on resuming NOAC therapy. AF patients with asymptomatic atherosclerosis or stenosis of the internal carotid and /or intracranial arteries should be treated with a statin and OAC, without the need for additional antiplatelet therapy, similar to the situation in stable coronary heart disease (see Chapter 9).

AF patients post intracranial haemorrhage

AF patients post intracerebral bleeding (ICB)

In addition to its' immediate prognosis, ICB in the setting of AF is also associated with later ischemic stroke and mortality, partly due to the cessation of anticoagulation after ICB. However, a history of a spontaneous ICB constitutes a contraindication for 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.

Evidence-based guidelines regarding use of NOACs in AF patients post ICB are not available but several RCTs are ongoing (PRESTIGE-AF (NCT03996772); APACHE-AF (NCT02565693); NASPAF-ICH (NCT02998905); ASPIRE (NCT03907046); SoSTART (NCT03153150); A_3ICH (NCT03243175); ENRICH-AF (NCT03950076)). Present knowledge is based on observational (mostly retrospective) data with varying proportions of ICB-patients with AF re-starting OAC, predominantly or exclusively with VKA.[1, 280, 297-299] Observational studies including AF patients with a history of ICB showed that restarting OAC with a NOAC vs. VKA was associated with similar to lower rates of ischemic stroke without difference (or even lower) rates of recurrent ICB.[300, 301] However publication and selection bias must be taken into account as with all observational non-randomized studies.[297] The ESO Karolinska Stroke Update Conference consensus paper states that in selected ICB patients (re-)initiation of OAC compared to no OAC may improve outcomes (Grade C), and that "NOACs should preferentially be used over VKA" (Grade C).[293] A recent ESO guideline concludes that "restarting oral anticoagulation can be considered after careful weighing of risks and benefits".[280]

Therefore, as stated in the 2020 ESC guidelines, a case-by-case consideration is needed whether or not to (re-)introduce anticoagulation of any type in patients who have experienced an OAC-related ICB (Figure 22).[1] Adequate blood pressure control is of paramount importance in all patients post ICB. Whether genetic polymorphisms, like the apolipoprotein E genotype, or low-density lipoprotein cholesterol levels predict the likelihood of recurrent ICB has to be proven by prospective trials.[302-304] Patients with cerebral amyloid angiopathy have a very high risk of recurrent ICB and should not be anticoagulated.[305]

Analogous to the management of VKA-related ICB, NOACs may be re-started 4-8 weeks after ICB, if the individual risk of cardio-embolic stroke is high and the risk of recurrent ICB is estimated to be lower.[281, 297, 306]

LAA occlusion is a potential alternative strategy to long-term anticoagulation in AF patients post ICB after careful weighing of risks and benefits, as outlined in the 2020 ESC AF guidelines and ESO recommendations.[1, 280, 293] However, this strategy requires a period of antiplatelet or anticoagulant treatment post deployment, which also carries a risk of recurrent ICB. The safety and effectiveness of shorter duration antiplatelet therapy is unknown. RCT evidence for LAA occlusion after OAC-related ICB is lacking as the number of AF patients with previous ICB in most randomized studies is not reported.[307] Patients with AF after ICB in whom LAA occlusion is being considered should ideally be included into an ongoing RCT such as 'Left Atrial Appendage CLOSURE in Patients With Atrial Fibrillation at High Risk of Stroke and Bleeding Compared to Medical Therapy: a Prospective Randomized Clinical Trial' (CLOSURE-AF, NCT03463317), 'Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Hemorrhage' (STROKECLOSE, NCT02830152), or 'Comparison of LAA-Closure vs Oral Anticoagulation in Patients With NVAF and Status Post Intracranial Bleeding' (CLEARANCE, NCT04298723).

AF patients post subarachnoid haemorrhage (SAH)

Incidence of SAH was <0.1% per year in AF patients on NOAC treatment in RCTs.[170, 282, 283] There is little evidence to guide the resumption of OAC treatment in patients with AF following SAH.[308] Thorough angiographic evaluation, treatment of any underlying aneurysm or arteriovenous malformation and multidisciplinary team (neurological/neurosurgical/neuro-radiological) evaluation of future risk of re-bleeding is needed prior to any consideration to restart OAC in the AF patient after a SAH. When SAH occurs in AF patients taking a NOAC in the absence of a remediable aetiology it seems prudent not to re-initiate OAC treatment. LAA closure may be considered (no RCT data available), ideally in the framework of a randomized trial.

AF patients post epidural haematoma or subdural haematoma (SDH)

In RCTs, incidence of subdural and epidural haematoma in AF patients on NOAC treatment was <0.2% and <0.1% per year, respectively. [170, 282, 283] Although there are no specific data, it appears to be safe to start or reinitiate OAC about 4 weeks after (surgical removal of) traumatic epidural or subdural haematoma, particularly in the absence of drug- / alcohol abuse or a substantial risk of falling (Chapter 12).[308] According to clinical presentation and hematoma extension, brain imaging (using CT or MRI) is recommended before (re-) starting OAC. However, adequately dosed NOAC or no anticoagulation at the time of non-traumatic epidural or subdural haematoma does not support (re-) initiation of oral

anticoagulation despite the fact that the risk of ischemic stroke is increased within 4 weeks after non-traumatic SDH according to a retrospective US cohort study.[309]

12. NOACs in advanced age and frailty

NOACs in older populations

The incidence of AF rises steadily with age; by 2050 4.4% of the world population will be older than 80 years.[310, 311] Stroke prevention in older AF patients is of great importance as stroke risk rises greatly with age.[312] The advent of NOACs has improved prescription rates in older people, but OAC remains underutilized in up to 30% of patients with high stroke risk.[313, 314]
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 were studied. Rates of stroke were similarly reduced in older age groups treated with NOAC compared to VKA. 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.[69, 315-317] While intracranial bleeding remains lower with all NOACs compared to VKA, a significant effect of age on increased extracranial major bleeding was observed on the higher dose of dabigatran.[170, 318] Conversely no age interaction on rates of extracranial major bleeding was seen with apixaban, edoxaban or rivaroxaban compared to the overall trial results. In addition major bleeding appeared lower with apixaban and edoxaban compared to VKA even in older age groups.[47, 69, 315, 316] Observational registries in older cohorts indicate that the risk of bleeding with age appears largely consistent with trial findings to date.[318-322]

Older patients with AF have more favorable outcomes on OAC than without, and on NOACs than on VKA.[56, 323-326] Therefore, NOACs are preferred in this cohort, consistent with current ESC guidelines.[1, 327, 328] The net clinical benefit for OAC declines with advanced age due to competing risks for bleeding and death but is maintained longer with NOACs than VKA.[329] While frailty and cognitive impairment syndromes are associated with greater mortality and underuse of OAC, the benefits of OAC are maintained in these cohorts.[330] Better predictive tools may help identify those least likely to benefit due to early mortality,[331] but robust evidence for reliably identifying individuals which should a priori not receive OAC are currently missing.

The ELDERCARE-AF trial represents the only placebo-controlled trial investigating a NOAC (very low-dose edoxaban, 15mg QD) in elderly AF patients deemed unsuitable for standard OAC therapy. In this trial (conducted in Japan and confined to Japanese patients) the use of Edoxaban 15mg QD resulted in a 4.4%/year absolute risk reduction in stroke ($p<0.001$) at the cost of a non-significant absolute increase in 1.5%/year of major bleeding.[102, 332] It is currently unclear whether these findings translate to non-Japanese populations. If confirmed in other ethnicities, such a strategy could constitute an alternative in older patients deemed unsuitable for or higher risk with approved, full dose NOAC therapy. It would be desirable that such confirmatory evidence is sought as very old age remains a clinical conundrum. As discussed in chapter 4, use of the lower-dose (30mg / 15mg) vs. higher-dose edoxaban regimen (60mg / 30mg) in the ENGAGE AF-TIMI 48 trial resulted in a 43% higher ischaemic stroke risk, while the risk of disabling or fatal strokes was similar between the two dosing regimens and the risk of major bleeding or of having a pre-defined primary net outcome event (stroke, systemic embolism, major bleeding or death) was lower with the lower-dose edoxaban regimen. These results were consistent (and possibly even more pronounced for the primary net outcome; p interaction = 0.077) in patients ≥ 75 years vs. <75 years.

In older patients the incidence of cerebral amyloid angiopathy and cerebral microbleeds (CMBs) are more prevalent and their presence increases the risk of intracerebral haemorrhage (see Chapter 11).[333] CMBs are markers of cerebral small vessel disease and can be identified in hemosiderin sensitive brain MRI sequences. An MRI may be helpful in assessing the risk of intracranial bleeding in older people especially with previous history of ICH.[334, 335] Although the prevalence of CMBs is similar, a significantly higher burden of CMBs in VKA-treated patients compared to NOAC exposure has been reported.[336] As indicated in the 2020 ESC guidelines, anticoagulation should not be withheld purely based on the presence of CMBs.[1]

Frailty & falls

Frailty

Frailty is commonly defined as a rules-based distinct phenotype and by clinical judgement of function-deficits in a frailty scale (Table 13).[337-339] Both models identify patients at risk of or with established poor physiological reserve, high risk of falls, depression and dementia, poor physical

functioning and increased mortality. Frailty and pre-frail states are common with advancing age and raise specific considerations regarding the risk-benefit of OAC. Expert consensus advocates comprehensive geriatric assessment in all older patients with frailty.[340] Frailty is associated with weight loss and a risk for deterioration in renal function. As a result, patients need to be weighed and their renal function monitored regularly (see Chapter 4) to ensure safe NOAC dosing. There may be no benefit to OAC in states of severe frailty or where life expectancy is likely to be limited (Table 13).

Risk of falling

The risk of falling can be estimated using simple or more sophisticated tools (Table 14). Older patients are more likely to fall. The annual prevalence of all-cause falls and non-accidental falls in community dwelling individuals >75 years of age may be as high as 25% and 8% respectively.[341] The rate of falls increases with polypharmacy and institutional care.[342] Falls have often been considered a contraindication to OAC due to risk of ICH.[343] A Markov decision analytic model published in 1999 demonstrated a patient would have to fall 295 times in order for the risk of a subdural haematoma to outweigh the benefit of anticoagulation with VKA.[344] These overview calculations come with relevant limitations and it is uncertain if they translate into the current day situation. Nevertheless, given the even lower risk of intracranial bleeding compared with VKA, the 'number needed to fall' would be even higher with the use of NOACs.

The issue of falls in NOAC-treated patients was specifically analyzed in subanalyses of two phase III trials. In the ENGAGE-AF TIMI 48 trial patients were prospectively classified as 'high-' or 'low falls risk' by presence of known risk factors and co-morbidities.[70] Patients at increased risk of falling were more likely to experience a bone fracture, major bleeding or life threatening bleeding, and death. Edoxaban was associated with reduced risk of severe bleeding, intracranial haemorrhage and the most severe net clinical benefit outcomes (secondary and tertiary net clinical outcome) compared to VKA in both patient categories, and the absolute risk reduction was greater with edoxaban in patients at increased risk of falling.[70]

In the ARISTOTLE trial patients with a history of falling were older and more likely to have dementia and cerebrovascular disease. These individuals had an increased risk of major bleeding and intracranial bleeding as well as death, but the safety and efficacy of apixaban over warfarin was not affected by falling status.[345] Among patients with a history of falls no subdural bleeding was recorded on apixaban.

This is also reflected in observational data indicating better outcomes on NOACs vs. VKA in patients at risk of falling.[346-348] Caution is prudent, however, as more delayed intracranial haemorrhage in patients with a fall on NOACs has also been reported.[349]

In summary, falling per se is not a contraindication to NOAC use (Table 14), but precautions should be taken and modifiable bleeding risk factors assessed (including, importantly, co-use of antiplatelet agents; Chapter 2). In addition, referral to a specialized falls assessment and intervention service should be offered to all patients to reduce risk of further falls.[350]

Cognitive impairment and dementia

Mild cognitive impairment as well as dementia (cognitive impairment severe enough to compromise social and/or occupational functioning) is common in older age groups.[351, 352] AF itself is a risk factor for dementia and conversely, encouraging evidence indicates that OAC use may be associated with a reduced risk of dementia.[353-357] This risk reduction may be similar with VKA and NOAC; however, low time in therapeutic range has been associated with dementia in VKA-treated patients.[357-359]

Stroke as well as intracerebral haemorrhage are significant events for patients with dementia with a greater risk of cognitive and functional decline, loss of independence and institutionalization compared to non-dementia patients.[360, 361] AF in patients with dementia therefore requires similarly rigorous assessment for stroke prevention.

Dementia does pose unique considerations of adherence and safety when considering OAC. 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. This should be documented and explanation given to both patient and next of kin / legal attorney with assent / consent sought as relevant.

Adherence to OAC intake is of crucial importance. Both dementia and twice daily dosing has been shown to affect adherence with NOACs;[362] as such, once daily medications, weekly tablet boxes, reminders or blister packing may be helpful (see Chapter 2). Paradoxically, the fact that others may be supervising medication with dementia patients may guarantee higher adherence.[363] Telemedicine to enhance treatment adherence in dementia and other assistive technologies may be useful in this population.[364] It is advisable to re-assess cognitive function in older AF patients on a regular basis

particularly considering and assessing their ability to adhere to the prescribed anticoagulation regimen.

13. NOACs in high- and low body weights

Weight and body mass index (BMI) are important variables in drug distribution and plasma concentration levels. Concerns exist in the absence of readily available measurements of anticoagulant effect that NOACs may not be as effective or safe at extremes of weight with a potential for both over- and underdosing. Weight or BMI was not an exclusion factor in the randomized NOAC-trials in AF (or VTE), although dose reductions for lower body weight (≤ 60kg) were mandated for both apixaban (if also age ≥ 80 years and/or creatinine ≥ 1.5mg/dL), and edoxaban.[46-49, 365]

NOACs in patients with high body weights

Effect of obesity on NOAC plasma levels

Since 1975, obesity has tripled and the WHO now considers it an epidemic. In 2016, 1.3 billion adults were overweight (body mass index of greater than 25 kg/m^2) of which 650 million were obese (body mass index (BMI) greater 30 kg/m^2).[365] Obesity increases both the risk of AF (possibly due to electro-modulation of the atrium) and risk of recurrent AF after successful ablation.[366-369] Weight loss is an integral part of the multidisciplinary approach to prevention and treatment of patients with AF and obesity.[370]

Obesity affects the pharmacokinetics of drugs, including the volume of distribution (of lipophilic drugs in particular) as well as drug clearance.[371] Renal blood flow and CrCl have been shown to be increased in obesity and could increase elimination of OACs.[372] A number of studies of VKA have indicated that obese patients require greater doses and longer lead-in periods for achieving therapeutic INR values.[373]

Initial studies of **dabigatran** reported no effect of weight on pharmacokinetic variables although analyses in older healthy individuals did not include very obese patients.[374-376] In the RE-LY trial, however, patients with a body weight > 100 kg had 21% lower dose-normalized trough concentrations than patients with 50-100 kg body weight.[97] The primary efficacy and safety outcomes were similar in patients with weight ≥ 100kg vs. 50-99 kg vs. <50 kg (Ezekowitz et al., presented at ESC 2014).[48, 170]
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.[377-380] In the ENGAGE AF-TIMI 48 trial, no changes in plasma concentrations of **edoxaban** or its pharmacodynamic effect on FXa were observed between obese and normal weight patients.[381, 382]

Efficacy and safety of NOACs in obese patients

Concerns have been expressed about the reliability of the anticoagulant effect of NOACs in obese patients.[383, 384] In the RE-LY trial, no differences in the occurrence of stroke or systemic embolism were observed with dabigatran vs. warfarin in obese (≥ 100kg) vs. non-obese patients.[48, 385] However, case reports of treatment failure with low plasma levels of dabigatran have been reported in cases of severe obesity (BMI ≥ 40 kg/m^2).[386, 387]

Similarly, no differences were observed with apixaban vs. warfarin in obese patients (both as defined by BMI > 40 kg/m^2 or 120 kg),[388, 389] rivaroxaban vs. warfarin (obesity defined as BMI ≥ 35 kg/m^2),[390] and edoxaban vs. warfarin (BMI > 40 kg/m^2).[381] However, only 620 patients from the ROCKET-AF trial had a very high BMI (≥ 40 kg/m^2), and data from the RE-LY trial for dabigatran were not reported for this range.[385, 390] In contrast, 1003 and 1149 patients with a BMI ≥ 40 kg/m^2 were included in ARISTOTLE and ENGAGE AF-TIMI 48, respectively.

No difference in the occurrence of major bleeds were observed for dabigatran vs. warfarin, rivaroxaban vs. warfarin and edoxaban vs. warfarin in obese vs. non-obese patients.[381, 385, 390] Relatively more major bleeds were observed with apixaban vs. warfarin in patients with a BMI ≥ 30kg/m^2 vs. lower BMIs as well as > 120kg vs. < 120kg, although the incidence was still lower with apixaban vs. VKA even in obese patients.[388, 389]

Several studies from daily clinical practice indicated no substantially higher incidence in endpoints in obese vs. non-obese patients on NOACs.[391] A systematic review and meta-analysis of the impact of weight on efficacy and safety of NOACs compared to VKA found overall better efficacy across all body weights (low, normal, overweight, obese) with no increased bleeding noted in low or obese categories, although the analysis had no additional high quality data other than the original four pivotal trials.[392] Two small retrospective comparative studies found similar efficacy and safety in the NOAC group compared to VKA in the extreme obesity cohort; most data were available for apixaban and rivaroxaban, one reported numerically higher numbers of TIA and stroke with dabigatran and neither study included data on edoxaban.[393, 394]

Based on the pharmacokinetic properties and the available evidence the use of all NOACs appears to be safe and effective up to a BMI of 40 kg/m^2 (barring other clinically relevant factors). At BMI ≥ 40 kg/m^2 data are less robust, but most data and largely consistent findings are currently available for apixaban and edoxaban.[381, 385, 388-390]

At a BMI ≥ 50 kg/m^2 plasma level measurements with any of the NOACs (including the inherent associated limitations, see Chapter 5) or conversion to VKA therapy may be reasonable (Figure 23). Whether trough or peak plasma levels are preferable is a topic of further research; due to better reproducibility and correlation with clinical outcomes we generally advise for trough level measurement with peak level assessment only in selected cases.

NOACs after gastric bypass surgery

Treatment of obesity with bariatric surgery may have important effects on drug levels due to effects of surgery on the site and surface area of absorption, pH, blood flow, intestinal transit time as well as the effect of post-operative restrictive diets.[395] The location of the (presumed) major absorption site varies by anticoagulant but is thought to occur mainly in the proximal small intestine and, to a lower extend, in the distal stomach.[396, 397] The nature of gastric bypass surgery is also relevant whereby a concomitant bypass of the proximal small intestine may result in delivery of drugs to more P-glycoprotein rich distal segments and reduce overall absorption.[398] VKA weekly dose-requirements are variable post bariatric surgery with most reports describing an initial decrease but subsequent steady rise in the post-acute phase of surgery.[399-401] While cases of warfarin resistance post gastric-bypass procedure have been described,[402] even large GI resections usually do not have a major lasting effect on warfarin anticoagulation.[395]

Absorption of **dabigatran** may be affected (reduced) by higher pH and use of antacids (Table 4). [403, 404] While this is not considered relevant under normal circumstance it may play a role in patients after gastric bypass surgery. Bioavailability of **rivaroxaban** as used for stroke prevention in AF (20 mg, 15 mg) is increased by food, likely due to its lipophilicity and limited aqueous solubility, and administration of rivaroxaban distal to the stomach may lead to reduced absorption and rivaroxaban plasma levels.[105, 405] Hence, rivaroxaban (in the stroke prevention dose) may not be a preferred primary choice after gastric bypass surgery due to potentially relevant reductions in rivaroxaban exposure.[398] One small study showed expected levels for **dabigatran** and **apixaban** but below-expected ranges for 5 of 7

patients on rivaroxaban (including all 4 who had a gastric sleeve procedure).[406] **Edoxaban** is highly and slightly soluble at acidic and neutral pH, respectively, and mainly absorbed in the proximal intestine. One study indicated that delivery directly to the distal intestine reduced both peak (Cmax) and total plasma levels (AUC).[407]

Ultimately, the choice of anticoagulant post-bariatric surgery is a case by case consideration as strong clinical evidence is lacking, particularly for NOACs. As VKA appear least affected by gastric bypass surgery and target INR ranges are well-established, reverting to a VKA may represent a valid alternative. If use of a NOACs is considered necessary assessment of plasma levels (trough as well as peak levels) seems advisable (see Chapter 5). This should be performed in the setting of a multidisciplinary team and at a center with ample experience; in addition, several physiologic parameters are volatile after gastric bypass surgery such that repeated measurements over time may be required.

NOACs in patients with low body weight

There is no universal definition of low body weight although a BMI < 18.5 kg/m^2 is considered by many western agencies as indicative of being underweight.[408] Low body weight may increase exposure to any NOAC and as such increase the risk of bleeding compared to normal weight patients.[409, 410] Bleeding may also be increased with VKA therapy in underweight patients.[410, 411] 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 chronic kidney disease. Of note, renal function may be overestimated in underweight patients due to their reduced muscle mass (especially with the MDRD formula).

Special care is needed when anticoagulating low weight patients (Figure 23). Body weight ≤ 60kg requires dose reduction of apixaban (in patients with age ≥ 80 yrs and/or serum Creatinine ≥ 133 µmol/ (1.5 mg/dl) as well as for edoxaban (Chapter 1, Table 2), whereas it is in itself not a factor for dose reduction of rivaroxaban or use of lower dose dabigatran.

Both **apixaban** and **edoxaban** showed consistent efficacy and safety compared to warfarin in underweight patients when compared with the overall study population.[98, 381, 389] Drug concentrations and inhibition of Factor Xa did not differ in patients with low body weight (range 30-

55 kg) from patients with middle body weight in an analysis from ENGAGE AF-TIMI 48. [382] 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 compared with the remainder of the study cohort but a signal for increased bleeding events in patients with a lower BMI (particularly < 20kg/m^2; Ezekowitz et al., presented at ESC 2014).[48] Observational studies have equally suggested that low BMI may be an independent predictor of bleeding events with dabigatran and a trend to greater bleeding was noted with high dose dabigatran in a metanalysis of low weight patients.[392, 412] Frequently co-existing chronic kidney disease may also make it a less preferable option for underweight patients.

Rivaroxaban showed similar efficacy and safety in an exploratory analysis of the ROCKET-AF trial for lower body weight, but only patients ≤70 kg were compared with those >70 kg.[46] No specific outcome data was available for patients with <60 kg or <50 kg in patients on the full AF dose of rivaroxaban. Subsequent meta-analyses and observational data are reassuring with regard to safety in low and severely underweight patients (<50 kg), but limitations (residual confounding in particular) persist.[392, 413]

If therapy with a NOAC is warranted in low and very low weight individuals, measurement of trough levels may be considered to check for accumulation of the drug.[414] However, no evidence-based recommendations can be given regarding (further) dose reduction in cases where trough levels are above the expected range (Chapter 5).

14. NOACs in other special populations

Special considerations for the use of NOACs in **athletes** and **women of reproductive age** are discussed in the Online Supplement.

Epilepsy and NOACs

Scope of the problem

Epilepsy can have both genetic and acquired causes, the latter including brain trauma, stroke, tumors and brain infections. Epilepsy after a stroke is not an uncommon finding.[415] Risk of seizures is reported between 7-11.5% overall post-stroke and in 3-6% of cardioembolic stroke.[416-420] Incidence of recurrent unprovoked seizure post-stroke may be as high as 71% and prevention of such events using antiepileptic drugs (AEDs) is desirable especially when patients are on OAC.[421-423] Many features of AF-associated stroke such as cortical involvement, cerebral artery territory, multiple infarcts, severe deficit and hemorrhagic transformation are also predictive of developing post-stroke epilepsy.[424, 425]
OAC poses a special risk for patients with epilepsy. While most seizures in older people and post- stroke are focal in onset, patients who suffer seizures without aura or rare atonic seizures are particularly vulnerable to head trauma. Tongue biting is a risk in the tonic component of generalized seizures.

Potential drug-drug interactions

Many AEDs relevantly induce hepatic enzymes (e.g., ethosuximide carbamazepine, phenobarbital, phenytoin, primidone) or are mild inducers (e.g., oxcarbazepine, lamotrigine, tiagabine) thereby potentially reducing the efficacy of VKAs as well as certain NOACs (Table 7). Other AEDs inhibit hepatic metabolism (felbamate, topiramate, valproate, vigabatrin) and can increase the risk of bleeding with VKAs. Valproate may have unpredictable effects on CYP3A4.[426] Conversely, animal and / or human studies have indicated that carbamazepine, levetiracetam, phenobarbital, phenytoin and valproic acid may *decrease* the effect of NOACs by inducing P-glycoprotein (P-gp) activity. Newer third generation AEDs such as brivaracetam, lacosamide and eslicarbazepine may have less potential for DDI.[427] In addition, AEDs can have an indirect effect on the coagulation system, e.g., by causing thrombocytopenia or platelet dysfunction.[428]

Sporadic case reports exist about drug-drug interactions (DDIs) between NOACs and AEDs (Table 7).[429, 430] The majority of DDIs to date have cited reduced efficacy of NOACs due to these mechanisms.[431] One series reported increased bleeding risk with phenytoin.[432] Another retrospective cohort of patients from Taiwan on NOACs and 11 different AEDs reported increased association of bleeding with concomitant prescription of phenytoin, valproic acid or levetiracetam but this may not be generalizable to other populations.[433] After inquiry also with the drug manufacturer there is unfortunately no study which reliably investigated the effect of levetiracetam on NOAC plasma levels and clinical events in a sufficiently large "real world" cohort of concomitantly treated patients. We strongly advise such studies should be conducted (not only with levetiracetam, but also with other antiepileptic drugs) in order to better enable clinical decision making in this difficult to treat patient population.

Practical advice

Robust evidence is lacking for DDI with NOACs and AEDs and there is poor concordance in international drug compendia on the subject.[434] Where AED therapy is desirable in AF patients with epilepsy treated with a NOAC vigilance for potential drug-drug interaction is warranted (see Chapter 3) and regular interdisciplinary review with the treating cardiologist, neurologist, primary care physician and clinical pharmacist is crucial. Especially in the context of comedication with anti-seizure drugs, NOAC plasma level measurements are frequently proposed, similar to plasma-level guided dosing of anticonvulsants.[435-438] However, as indicated and discussed in chapter 5 - and in contrast to the situation with anti-epileptic drug level measurements - such an approach is without any endpoint-derived clinical trial evidence, especially with respect to dosing NOACs according to their measured trough levels.[437, 438] Therefore, such patients should be treated at expert centers with extensive experience in the measurements of NOAC plasma levels and their interpretation.

NOACs in Asians and other non-Caucasian ethnicities

In the past, ethnicity has been shown to be a factor in VKA underuse, poor INR control, and increased stroke- and death rates in Non-White vs. White populations.[439-442] Differences in body mass, genetic polymorphisms of the cytochrome P450 system affecting drug metabolism have been suggested as relevant factors for this difference impacting on efficacy and safety of stroke prevention in AF. Importantly, environmental factors around diet and lifestyle, socioeconomic and educational status

are important confounders which are not always easy to separate from biological effects.[443-445] Concerns are nonetheless frequently raised that the outcomes observed in the large NOAC trials might not be generalizable to all ethnicities encountered in daily clinical practice.

All four phase III trials of dabigatran, rivaroxaban, apixaban, and edoxaban in AF included a predominantly white population, i.e., 70%, 82.9%, 62.7% and 76.5%, respectively. While the number of Asian patients who were enrolled was relatively large (16%, 12.7%, 14.5% and 13.6% in RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48, respectively) a much lower percentage of Black (1%, 1.3%, 1.2%; not reported in ENGAGE AF-TIMI 48) and a relatively lower number of Hispanic patients (6.9%, not reported in ROCKET-AF, 19.8% and 12.4%, respectively) was included.[46-49]

NOACs in Asians

Overall, Asians are a very diverse ethnic group. Asian patients are at an increased risk for both stroke and bleeding. Indeed, recent data suggests that the risk of stroke may rise from age 50-55 years upwards and that a modified CHA_2DS_2-VASc score may need to be used in Asian patients.[1, 446-448] In VKA users, efficacy for the prevention of ischemic strokes was shown to be lower and the risk of intracerebral hemorrhage higher in Asian- vs. non-Asian patients,[445, 449, 450] possibly linked to a lower TTR combined with more frequent non-cardioembolic stroke sources. Asian ethnicity may also have an impact on metabolism and clearance of NOACs, trough concentrations and anti-FXa activity due to lower body weight and increased rates of renal disease thereby limiting the ability to simply extrapolate data from Caucasians.[451, 452]

Across the four phase III NOAC trials > 8,600 Asian patients were included. As in previous studies, rates of intracranial hemorrhage as well as ischemic stroke were higher in Asians as compared to Non-Asians.[452-455] The reduction in major (especially intracranial) bleeding was at least as pronounced if not greater with NOACs vs. VKA in Asians indicating a possibly even greater safety advantages as compared to non-Asian patients.[450, 452-455] In addition, and importantly, there were no signs for a reduced efficacy in the prevention of stroke and systemic embolism across the approved NOAC regimens. These findings were largely confirmed in observational registries.[55, 456, 457]

Taken together, these data indicate that NOACs may represent a preferred option for anticoagulation also in Asian patients.[450, 452] This extends also to Asian patients with low body weight.[413]

Black, Hispanic, and other ethnicities

Black patients have been shown to have a lower incidence of AF but appear to be at higher risk of stroke.[458-460] The rate of stroke in AF equally appears higher and outcomes may be worse in Hispanics vs. Non-Hispanic patients.[461, 462] As such, also these patients would be of particular interest regarding their outcome on NOACs, yet (as indicated above) the number of Black and Hispanic patients included into the four landmark NOAC trials was relatively low.

Subanalyses for ethnicities showed

- Dabigatran (RE-LY):
    - preserved efficacy and reduced incidence of ICH across ethnicities compared to VKA.[48, 453]
    - Efficacy and safety vs. warfarin preserved in patients included in Latin America.[463]
- Rivaroxaban (ROCKET-AF):
    - Efficacy and safety vs. warfarin similar across ethnicities and regions of inclusion.[46]
    - Reduced incidence of ICH vs. VKA in all ethnicities (with higher rates of ICH in Blacks compared to Whites).[464]
- Apixaban (ARISTOTLE):
    - No difference for patients included in Latin America as compared to North America or Europe regarding efficacy and safety vs. VKA[47]
    - Risk of ICH higher in patients included in Latin America vs. Europe.[283]
- Edoxaban (ENGAGE AF-TIMI 48):
    - Higher risk of ICH in Latin American patients compared to Non-Latin American patients.[465]
    - Significant reduction in ICH in both populations on edoxaban vs. VKA.[465]

In totality, these data hence indicate that NOACs should also be the preferred therapy for Black or Hispanic patients, particularly due to the oftentimes difficult and suboptimal alternative of VKA therapy (which may at least in part be due to confounding, as indicated above). However, and similar to all other settings (see Chapter 2), measures to improve care including an increase in the awareness of the disease and its consequences, optimal control of comorbidities (particularly blood pressure, diabetes, etc.), frequent medication review and careful assessment for dose reduction criteria are crucial to realize the advantages in daily clinical care. In addition, these findings also indicate the clear

necessity for more high-quality data to better understand the efficacy and safety profile of NOACs in diverse ethnic populations.

Patients with thrombocytopenia

NOAC therapy in thrombocytopenia

Platelet count < 100 x 10^3/µL was an exclusion criterion in the RE-LY (dabigatran versus VKA) and ENGAGE AF-TIMI 48 trials (edoxaban versus VKA) and a count < 90 x 10^3/µL in the ROCKET-AF trial (rivaroxaban versus VKA) in AF.[46, 48, 49] Thrombocytopenia was not a listed exclusion factor in the ARISTOTLE trial of apixaban vs. VKA in AF.[47] Patients with platelet counts as low as 50 x 10^3 µL were included in trials of edoxaban and rivaroxaban,[466, 467] and 75 x 10^3 µL for apixaban in treatment of cancer-related VTE.[468]

Real-life data indicate that NOACs are associated with a similar rate of ischemic stroke and systemic embolism and a lower incidence of bleeding than VKA in thrombocytopenic AF-patients.[469] A small prospective study looking at patients with AF and mild thrombocytopenia (50-100 x 10^3/µL) on reduced dose dabigatran (110 mgs BD), apixaban (2.5 mgs BD) and rivaroxaban (15 mgs QD) found no difference in the rates of major bleeding or ischemic stroke compared to patients with normal thrombocyte count on the recommended doses of those agents.[470]

There is no "safe" cut-off above which NOAC therapy is without risk in patients with thrombocytopenia. In addition to the absolute number of platelets the dynamics of the platelet count, the underlying reason for thrombocytopenia, and special risk factors (including the likelihood of dysfunctional platelets as well as other coagulation abnormalities) need to be considered.[471] Our general advice is summarized in Figure 24. Given the lack of a large evidence base for guidance the decision for NOAC treatment needs to follow an individualized, team-based approach including the patient and his/her needs and expectations (shared decision-making).

NOACs and heparin-induced thrombocytopenia

Thrombocytopenia is listed in the individual SmPCs as ‘uncommon’ (≥ 1/1,000 to < 1/100 patients) as a side effect of NOACs,[403, 405, 472, 473] but isolated cases have been reported.[474-479] In heparin-induced thrombocytopenia +/- thrombosis (HIT/ HITT) there is growing evidence that NOACs are not recognized by pre-existing HIT antibodies, do not complex with platelet factor 4 and do not cause platelet

aggregation.[480-482] NOAC therapy may hence constitute a viable less expensive and easier to administer alternative to parenteral heparin substitutes (e.g., argatroban, fondaparinux) especially if the latter are not available or are deemed unsuitable.[483, 484] Further research is also required in this field to confirm and strengthen these first positive experiences.

15. NOACs in patients with atrial fibrillation and malignancy

The scope of the problem

Cancers are not infrequent in older patients, similar to AF.[485] Cancer and cancer therapy may in turn precipitate AF, while both age and malignancy are independent risk factors for thrombosis and bleeding. The scope of the problem of AF and malignancy is outlined in detail in the Online Supplement.

Anticoagulant therapy in patients with malignancy

In the phase III **VTE** trials specifically targeting cancer patients, edoxaban (Hokusai Cancer)[466], rivaroxaban (Select-D)[467] and apixaban (Caravaggio)[486] were non-inferior to dalteparin in the prevention of recurrent VTE. While there was a signal of improved efficacy with both edoxaban and rivaroxaban vs. dalteparin, bleeding tended to be higher with the two NOACs as compared to dalteparin, which was driven mainly by patients with gastrointestinal cancers. For apixaban, efficacy and safety were broadly similar between the NOAC and LMWH.

Concerning the prevention of stroke and systemic embolism in **AF patients** with cancer, available evidence is less strong, as active malignancy was an exclusion criterion in most NOAC AF Phase III trials. In a recent meta-analysis[487] of 5 studies (post-hoc analyses of the ROCKET AF,[488] ENGAGE AF-TIMI 48[489] and ARISTOTLE[490] trials, and 2 retrospective population-based cohorts),[491, 492] the use of NOACs compared to warfarin was associated with a significantly reduced risk of stroke, systemic embolism and VTE, a strong trend towards fewer ischaemic strokes (p=0.05) and a numerically lower incidence of myocardial infarction, all-cause mortality and cardiovascular death. There was a strong trend towards fewer major bleedings (p=0.05), significantly fewer intracranial or GI bleedings, and a comparable number of clinically relevant major or non-major blees with NOACs. Pooling the 3 post-hoc studies showed similar rates of efficacy and safety outcomes with NOACs versus warfarin in AF patients with and without cancer.

A large registry using s prescription-based analysis for AF patients on VKA or NOAC with and without cancer reported equivalence for bleeding and thromboembolic incidence and cancer status, although

the rates of both were lower in the NOAC population.[493] However, much is still unknown about drug-drug interactions between NOACs and specific chemotherapeutic agents, urging further caution (Table 6).[494]

Overall, anticoagulation with NOACs may appear as a valid option in patients with AF and malignancy based on the few available data from RCTs as well as using extrapolations from cancer-related VTE treatment. Antithrombotic therapy in patients with AF suffering from a malignancy needs a dedicated interdisciplinary team approach (Figure 25).[495] 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.

16. Optimizing dose adjustments of Vitamin-K Antagonists

Specific considerations for optimizing dose adjustments of VKA are discussed in the Online Supplement. One algorithm to optimize VKA dosing is presented in Table 15, derived from the warfarin arm of the RE-LY trial.

Figure Legends

Figure 1: Selection of possibilities to increase adherence to NOACs

Note to editorial office: The image for " Pill organizer & medication boxes" is new and was taken from the internet. Hence, needs to be re-drawn. All other images are from the 2018 version.

Figure 2: The EHRA NOAC card

A patient information card is crucial, both for the patient (instructions on correct intake; contact information in case of questions) as for healthcare providers. This generic and universal card should document each visit, each relevant observation or examination, and any medication change.

Figure 3: Initiation and structured follow-up of patients on NOACs

It is crucial to ensure a structured follow-up of patients on NOACs. The anticoagulation card, as proposed in Figure 2, is intended to document each visit so that every person following up on the patient is well-informed. Moreover, written communication between different healthcare providers is required to inform them about the follow-up plan and execution.

Figure 4: Switching between NOACs and other anticoagulants.

Figure 5: Absorption and metabolism of the different NOACs.

There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolization and excretion. *also via CYP1A2, CYP2J2, CYP2C8, CYP2C9, and CYP2C19

Figure 6: NOAC selection based on drug-drug interactions and / or risk of bleeding.

Dose reduction of all NOACs is primarily recommended along the published dose reduction criteria (see Chapter 1, Table 2). Whenever possible, the tested and approved dosing regimen of NOACs should be used. See text for details.

*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 centers with great experience in the performance and interpretation of such assays as well as the care of NOAC-treated patients (see Chapter 5).

Figure 7: Use of NOACs according to renal function

* 110mg BID in patients at high risk of bleeding (per SmPc)

Other dose reduction criteria may apply (weight ≤ 60 kg, concomitant potent P-Gp inhibitor therapy). According to EMA SmPc edoxaban should be used in "high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk".[473] See text for details

$ 2x2.5 mg only if at least 2 out of 3 fulfilled: Age ≥ 80 years, Body weight ≤ 60 kg, Creatinine ≥ 1.5 mg/dl (133 µmol/l)

Orange arrows indicate cautionary use; see text for details.

Figure 8: NOACs in patients with liver disease

Figure 9: Management of bleeding in patients taking NOACs.

Figure 10: Application and effect of idarucizumab and andexanet alpha

Per Andexanet Alpha SmPc[496]

or unknown

Andexanet alpha is currently only approved for reversal of life-threatening uncontrollable bleeding in patients taking apixaban or rivaroxaban. In view of the very similar mode of action it can be assumed that it will have a similar effect in patients on edoxaban. The edoxaban dosing provided in this scheme is based on the (final) protocol of the ANNEXA-4 trial.[179]

Figure 11: (Re-) initiation of anticoagulation after gastrointestinal (GI) bleeding

without evidence; ideally include patient in ongoing trial

Figure 12: NOAC management in the setting of unplanned surgery

Figure 13: Perioperative NOAC management

Figure 14: Timing of last NOAC intake before an elective intervention

Figure 15: Stopping and re-initiation of NOAC therapy in elective surgery

Yellow star – Time point of the intervention / operation

Parentheses indicate optional pre-/ postoperative intake, especially in patients not at high risk of drug accumulation / bleeding.
Consider +24 hours of interruption in situations likely resulting in increased plasma levels (e.g., body weight < 50kg, significant interactions (see Chapter 3))
* Intake of this dose of Dabigatran if CrCl is in the indicated range; otherwise skip this dose
** Consider measurement of plasma levels in very special situations, e.g., highest risk neurosurgery / cardiac surgery, severely impaired renal function, combination of factors predisposing to higher NOAC levels (see Chapter 5).
Rivaroxaban needs to be taken with food for stroke prevention in AF, which needs to be considered (also) in the post-operative setting

Figure 16: NOAC management before and after atrial fibrillation ablation
TSP - transseptal puncture

Figure 17: Anticoagulation therapy after elective PCI or ACS in patients with AF.
"Shorten/de-intensify": e.g., discontinuing Aspirin or P_2Y_{12} inhibitor at an earlier stage
"Lengthen/intensify": e.g., continuing triple combinations longer, or continuing P_2Y_{12} inhibitor longer
A: aspirin 75–100 mg QD; C: clopidogrel 75 mg QD; Tica: Ticagrelor 90 mg BID
* If triple therapy needs to be continued after discharge clopidogrel is preferred over ticagrelor (due to lack of data)

Figure 18: Acute management of elective PCI or ACS in AF patients treated with NOAC

Figure 19: Cardioversion workflow in AF patients treated with NOAC, depending on the duration of the arrhythmia and prior anticoagulation

Figure 20: Acute management of acute ischaemic stroke with relevant neurological deficit in a patient on NOAC
[#] Systemic thrombolysis only indicated if there are no (other) contra-indications for intravenous application of rt-PA according to its label
[%] Endovascular thrombectomy only indicated if there is a target vessel occlusion and procedure is indicated and feasible according to present evidence

** According to expert consensus[497]

Figure 21: (Re-) initiation of anticoagulation after TIA/stroke.

Without proven evidence / RCT data available, based on expert opinion. Consider inclusion of patient in an ongoing trial. (Re-)start only in the absence of contraindications and if stroke size is not expected to substantially increase the risk of secondary hemorrhagic transformation. Consider shorter delays to (re-)start a NOAC in case of a very high risk of stroke recurrence (e.g., LA(A) thrombus) and no hemorrhagic transformation on follow-up brain imaging (using CT or MRI).

Figure 22: (Re-) initiation of anticoagulation post intracranial bleeding

Without evidence; ideally include patient in an ongoing trial

* Brain imaging mandatory before (re-)initiation of (N)OAC

Figure 23: NOACs in under- and overweight patients

* Most RCT / plasma level data for BMI ≥ 40 kg/m^2 for apixaban and edoxaban. See text for details.

Figure 24: NOACs in patients with thrombocytopenia

Figure 25: Important aspects in the management of AF patients with malignancies

Tables

Table 1: Selected indications and contra-indications for NOAC therapy in AF patients

Condition	Eligibility for NOAC	Comment
Mechanical prosthetic valve	Contraindicated	Excluded from pivotal RCTs Data indicating worse outcome [15, 16]
Moderate to severe mitral stenosis (usually rheumatic)	Contraindicated	Excluded from pivotal RCTs Little rationale for less efficacy and safety vs. VKA
Other mild to moderate valvular disease (e.g., degenerative aortic stenosis, mitral regurgitation etc.)	Included in NOAC trials	Data regarding efficacy and safety overall consistent with patients without valvular heart disease [12, 17-22]
Bioprosthetic valve / valve repair (after > 3 months post op)	Acceptable	Some data from NOAC RCTs. Single RCT indicating non-inferiority to VKA. [24] Patients without AF usually on ASA after 3-6 months post-surgery, hence NOAC therapy acceptable for stroke prevention if diagnosed with AF
Severe aortic stenosis	Limited data (excluded in RE-LY)	No pathophysiological rationale for less efficacy and safety. Most will undergo intervention
Transcatheter aortic valve implantation	Acceptable	Single RCT + observational data May require combination with APT [25, 26]
Percutaneous transluminal aortic valvuloplasty	With caution	No prospective data May require combination with APT
Hypertrophic cardiomyopathy	Acceptable	No rational for less efficacy and safety vs. VKA Observational data positive for NOACs [33-36]

Hatched – Limited data;. See text for details.

Table 2: NOACs and approved / studied doses across indications

"SmPc" refers to European SmPc

Stroke prevention in Atrial Fibrillation (SPAF)

	Standard dose	Comments / dose reduction
Apixaban[47]	5 mg BID	2.5 mg BID if 2 out of 3: Weight ≤ 60 kg, Age ≥ 80 yrs, serum Creatinine ≥ 133 µmol/l (1.5 mg/dl) [*or* single criterion: if CrCl 15-29 ml/min]
Dabigatran[48]	150 mg BID / 110 mg BID	No pre-specified dose-reduction criteria in phase III trial*
Edoxaban[49]	60 mg QD	30 mg QD if: Weight ≤ 60 kg *or* CrCl 15-49 ml/min *or* concomitant therapy with strong P-Gp inhibitor (see Chapter 3)
Rivaroxaban[46]	20 mg QD	15 mg QD if CrCl ≤ 15-49 ml/min

**SmPC: 110 mg BID if age ≥ 80 years, concomitant verapamil, increased risk of GI bleeding*

NOAC dosing in AF patients post ACS / PCI (see Chapter 9)

	Standard dose	Comments / dose reduction
Apixaban[244]	5mg BID	Dose reduction as for SPAF
Dabigatran[247]	150 mg BID or 110 mg BID	110mg as for SPAF[403]
Edoxaban[245]	60mg QD	Dose reduction as for SPAF
Rivaroxaban[246]	15mg QD	Dose reduction to 10mg QD if CrCl 30-49 ml/min

In addition to single / dual antiplatelet therapy, where applicable. See chapter 9 for details.

Treatment of DVT / PE

	Initial Therapy	Remainder of treatment phase
Apixaban[498]	10 mg BID, 7 days	5 mg BID, no dose reduction
Dabigatran[499]	Heparin / LMWH	150mg bid, no dose reduction[#]
Edoxaban[500]	Heparin / LMWH	60 mg QD, **same dose reduction as for SPAF! (see above)**
Rivaroxaban[501, 502]	15 mg BID, 21 days	20 mg QD, no dose reduction[**]

[#] Per SmPC: 110mg BID if age ≥ 80 years, concomitant verapamil, increased risk of GI bleeding (based on pharmacokinetic / pharmacodynamic (PK/PD) analyses; not studied in this setting)

*** Per SmPc: 15 mg if risk of bleeding outweighs risk for recurrent DVT and PE (based on PK/PD analyses; not studied in this setting)*

Long-term prevention of recurrent DVT / PE

	Standard dose	Comments / dose adjustment
Apixaban[503]	2.5mg BID	
Dabigatran[504]	150mg BID	No pre-specified dose-reduction criteria in clinical trial [#]
Edoxaban[473, 500, 505]	60mg QD*	
Rivaroxaban[506]	10mg QD	**

[#] SmPC: 110mg BID if age ≥ 80 years, concomitant verapamil (both based on pharmacokinetics / pharmacodynamics analyses; not studied in this setting)
** not specifically studied, follow up data available up to 12 months in phase III trial*
*** SmPc: 20mg QD in patients at high risk of recurrence*

VTE prevention post major orthopedic surgery

	Standard dose	Comments / dose reduction
Apixaban[507]	2.5mg BID	
Dabigatran[508, 509]	220 mg QD / 150mg QD	**
Edoxaban[510, 511]	30mg QD	Not approved in Europe (only studied in Asia)
Rivaroxaban[512-515]	10mg QD	

** SmPc: 1x 150 mg if CrCl 30-50 ml/min; concomitant verapamil, amiodarone, quinidine; age >75 years

Secondary prevention of atherothrombotic events post ACS in patients without AF (i.e., no OAC indication)

	Standard dose	Comments / dose reduction
Rivaroxaban[115]	2.5mg BID	In addition to aspirin +/- P2Y12 inhibitor

Secondary prevention of atherothrombotic events in patients with chronic coronary syndrome and / or symptomatic peripheral artery disease patients without AF (i.e., no OAC indication)

	Standard dose	Comments / dose reduction
Rivaroxaban[516]	2.5mg BID	In addition to aspirin

Table 3: Checklist during follow-up contacts of AF patients on anticoagulation

	Interval	Comments
1. Adherence	Each visit	• Instruct patient to bring NOAC card and complete list of medication: make note and assess adherence. • Re-educate on importance of strict intake schedule. • Inform about adherence aids (special boxes; smartphone applications; …). Consider specific adherence measuring interventions (see Chapter 2) • Inform about minor bleeding (gum, epistaxis, small ecchymosis) and instruct not to skip any dose • Assess cognitive function
2. Thromboembolism	Each visit	• Systemic circulation (TIA, stroke, peripheral). • Deep vein thrombosis, pulmonary embolism
3. Bleeding	Each visit	• For every bleeding: Look for reason. Cancer? Ulcer? Other causes, lesions etc.? Treatment or prevention possible? • "Nuisance" bleeding: Reason? Treatment / prevention (see above)? • Assess impact on quality of life.
4. Other side effects	Each visit	• Carefully assess relation with NOAC: decide for continuation (and motivate) or change NOAC.
5. Co-medications	Each visit	• Prescription drugs; over-the-counter drugs. • Careful interval history (also temporary use, e.g., NSAIDs)
6. Blood sampling (incl. Hb, renal and liver function)	Yearly	• In all patients except those below
	4-monthly	• ≥75y (especially if on dabigatran), or frail.
	variable	• If renal function CrCl ≤ 60 ml/min: CrCl / 10 = minimum recheck interval [in months]
	If needed	• In case of intercurrent conditions, especially with potential impact on renal or hepatic function (e.g., infection, NSAID use, dehydration etc.).
7. Re-assess stroke risk	Each visit	• CHA_2DS_2-VASc score, as recommended by current guidelines[1]
8. Assessing and minimizing modifiable risk factors for bleeding	Each visit	• As recommended by current guidelines[1]
		• Particularly: – Uncontrolled hypertension (systolic >160 mmHg) – Medication predisposing for bleeding (e.g., aspirin, NSAIDs) – Labile INR (if on VKA) – Excessive alcohol intake – Falls

9. Assessing for optimal NOAC and correct dosing[1]	Each visit	• Especially based on the above, re-assess whether – The chosen NOAC is the best for the patient – The chosen dose is correct

For frequency of visits: see Figure 3.

Table 4: Absorption and metabolism of the different NOACs

	Dabigatran[106, 376]	**Apixaban**[517]	**Edoxaban**[518]	**Rivaroxaban**[519, 520]
Bio-availability	3-7%	50%	62%	15 mg / 20 mg: 66% without food, 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% (not dialysable)	n.a. (not dialysable)	n.a. (not dialysable)
Metabolism	Glucoronic acid conjugation	CYP3A4 (25%), CYP1A2, CYP2J2, CYP2C8, CYP2C9 CYP2C19	CYP3A4 (<4% of elimination)	CYP2A4 (18%)[519], CYP2J2
Absorption with food	No effect	No effect	6-22% more; minimal effect on exposure	+39% more (see above)
Absorption with H2B/PPI	-12-30% (not clinically relevant)	No effect	No effect	No effect
Time to peak levels [h]	3	3	2-4	2-4
Elimination half-life [h]	12-17	12	10-14	5-9 (young) 11-13 h (elderly)

Table 5: Effect of drug-drug interactions and clinical factors on NOAC plasma levels and anticoagulant effects

Color coding is based on the respective NOAC SmPC, drug interaction databases, or expert opinion. The hatched color coding indicates no clinical or PK data available. Some of the color codes will likely require adaptation as more data become available over time.

White: No relevant drug-drug interaction anticipated.

Yellow: Caution required, especially in case of polypharmacy or in the presence of ≥2 yellow / bleeding risk factors (see Figure 6).

Purple: Lower dose (dabigatran) or dose reduction (edoxaban) recommended according to label

Red: Contraindicated / not advisable due to increased plasma levels.

Blue (dark): Contraindicated due to *reduced* NOAC plasma levels.

Blue (light): Caution required, especially in case of polypharmacy or in the presence of ≥2 light blue interactions due to *reduced* NOAC plasma levels.

[a] Based on in vitro investigations, comparing the IC50 for P-gp inhibition to maximal plasma levels at therapeutic dose, and/or on interaction analysis of efficacy and safety endpoints in the Phase-3 clinical trials.[46],[47] No direct PK interaction data available.

[b] Dose reduction based on published criteria (see Table 2).

[c] Age had no significant effect after adjusting for weight and renal function.

[d] Data from Phase I study. Interpret in the light of data from Re-DUAL PCI (see Chapter 9 for details).[247]

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[519]
Antiarrhythmic drugs					
Amiodarone	Moderate P-gp inhibition	+12 to 60%[SmPC]	No PK data[a]	+40% [521-523]	Minor effect[a]
Digoxin	P-gp competition	No effect[SmPC]	No effect [524]	No effect[523]	No effect [525]
Diltiazem	Weak P-gp and CYP3A4 inhibition	No effect[SmPC]	+40% [526]	No data yet	No effect
Dronedarone	P-gp and CYP3A4 inhibition	+70 to 100%	With caution	+85%[b 523] (dose reduction to 30 mg once daily by label)	Moderate effect; should be avoided
Quinidine	P-gp inhibition	+53%[SmPC]	No data yet	+77% [523] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp inhibition and weak CYP3A4 inhibition	+12 to 180%[SmPC] (if taken simultaneously) (110 mg BID by label)	No PK data	+53% (SR) [523] (no dose reduction required by label)	+40%[527] (probably not relevant) [528]

	via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Other cardiovascular drugs					
Atorvastatin	P-gp inhibition and CYP3A4 competition	No relevant interaction [529]	No data yet	No effect [523]	No effect [530]
Ticagrelor (see also Chapter 9)	P-gp inhibition	+24 to 65% [SmPC] (give loading dose 2h after dabigatran)[d]	No data – carefully monitor	No data – carefully monitor	No data – carefully monitor
Antibiotics					
Clarithromycin; Erythromycin	P-gp inhibition and strong CYP3A4 inhibition	Clarithromycin: +19% AUC; +15% C_{max} (SmPC)	Clarithromycin: +60% AUC; +30% C_{max} (SmPC)	Erythromycin: +85% AUC; +68% C_{max} [531] (dose reduction to 30 mg once daily by label)	Clarithromycin: +50% AUC; +40% C_{max} Erythromycin: +30% AUC; +30% C_{max} (SmPC)
Rifampicin	P-gp/ BCRP and CYP3A4 induction	minus 66% AUC; minus 67% Cmax (SmPC)	minus 54% AUC; minus 42% Cmax (SmPC)	minus 35% AUC, (but with compensatory increase of active metabolites) [532]	minus 50% AUC; minus 22% Cmax (SmPC)

	via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Antiviral Drugs					
HIV protease inhibitors (e.g., ritonavir)	P-gp and BCRP inhibition or induction; CYP3A4 inhibition	Variable increase / decrease [533, 534]	Strong increase	No data yet	+153% AUC +55% C_{max} (Ritonavir 600 BID) [94]
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% AUC; +30% C_{max} (if given systemically) [94]
Itraconazole; Ketoconazole	Potent P-gp and BCRP competition; strong CYP3A4 inhibition	+140 to 150% (ketoconazole) (US: 2 x 75 mg if CrCl 30-50 ml/min)	+100% AUC; +64% C_{max} (ketoconazole) [526]	+87% AUC; +89% C_{max} (dose reduction to 30 mg once daily by label) (ketoconazole) [531]	+160% AUC; +72% C_{max} (ketoconazole, SmPc)
Voriconazole	Strong CYP3A4 inhibition	No data yet	SmPC	No data yet	SmPC
Posaconazole	Mild to moderate P-gp inhibition, strong CYP3A4 inhibition	SmPC	SmPC		SmPC
Other drugs					
Naproxen	P-gp competition; pharmacody-namically (increased bleeding time)	No data yet	+55% AUC; +61% C_{max} [535]	No difference in AUC [536]	No relevant increase of AUC [537]

	via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
H_2-blockers; PPI; Al- Mg-hydroxide	GI absorption	Minor effect, not clinically relevant[SmPC]	No effect	Minor effect, not clinically relevant[SmPC]	No effect [105, 538]
SSRIs; SNRIs	Pharmacodynamic effect on platelets	SmPC	SmPC	SmPC	SmPC
St. John's wort	P-gp/ BCRP and CYP3A4 induction				
Other factors					
Age ≥ 80 years	Potential for increased plasma levels	110mg BID (SmPC)	b	c	
Age ≥75 years	Potential for increased plasma levels			c	
Weight ≤ 60 kg (see Chapter 13)	Potential for increased plasma levels		b	b	
Weight ≥ 120 kg (see Chapter 13)	Potential for decreased plasma levels				
Chronic kidney disease	Potential for increased plasma levels				
Other factors with potentially increased bleeding risk		E.g.: • Concomitant antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants • Severe Frailty / falls risk • H/o bleeding or predisposition (anemia, thrombocytopenia)			

Table 6: Anticipated effects of common anti-cancer drugs on non-vitamin K antagonist oral anticoagulants plasma levels

Color coding is based on the respective NOAC SmPC, drug interaction databases, or expert opinion. The hatched color coding indicates no clinical or PK data available. Some of the color codes will likely require adaptation as more data become available over time.

White: No relevant drug-drug interaction anticipated.

Yellow: Caution required, especially in case of polypharmacy or in the presence of ≥2 yellow / bleeding risk factors (see Figure 6).

Orange: Consider avoiding concomitant use, careful monitoring required if combined. See Figure 6.

Red: Contraindicated / not advisable due to increased plasma levels.

Purple: Dose reduction (edoxaban) recommended according to label

Blue (dark): Contraindicated / not advisable due to *reduced* NOAC plasma levels.

Blue (light): Caution required, especially in case of polypharmacy or in the presence of ≥2 light blue interactions due to *reduced* NOAC plasma levels.

Where no data or SmPC instructions were available, expert opinion was generally based on the following principles:

- Strong CYP3A4 and/or P-gp inducer — should not be used (dark blue).
- Moderate CYP3A4 or P-gp inducer — use with caution or avoid (light blue).
- Strong CYP3A4 and/or inhibitor — should not be used (red).
- Moderate CYP3A4 and/or P-gp inhibitor — use with caution or avoid (orange)
- Mild CYP3A4 and/or P-gp inducers or inhibitors — caution required especially with polypharmacy or in the presence of ≥ 2 bleeding risk factors (yellow).

Purine analogs: Mercaptopurine, Thioguanine, Pentostatin, Cladribine, Clofarabine, Fludarabine.

Pyrimidine analogs: Fluorouracil, Capecitabine, Cytarabine, Gemcitabine, Azacitadine, Decitabine.

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	≈25%	<4%	≈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	CYP3A4/P-gp competition				
Antimetabolites					
Methotrexate	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				

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
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				
Cyclophosphamide	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				

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Intercalating agents					
Bleomycin, Dactinomycin	No relevant interaction anticipated				
Mitomycin C	P-gp competition; 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 inhibition; 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				

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
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				

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Immune-modulating agents					
Ciclosporine	Strong-to-moderate P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC	SmPC	+73% AUC (dose reduction to 30 mg once daily by label)	
Dexamethasone	Moderate CYP3A4 induction; CYP3A4 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				

Table 7: Anticipated effects of common antiepileptic drugs on non-vitamin K antagonist oral anticoagulants plasma levels

Color coding is based on the respective NOAC SmPC, drug interaction databases, or expert opinion.[426] The hatched color coding indicates no clinical or PK data available. Some of the color codes will likely require adaptation as more data become available over time.

White: No relevant drug–drug interaction anticipated.

Blue (dark): Contraindicated due to reduced NOAC plasma levels.

Blue (light): Caution required, especially in case of polypharmacy or in the presence of ≥2 light blue interactions due to *reduced* NOAC plasma levels.

	Via[426, 539-541]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Brivaracetam	--	No relevant interaction known/assumed			
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	-29% [542]	-50% (SmPC)	SmPC	SmPC
Ethosuximide	CYP3A4 competition	No relevant interaction known/assumed			
Gabapentin	--	No relevant interaction known/assumed			
Lacosamide	--	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/possible P-gp induction		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC [543]	SmPC	SmPC	SmPC
Pregabalin	--	No relevant interaction known/assumed			
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction/inhibition				Ref 544
Zonisamide	CYP3A4 competition; weak P-gp inhibition	No relevant interaction known/assumed (SmPc)			

Table 8: Anticipated effects of common herbal medicines on non-vitamin K antagonist oral anticoagulants plasma levels

Color coding is based on the respective NOAC SmPC, drug interaction databases, or expert opinion. The hatched color coding indicates no clinical or PK data available. Some of the color codes will likely require adaptation as more data become available over time.

Major limitations regarding the assessment of NOACs - herbal drug interactions include the possibility of several hypothetical pharmacokinetic and pharmacodynamic pathways, unknown mechanisms of interaction, and the inherent variation in composition.

White: No relevant drug–drug interaction anticipated.

Yellow: Caution required, especially in case of polypharmacy or in the presence of ≥2 yellow / bleeding risk factors (see Figure 6).

Blue (dark): Contraindicated / not advisable due to reduced NOAC plasma levels.

Where no data or SmPC instructions were available, expert opinion was generally based on the following principles:

- Strong CYP3A4 and/or P-gp inducer — should not be used (dark blue).
- Mild CYP3A4 and/or P-gp inducers or inhibitors or pharmacodynamic interaction — caution is needed especially with polypharmacy or in the presence of ≥ 2 bleeding risk factors (yellow).

	Via [545, 546; 547]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Curcumin	P-gp inhibition				
Echinacea purpurea	Mild CYP3A4 inhibition				
Garlic	Mild CYP3A4 inhibition; anticoagulation / antiplatelet effect				
Ginger	Anticoagulation / antiplatelet effect				
Ginkgo biloba	P-gp inhibition; anticoagulation / antiplatelet effect				
Ginseng	Anticoagulation / antiplatelet effect				
Green Tea	P-gp inhibition; anticoagulation / antiplatelet effect				
Horse chestnut	Anticoagulation / antiplatelet effect				
St. John's wort	P-gp/ BCRP and CYP3A4 induction	Should be avoided (per SmPc)	"With caution" (per SmPc)	"With caution" (per SmPc)	Should be avoided (per SmPc)
Valerian	Mild CYP3A4 inhibition				

Table 9: Anticipated effects of Medications used in the treatment of Covid-19 on non-vitamin K antagonist oral anticoagulants plasma levels

Color coding is based on the respective NOAC SmPC, drug interaction databases, or expert opinion. The hatched color coding indicates no clinical or PK data available. Some of the color codes will likely require adaptation as more data become available over time.

Major limitations regarding the assessment of NOACs - herbal drug interactions include the possibility of several hypothetical pharmacokinetic and pharmacodynamic pathways, unknown mechanisms of interaction, and the inherent variation in composition.

White: No relevant drug–drug interaction anticipated.

Yellow: Caution required, especially in case of polypharmacy or in the presence of ≥2 yellow / bleeding risk factors (see Figure 6).

Orange: Consider avoiding concomitant use, careful monitoring required if combined. See Figure 6.

Red: Contraindicated/not advisable due to increased NOAC plasma levels.

Pink: No information retrievable

Where no data or SmPC instructions were available, expert opinion was generally based on the following principles:

- Strong CYP3A4 and/or inhibitor — should not be used (red).
- Moderate CYP3A4 and/or P-gp inhibitor — use with caution or avoid (orange)
- Mild CYP3A4 and/or P-gp inducers or inhibitors — caution is needed especially with polypharmacy or in the presence of ≥ 2 bleeding risk factors (yellow).

[a] The use of NOACs is not advisable when atazanavir is given in combination with its enhancers ritonavir or cobicistat

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Azithromycin	P-gp inhibition	No PK data	No PK data	No PK data (no dose reduction required by label)	No PK data
Atazanavir	CYP3A4 inhibition	No PK data[a]	No PK data[a]	No PK data[a]	No PK data[a]
Lopinavir / Ritonavir	P-gp and BCRP inhibition or induction; CYP3A4 inhibition	No PK data	No PK data	No PK data	+153% (ritonavir) [94]
Darunavir / Cobicistat	CYP3A4 inhibition, P-gp and BCRP inhibition	SmPC	SmPC	SmPC	SmPC
Ribavirin	--				
Remdesivir	--				
Favipiravir	--				
Bevacizumab	--				
Eculizumab	--				
Tocilizumab	--				
Fingolimod	--				
Interferon	--				
Pirfenidone	--				
Methylprednisolone	--				
Nitazoxanide	--				

Table 10: Criteria for diagnosing CKD; estimation of renal function and categories of renal dysfunction

Decreased GFR*	- GFR <60 mL / min / 1.73m^2		
Markers of kidney damage (≥1)	- Excessive albuminuria (AER ≥30 mg/24h; 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 ***	**Description**
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)

*** [ml/min/1.73m^2]**

Estimation of renal function in NOAC patients best by Creatinine Clearance (Cockcroft-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.

Table 11: Plasma levels and coagulation assays in patients treated with NOACs for stroke prevention in AF

	Dabigatran [548, 549] (Phase II)	Apixaban[550] (SmPc)	Edoxaban[98, 100] (Phase III)	Rivaroxaban[519, 520, 551] (Phase I-II)
Expected plasma levels of NOACs in patients treated for AF (5-95% percentiles, [ng/ml])				
Peak levels	64 - 443	91 - 321	50 - 288	178 - 343
Trough levels	31 - 225	41 - 230	5 - 43	12 - 137
Expected impact of NOACs on routine coagulation tests[148, 150, 158, 549, 552-554]				
PT	(↑) at peak (↑) if supratherapeutic[149]	(↑) at peak	↑ at therapeutic levels (if sensitive assay is used). Normal values do not exclude trough levels.	↑ at therapeutic levels (if sensitive assay is used). Normal values do not exclude trough levels.
aPTT	↑↑(↑) Normal values exclude supratherapeutic but not therapeutic levels.	(↑) at peak	(↑) at peak	(↑) at peak
ACT	↑(↑) Consistent with effect on aPTT.	(↑)	(↑)	(↑)
TT	↑↑↑↑ Normal values exclude presence of Dabigatran.	-	-	-

Table 12: Classification of elective surgical interventions according to bleeding risk

For each patient, individual factors relating to bleeding and thromboembolic risk need to be taken into account and be discussed with the operating physician and the patient (see Figure 13).

Minor risk interventions (i.e., infrequent bleeding and with low clinical impact)
Dental extractions (1-3 teeth), paradontal surgery, implant positioning, subgingival scalling / cleaning
Cataract or glaucoma intervention
Endoscopy without biopsy or resection
Superficial surgery (e.g., abscess incision; small dermatologic excisions, skin biopsy)
Pacemaker or ICD implantation (except complex procedures)
Electrophysiological study or catheter ablation (except complex procedures)
Routine elective coronary / peripheral artery intervention (except complex procedures)
Intramuscular injection (e.g., vaccination)
Low risk interventions (i.e., infrequent bleeding or with non-severe clinical impact)
Complex dental procedures
Endoscopy with simple biopsy
Small orthopedic surgery (foot, hand, arthroscopy, …)
High risk interventions (i.e., frequent bleeding and / or with important clinical impact)
Cardiac surgery
Peripheral arterial revascularization surgery (e.g., aortic aneurysm repair, vascular bypass)
Complex invasive cardiological interventions, including lead extraction, (epicardial) VT ablation, chronic total occlusion PCI etc.
Neurosurgery
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Complex endoscopy (e.g., multiple / large polypectomy, ERCP with sphincterotomy etc.)
Abdominal surgery (incl. liver biopsy)
Thoracic surgery
Major urologic surgery / biopsy (incl. kidney)
Extracorporeal shockwave lithotripsy
Major orthopedic surgery

Table 13: NOAC use in frail patients

The 'Canadian Study of Health and Aging' (CHSA) Clinical Frailty Scale, based on comprehensive geriatric assessment including structured interview (http://www.csha.ca and Ref.[338])

The decision to anticoagulate frail patients depends on multiple aspects (see text for details). While fit or mild frailty per se generally does not pose a problem (green), severe frailty and terminal illness typically indicate a contraindication to anticoagulation (red).

Very Fit	People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.
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.
Managing Well	People whose medical problems are well controlled but are not regularly active beyond routine walking.
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.
Mildly Frail	These people often have more evident slowing and need help in high order with ADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.
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.
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).
Very Severely Frail	Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.
Terminally Ill	Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Table 14: Examples of falls risk assessment

A) High risk of falls* [1]

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 [#] [2]

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 10s	Yes / No			
Alternate step test 10s	Yes / No			
Sit to stand 12s	Yes / No			
Score:	**0-1**	**2-3**	**4-5**	**6+**
Probability of fall per year	7%	13%	27%	49%

Multidisciplinary team approach, including formal geriatric assessment recommended.

***adapted from** Steffel J, Giugliano RP, Braunwald E, Murphy SA, Mercuri M, Choi Y, Aylward P, White H, Zamorano JL, Antman EM, Ruff CT. Edoxaban Versus Warfarin in Atrial Fibrillation Patients at Risk of Falling: ENGAGE AF-TIMI 48 Analysis. J Am Coll Cardiol. 2016 Sep 13; 68(11):1169-1178.[70]

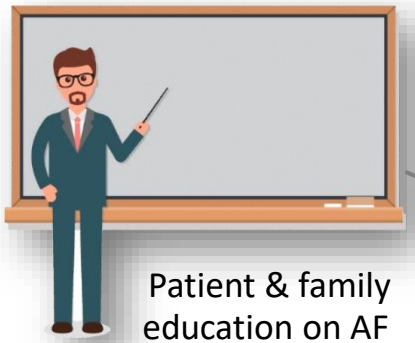
[#] **adapted from** Tiedemann A, Lord SR, Sherrington C. the development and validation of a brief performance-based fall risk assessment tool for use in primary care. J Gerontol A Biol Med Sci 2010; Aug;65(8):896-903 doi;10.1093/Gerona/glq067.[555]

Table 15: Maintenance warfarin dosing for out-of-therapeutic-range international normalized ratio

Suggested dose adjustment in case of out-of-therapeutic-range INR.[556] Importantly, dosing is optimized not using daily dose adjustments but adjustments based on the weekly intake in warfarin.

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

Fig. 1: Measures to optimize adherence to NOACs



Patient & family education on AF and anticoagulation

Involvement of family members

Prespecified follow-up

Optimal adherence

Pharmacy database

Once vs. twice daily regimens

(Remote) electronic monitoring

Technology aids

Pill organizer & medication boxes (+/- intake logbook)

Fig. 2: EHRA universal NOAC card

Atrial Fibrillation Oral Anticoagulation Card
for Non-Vitamin K Antagonist Oral Anticoagulants (NOACs)

Name of patient:

_____

Date of Birth:_____

Address:_____

_____

Oral anticoagulant:

_____

Dosing:_____

Timing:_____

With or without food:_____

Started on:_____

Physician or clinic coordinating NOAC treatment

Name of physician:

_____

Address:_____

_____

Tel. :_____

Emergency information

In case of an emergency, please contact the relative(s) of the patient or the following person:

Name: _____

Tel. :_____

Name: _____

Tel. :_____

Important patient instructions

- A NOAC reduces the risk of dangerous blood clots which may cause a stroke.
- Not taking the drug means no protection
- Take your drug exactly as prescribed (once or twice daily).
- Do not skip a prescribed dose or stop your medication without consulting your physician.
- After a trauma or bleeding event, consult with your physician regarding further management
- If you experience any side effects consult your prescribing physician
- Do not add any additional medication without consulting your physician, not even short-term painkillers which are available without prescription.
- Alert your dentist, surgeon or other physician before an intervention.

It is important to carry this card with you at all times. Please show this card to every physician, dentist, pharmacist or other healthcare provider.

What to do in certain situations

When should I contact a healthcare provider?
Bleeding is the most common side effect of an anticoagulant. Contact your healthcare provider if you have any signs or symptoms of bleeding such as:

- Unusual bruising, nosebleeds, bleeding of gums, bleeding from cuts that take a long time to stop
- Menstrual flow or vaginal bleeding that is heavier than normal
- Blood in urine, red or black stools
- Coughing up blood or vomiting blood
- Dizziness, paleness or weakness

What should I do if I missed a dose?

- Twice daily NOAC: Take missed dose if within 6 hours, otherwise leave out
- Once daily NOAC: Take missed dose if within 12 hours, otherwise leave out

What if I accidently took two doses at the same time?

- Twice daily NOAC: you can opt to leave out the next planned dose and restart after 24 h.
- Once daily NOAC: you can continue the normal regimen without skipping a dose.

Information for healthcare providers

- NOACs act as a direct thrombin inhibitor (dabigatran) or direct factor Xa inhibitors (apixaban, edoxaban, rivaroxaban).
- Check contraindications for NOACs according to the local SmPc (e.g., mechanical heart valve; rheumatic mitral stenosis).
- Standard tests (such as INR, PT or aPTT) do not adequately reflect level of anticoagulation.
- For certain procedures, NOAC should be stopped in advance but without bridging (for timing see EHRA NOAC Practical Guide).

Information for healthcare providers
Blood sampling follow-up

- **Routine monitoring of anticoagulation level is not required**
- **Yearly:** Hb, renal and liver function
- **If ≥ 75 years or frail:** 6-monthly renal function
- **If CrCl ≤ 60 ml/min:** recheck interval in months = "CrCl:10" (e.g., every 4 months if CrCl = 40)
- **If intercurrent condition that may have impact:** renal and/or liver function

Date	Serum creatinine	Creatinine clearance	Hemo-globin	Liver tests

Planned or unplanned visits

Provide: date, site (GP, cardiologist, clinic, pharmacist,…) visits and to-dos or findings.

Concomitant medication

Name:	Dose:

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

_____

_____

Follow-up

Check each visit:
1. Adherence (pt. should bring remaining meds)
2. Thromboembolic events
3. Bleeding events
4. Other side effects
5. Co-medications / over-the-counter drugs
6. Need for blood sampling
7. Modifiable risk factors
8. Optimal NOAC and correct dosing

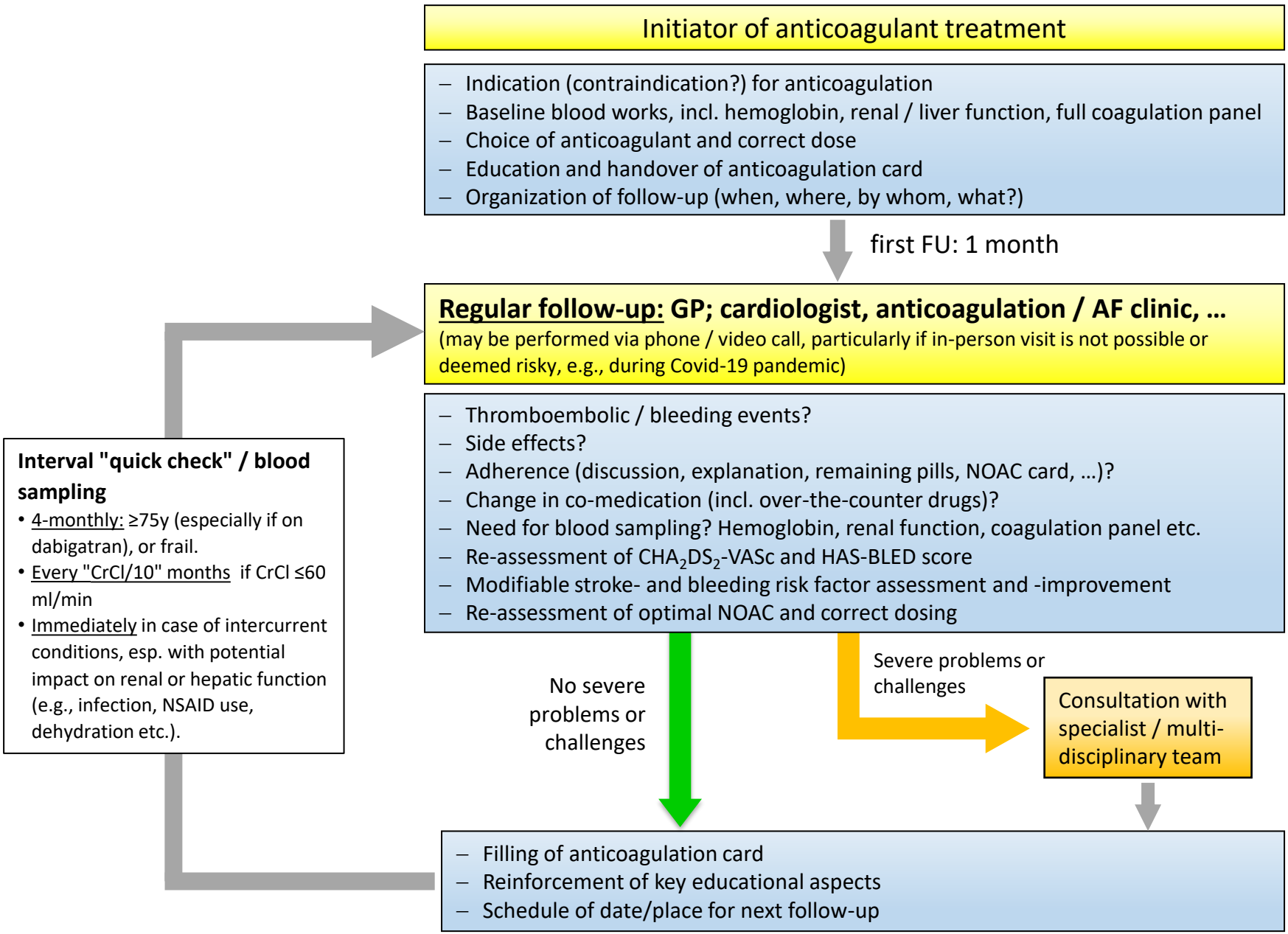
(see **www.NOACforAF.eu** for more information)

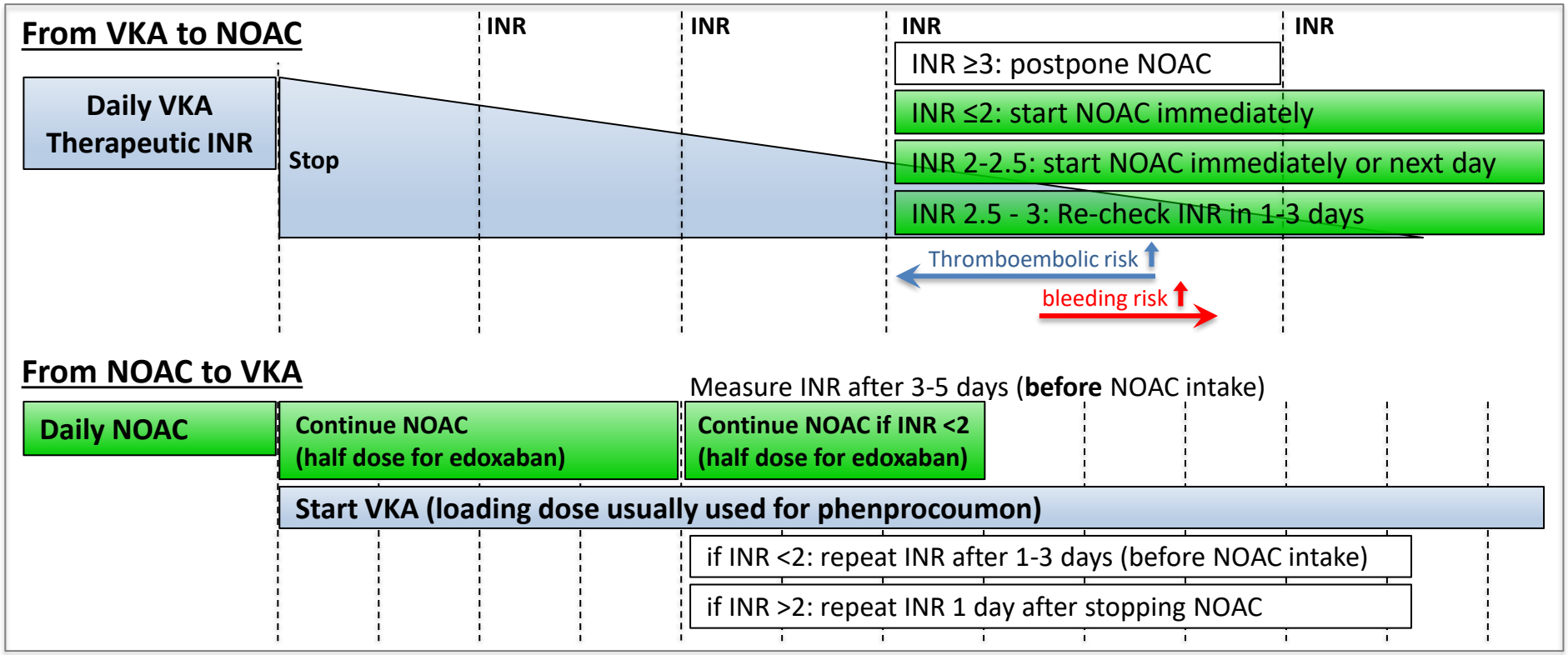
EUROPEAN Heart Rhythm ASSOCIATION

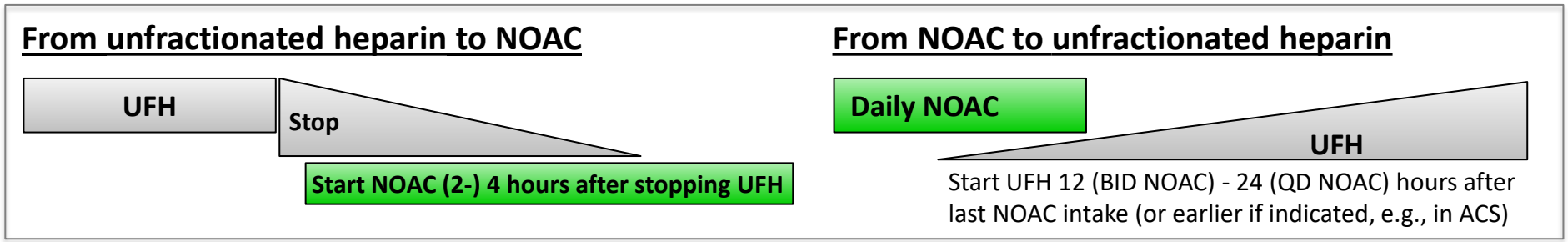
EUROPEAN SOCIETY OF CARDIOLOGY®

The full EHRA Practical Guide on the use of NOACs is available at:
www.NOACforAF.eu
www.noacforaf.eu

Fig. 3: Structured Follow-up for NOAC treated patients




From VKA to NOAC
INR
INR
INR
INR
Daily VKA
Therapeutic INR
Stop
INR ≥3: postpone NOAC
INR ≤2: start NOAC immediately
INR 2-2.5: start NOAC immediately or next day
INR 2.5 - 3: Re-check INR in 1-3 days
Thromboembolic risk
bleeding risk
From NOAC to VKA
Measure INR after 3-5 days (before NOAC intake)
Daily NOAC
Continue NOAC
(half dose for edoxaban)
Continue NOAC if INR <2
(half dose for edoxaban)
Start VKA (loading dose usually used for phenprocoumon)
if INR <2: repeat INR after 1-3 days (before NOAC intake)
if INR >2: repeat INR 1 day after stopping NOAC


From unfractionated heparin to NOAC
UFH
Stop
Start NOAC (2-) 4 hours after stopping UFH
From NOAC to unfractionated heparin
Daily NOAC
UFH
Start UFH 12 (BID NOAC) - 24 (QD NOAC) hours after
last NOAC intake (or earlier if indicated, e.g., in ACS)


From BID NOAC to QD NOAC
From BID NOAC to LMWH
From QD NOAC to BID NOAC
From QD NOAC to LMWH

Fig. 5: NOAC metabolism

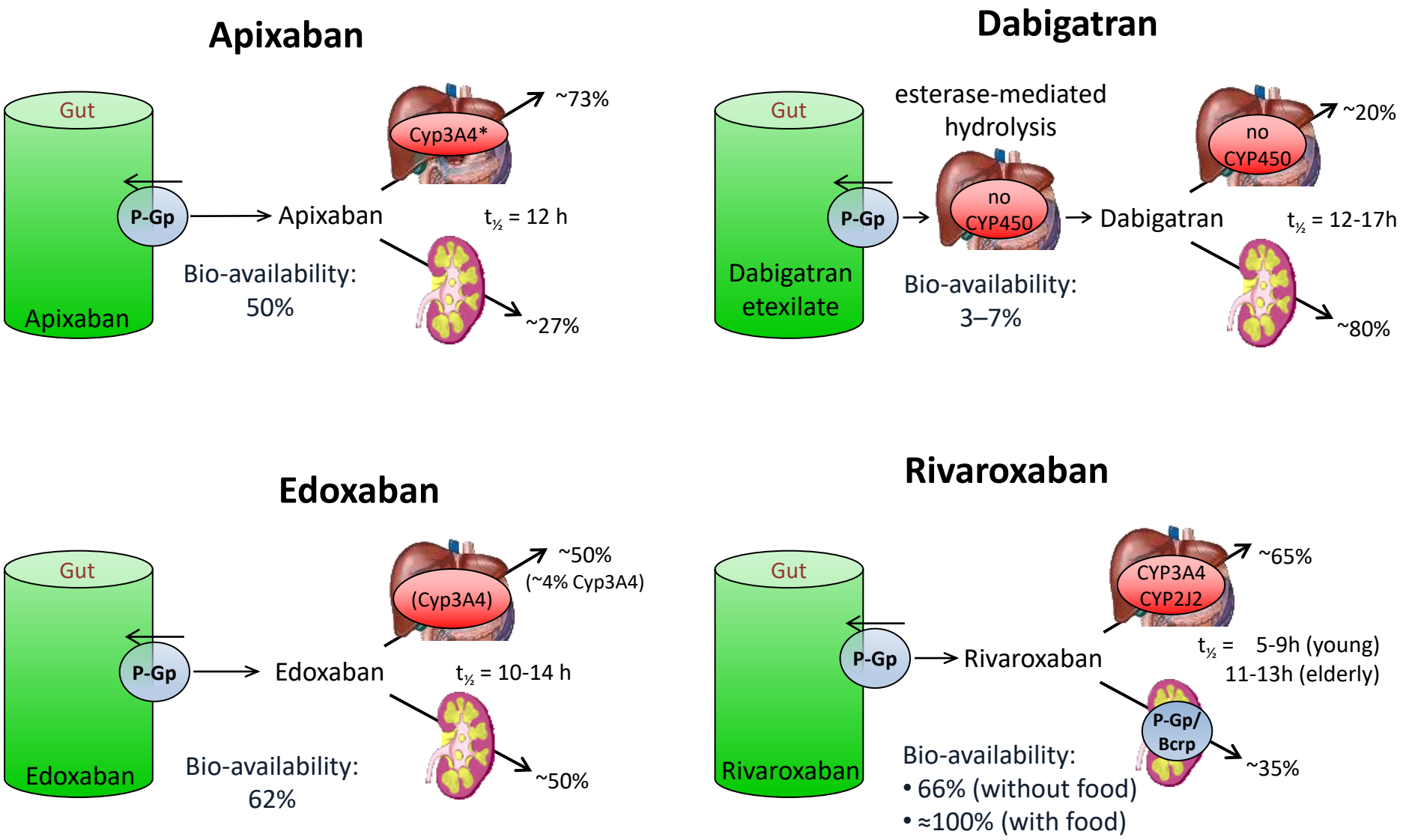


Fig. 6: Choosing a NOAC based on drug-drug interactions and / or risk of bleeding

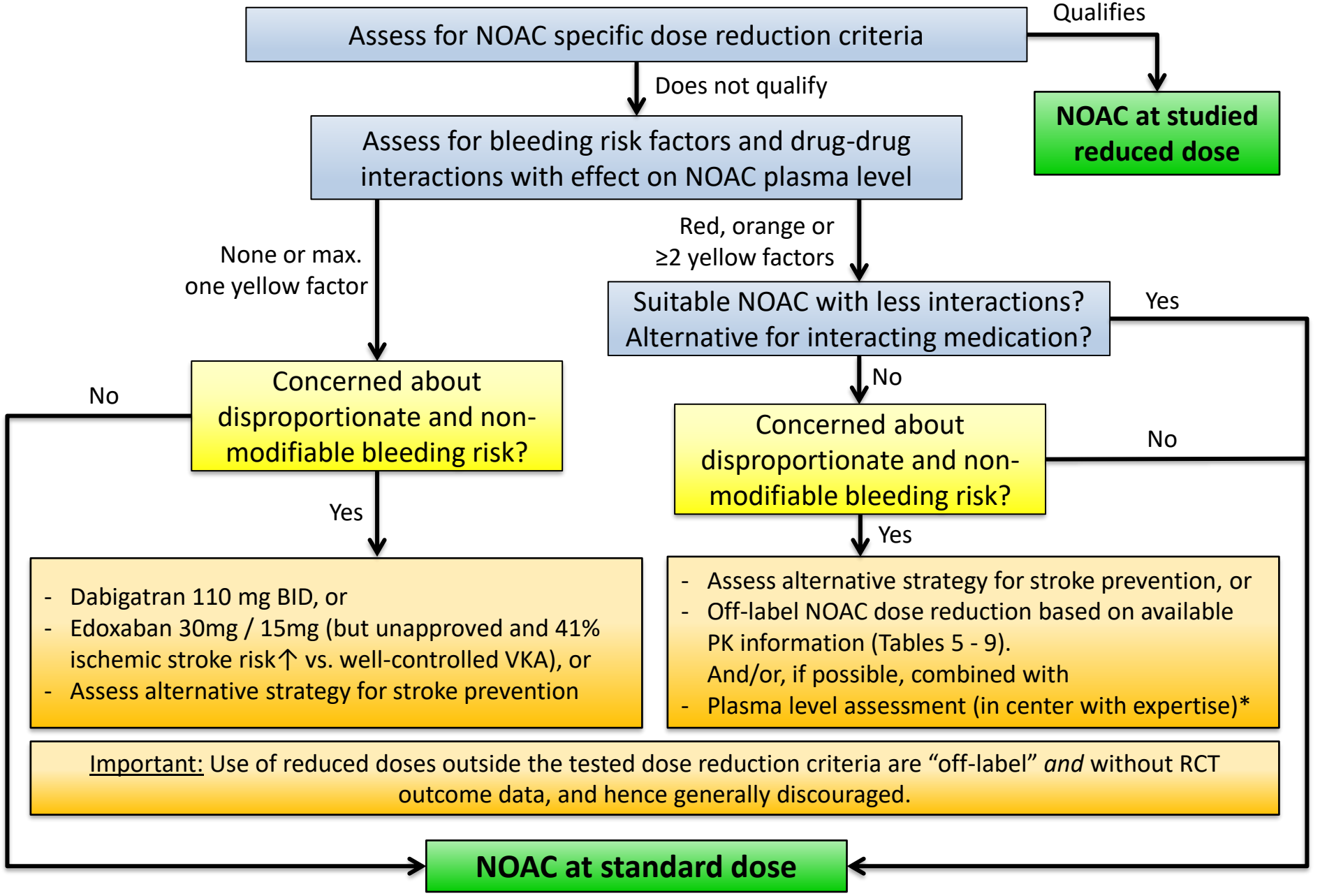


Fig. 7: NOACs in Chronic Kidney Disease

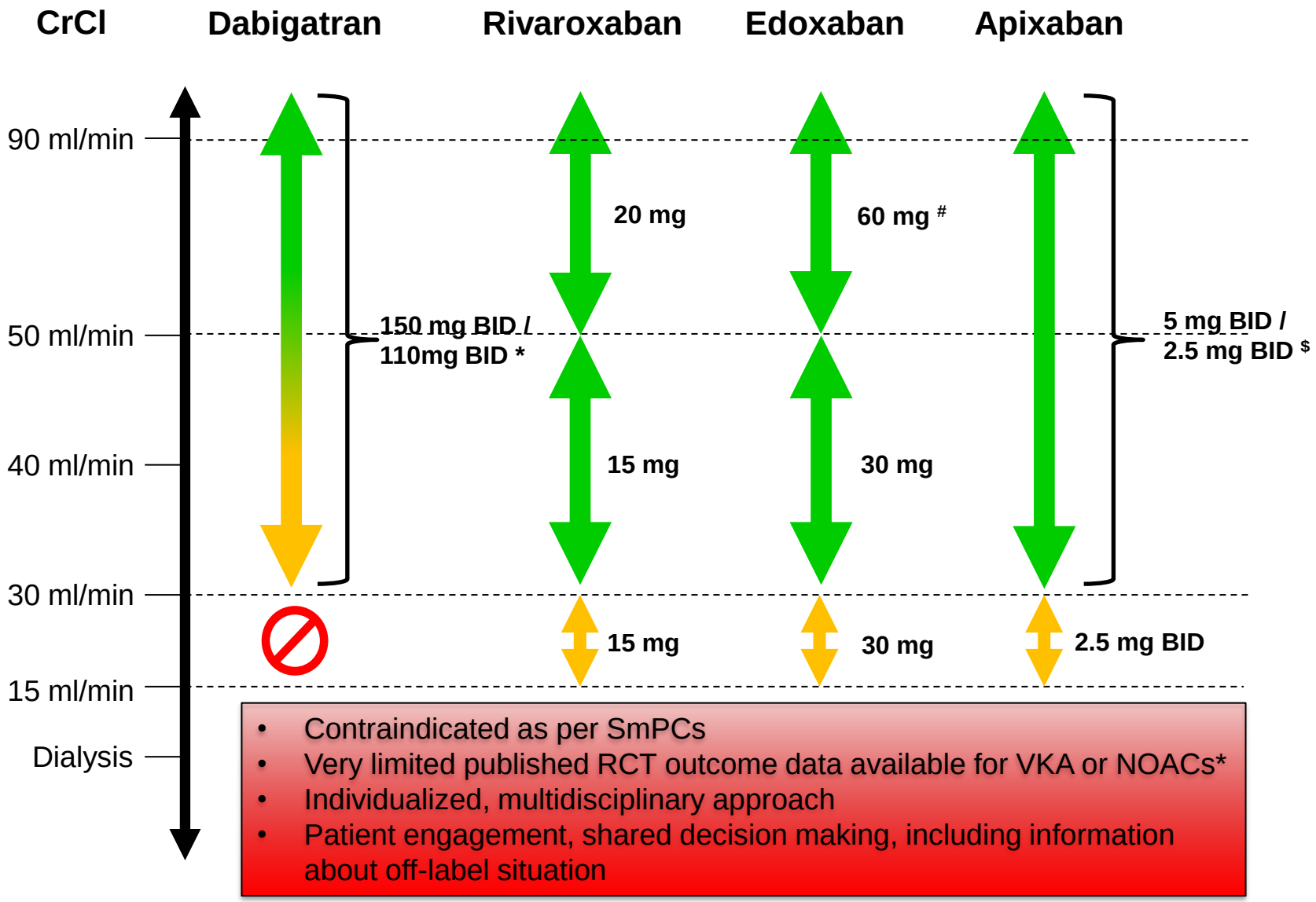


Fig. 8: NOAC in patients with liver disease

Baseline assessment:

- H/o thromboembolism or bleeding?
- Relevant co-medications and over-the-counter drugs?
- CBC, liver function test, PT/INR, APTT, renal function
- High bleeding risk (e.g., H/o major bleeding (varices), uncontrolled alcohol intake, etc.)?

Highest risk patients → Consider no anticoagulation / evaluate alternative stroke prevention strategy

All other patients

Parameter	1 point	2 points	3 points
Encephalo-pathy	No	Grade 1-2	Grade 3-4
Ascites	No	Mild	≥ Moderate
Bilirubin	< 2 mg/dL < 34 µmol/L	2-3 mg/dL 34-50 µmol/L	> 3 mg/dL > 50 µmol/L
Albumin	> 3.5 g/dL > 35 g/L	2.8-3.5 g/dL 28-35 g/L	< 2.8 g/dL < 28 g/dL
INR	< 1.7	1.71-2.30	>2.30

NOAC Use recommendations in liver disease

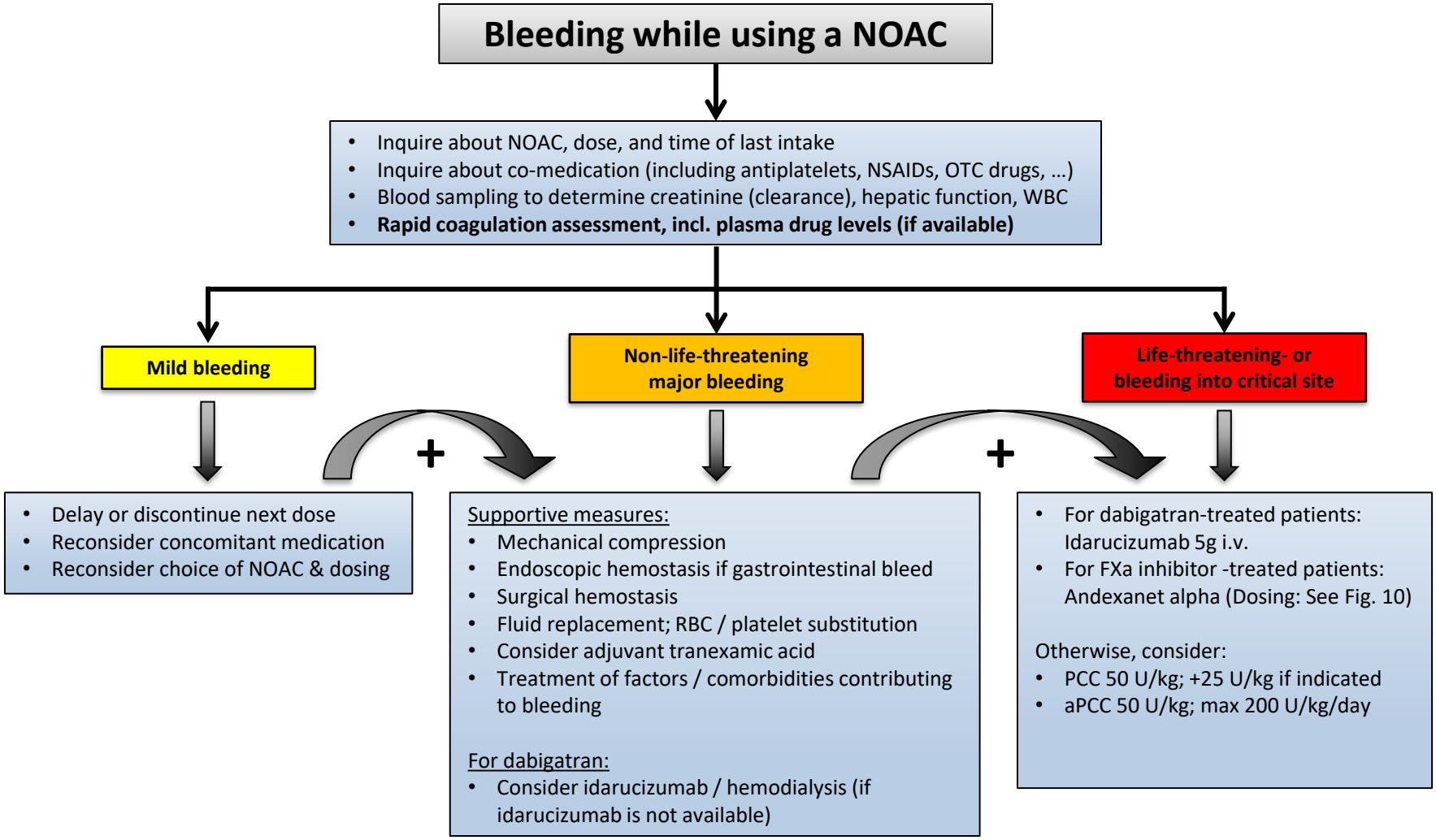
	A (<7 pts)	B (7-9 pts)	C (>9 pts)
Dabigatran	Normal dose	Use with caution	Not recommended
Apixaban			
Edoxaban			
Rivaroxaban		Not recommended	

- ✓ Assess Child-Pugh score
- ✓ Check NOAC use recommendations in liver disease
- ✓ Check for drug-drug interactions
- ✓ Discuss in multidisciplinary team

Close follow-up (see also Fig. 3)

- – Signs of (occult) bleeding?
- – Adherence? Side effects?
- – (New) co-medications, incl. NSAIDs, aspirin, OTC?
- – CBC, liver function, PT/INR, aPTT, renal function
- – Continue bleeding risk minimization strategies
- – Re-enforce education, incl. alcohol abstinence

Fig. 9: Management of bleeding while on NOAC



Post-bleeding management

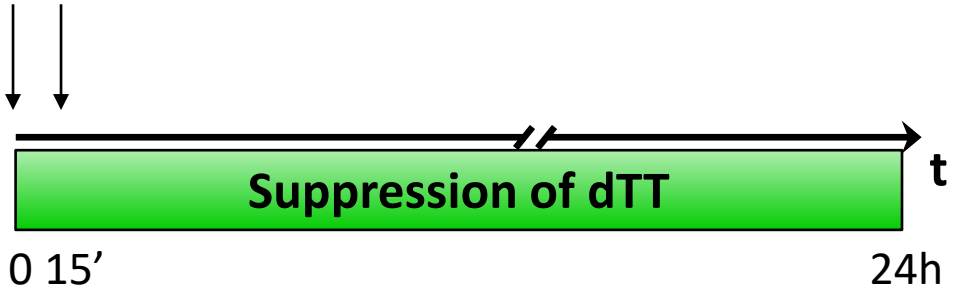
- Discuss impact of bleeding on patient's consideration of risks and benefits of anticoagulation
- Assess risk of repeat bleeding
- Re-evaluate modifiable bleeding risk factors
- Review correct choice and dosing of NOAC

→ **Re-initiate anticoagulation in the absence of absolute contraindication (shared decision making).**

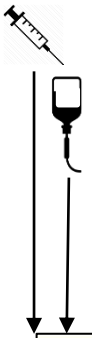
Fig. 10: Application of NOAC reversal agents

Application of Idarucizumab

5g i.v. in two consecutive infusions of 2.5g i.v. over 5-10 minutes each



Application of Andexanet Alpha



Last dose	Timing of last dose: < 8 hours#	Timing of last dose: ≥ 8 hours
Apix ≤ 5 mg / Riva ≤ 10 mg / Edo ≤ 30 mg	Low dose	Low dose
Apix > 5 mg / Riva > 10 mg / Edo > 30 mg	High dose	

Low dose:
- Bolus: 400mg (at 30 mg/min)
- Infusion: 4 mg/min (=480 mg)

High dose:
- Bolus: 800mg (at 30 mg/min)
- Infusion: 8 mg/min (=960 mg)

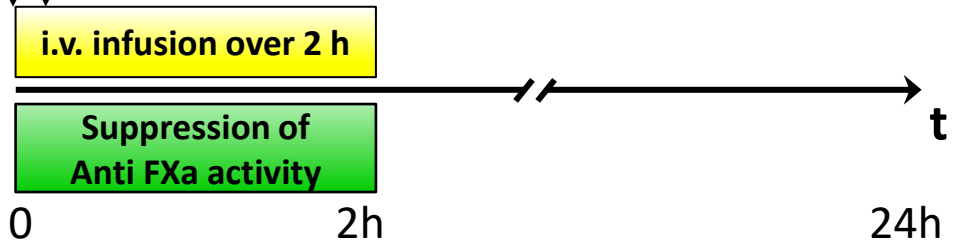


Fig. 11: Stroke prevention post GI bleeding

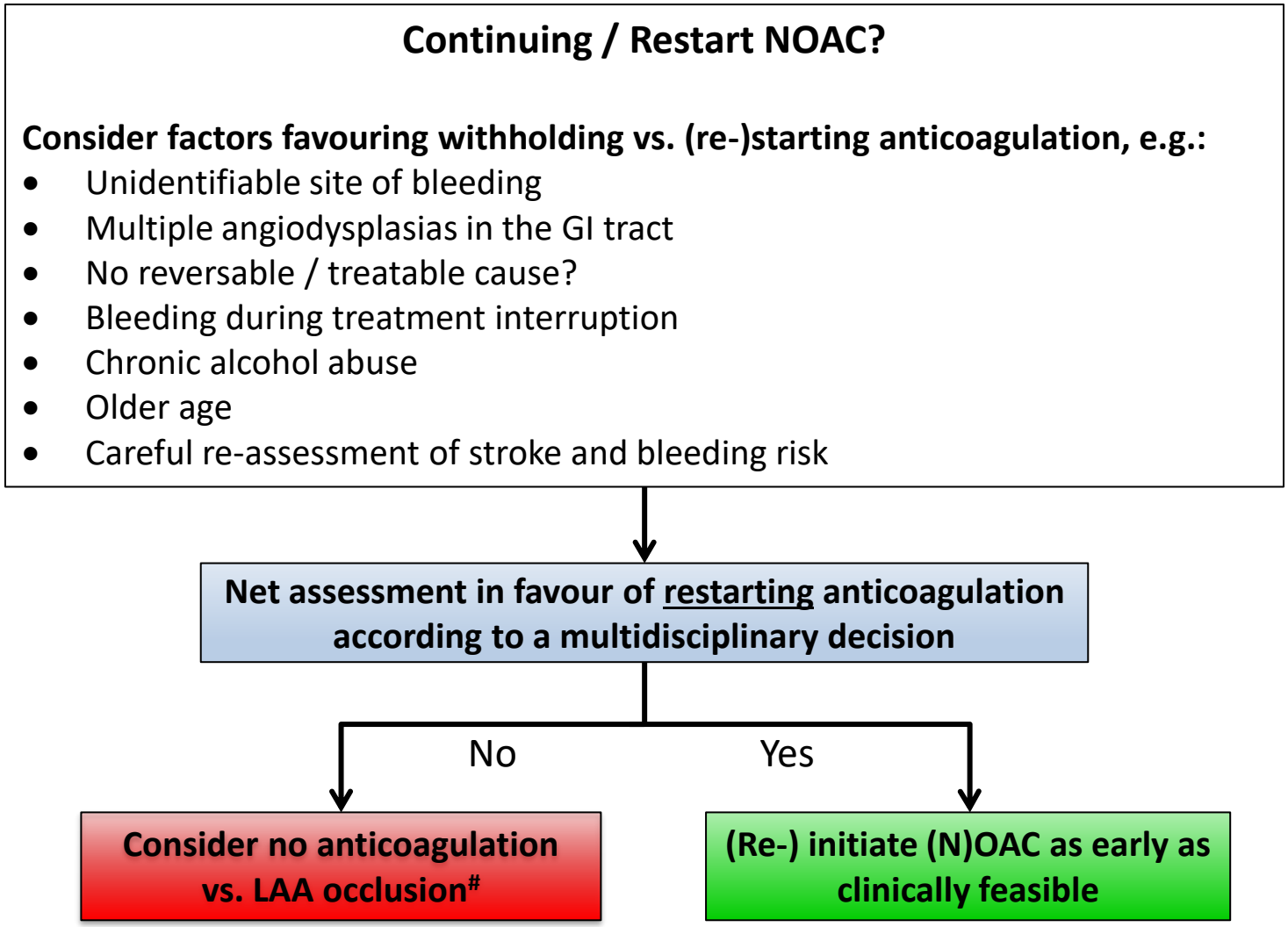


Fig. 12: Patient requiring unplanned surgery on NOAC

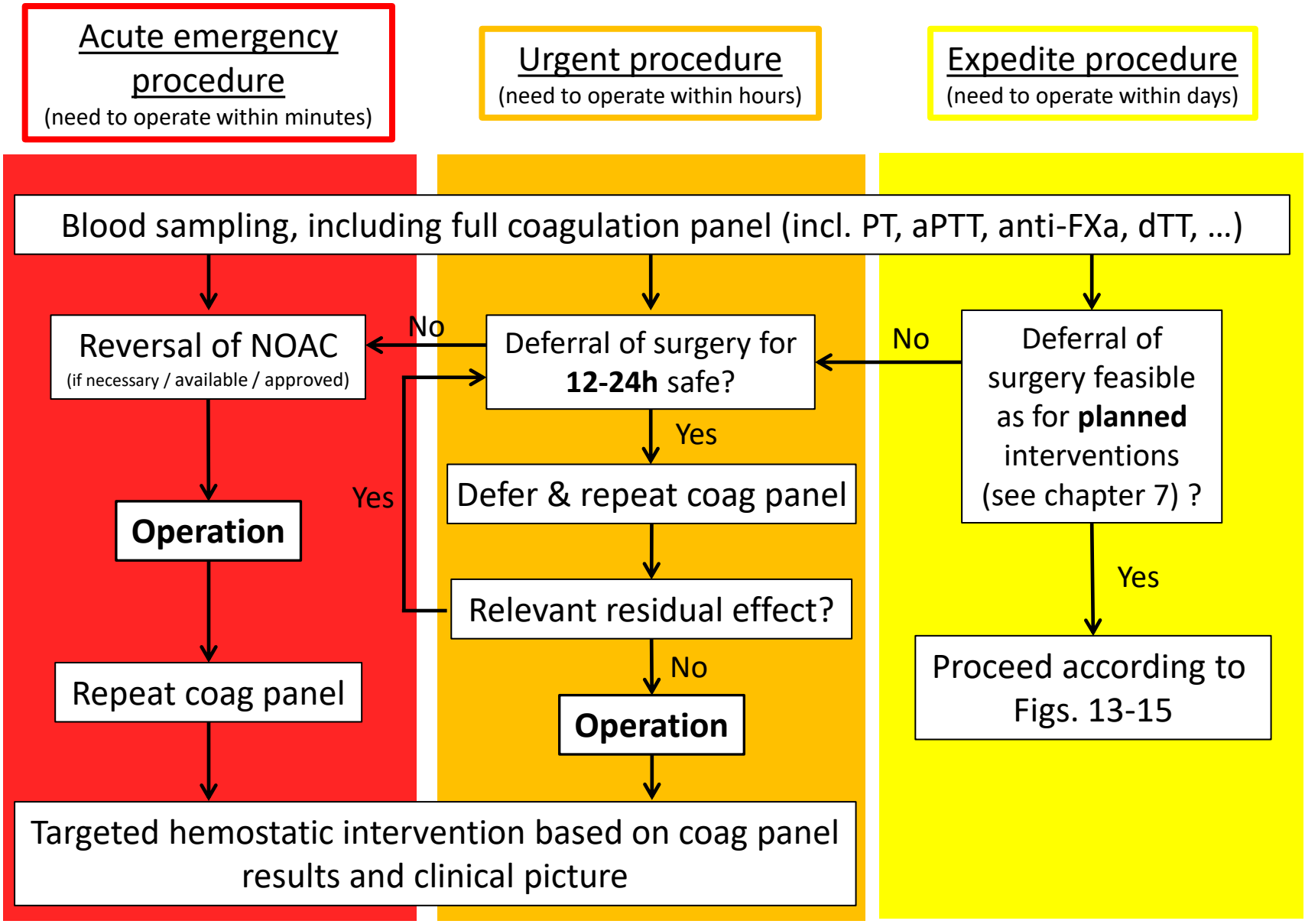


Fig. 13: Perioperative NOAC management

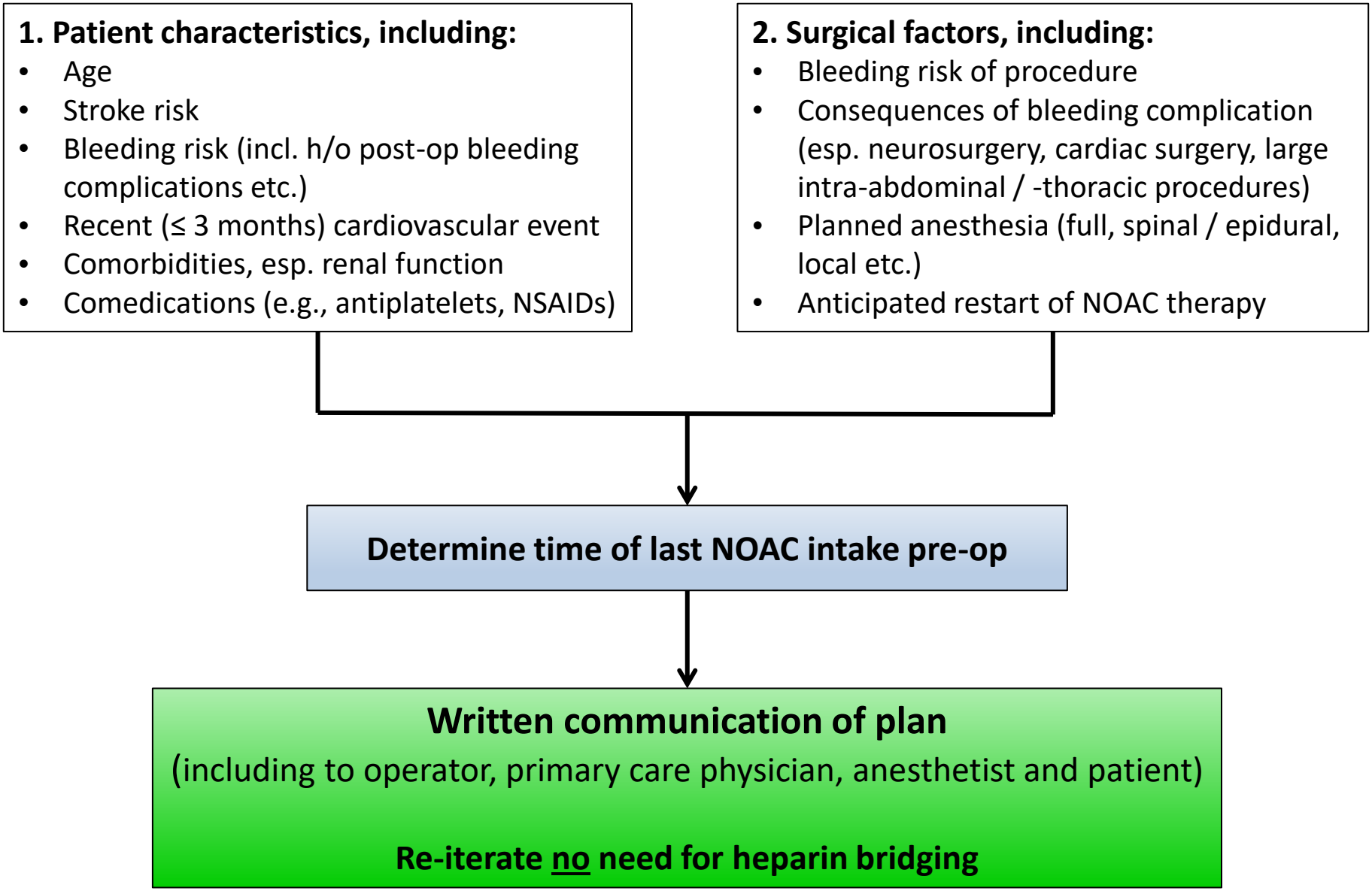


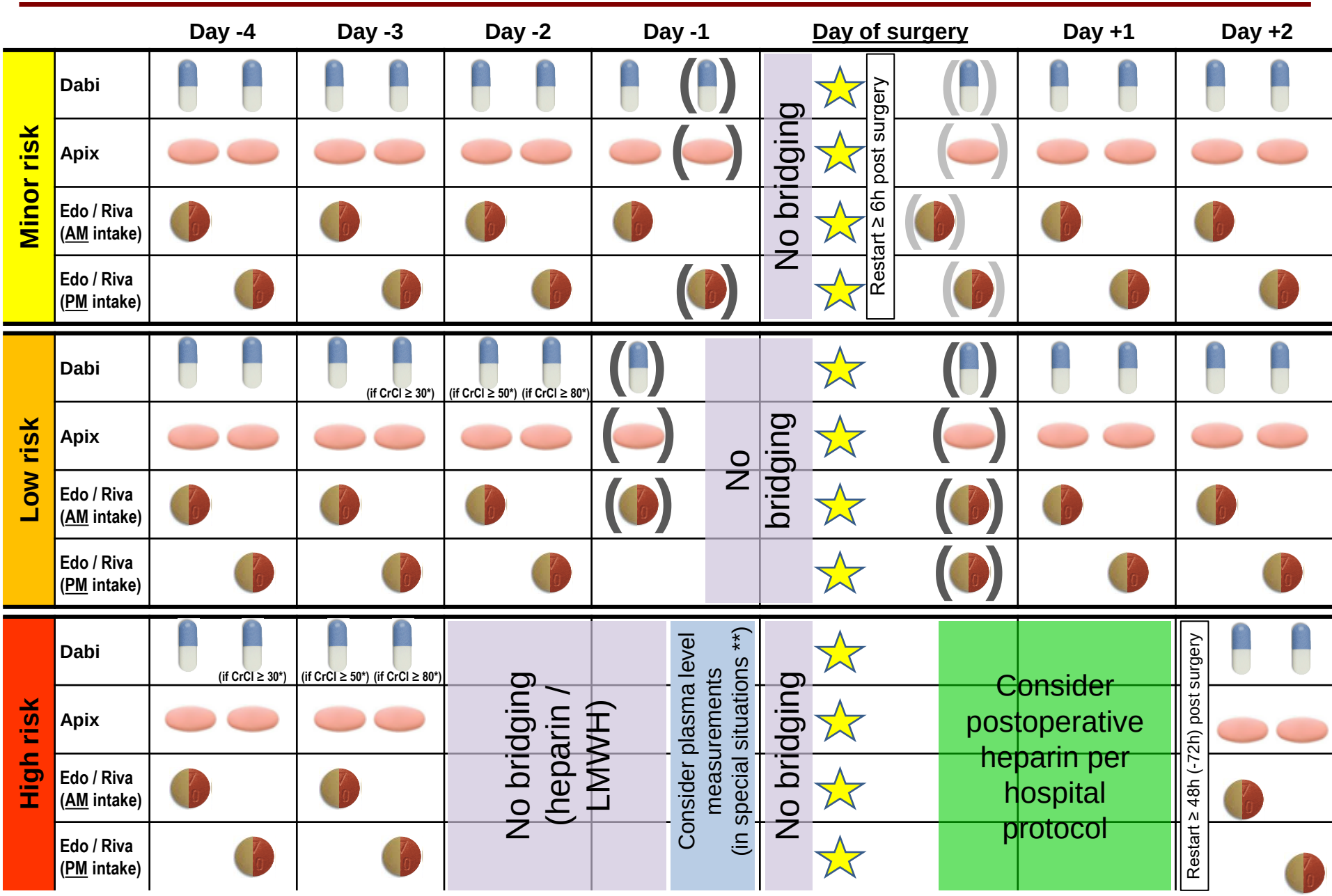
Fig. 14: Perioperative cessation of NOACs

	Dabigatran		Apixaban - Edoxaban - Rivaroxaban	
No perioperative bridging with LMWH / UFH				
Minor risk procedures: - Perform procedure at NOAC trough level (i.e., 12 h / 24 h after last intake). - Resume same day or latest next day.				
	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**		
CrCl 30-49 ml/min	**≥ 48 h**	**≥ 96 h**		
CrCl 15-29 ml/min	Not indicated	Not indicated	**≥ 36 h**	
CrCl <15 ml/min	No official indication for use			

Important:

- Timing of interruption may require adaptation based on individual patient characteristics (Fig. 13)
- In patients / situations with risk of NOAC accumulation (renal insufficiency, older age, concomitant medication, see Fig. 6) pausing the NOAC 12-24 hours earlier may be considered.[Add REF: PAUSE trial, EMIT]
- Resume full dose of NOAC 24h after low-risk- and 48 (-72) h after high-risk interventions

Fig. 15: Perioperative management on NOACs



Important: Timing of interruption may require adaptation based on individual patient characteristics (Fig. 13)

Fig. 16: Patient on NOAC undergoing AF ablation

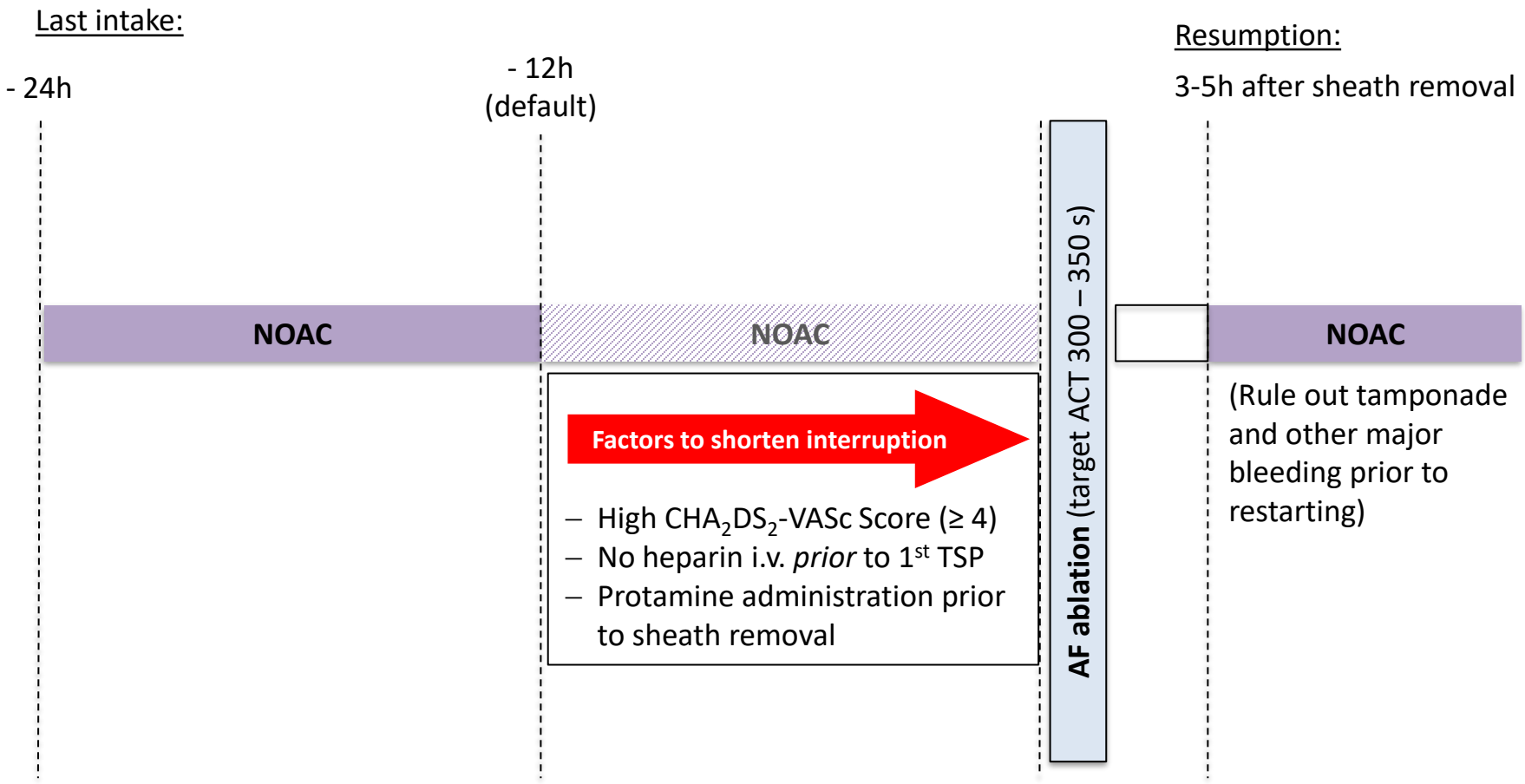
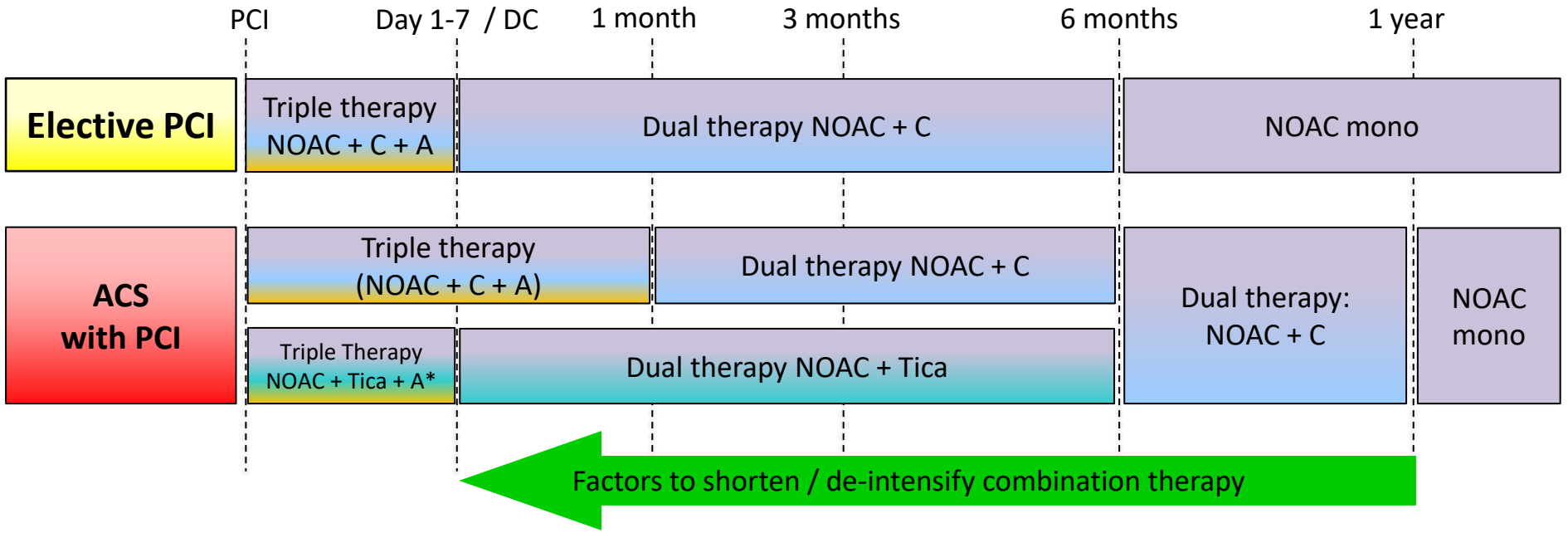


Fig. 17: Anticoagulation post PCI / ACS



- (Uncorrectable) high bleeding risk
- Low atherothrombotic risk (by REACH or SYNTAX score if elective; GRACE < 140 if ACS)

Factors to lengthen / intensify combination therapy

- High atherothrombotic risk (scores as above; stenting of left main, proximal LAD, proximal bifurcation; recurrent MIs; stent thrombosis etc.) and low bleeding risk

In all patients:

- Avoid use of BMS / first generation DES
- Use PPI if on triple (+ dual) therapy
- Minimize bleeding risk by assessing and treating modifiable bleeding risk factors (e.g., hypertension, etc.)
- Close follow-up; check for signs of (occult) bleeding

Fig. 18: AF patient on NOAC with ACS / elective stenting

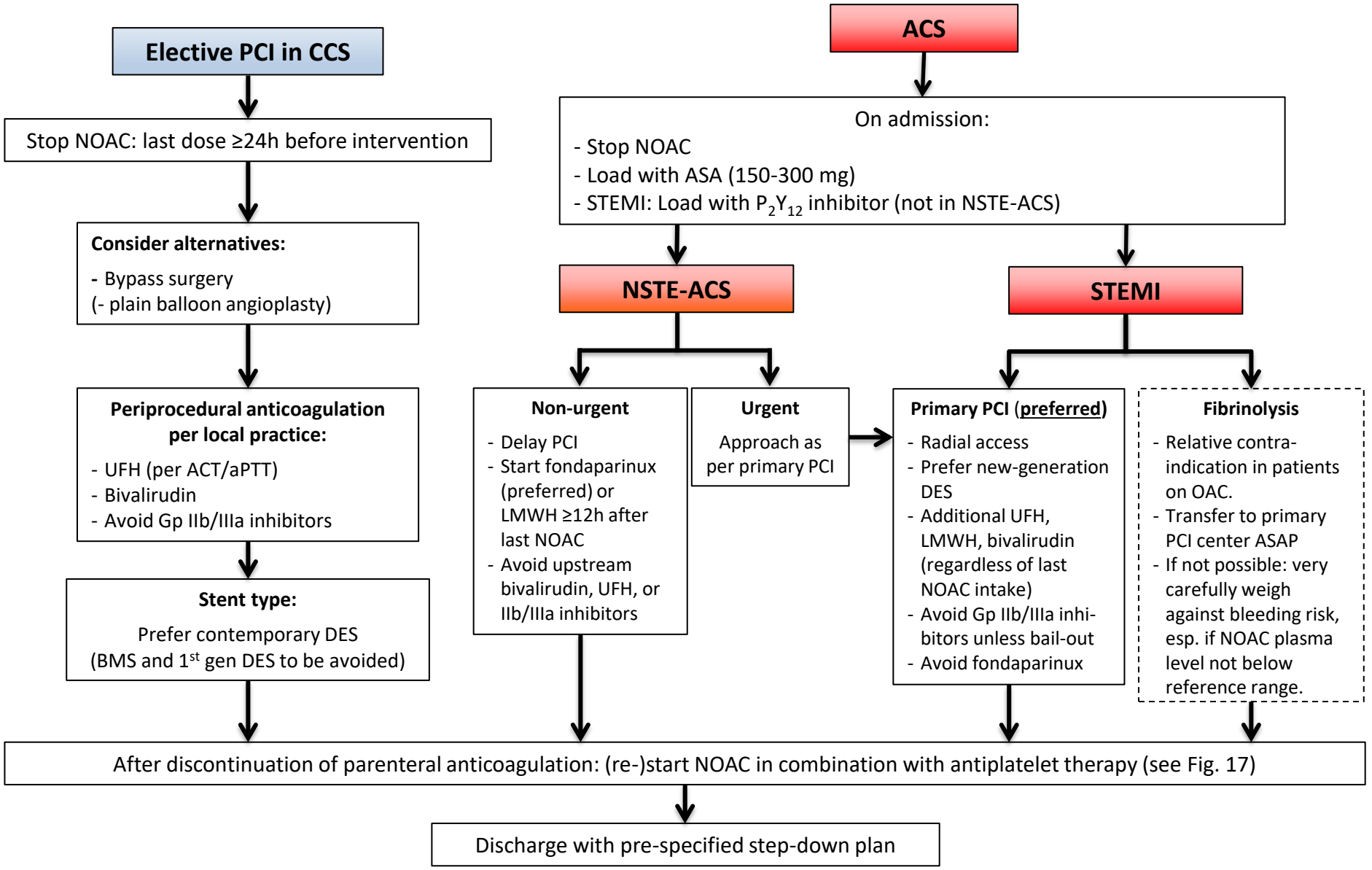


Fig. 19: Patient undergoing cardioversion

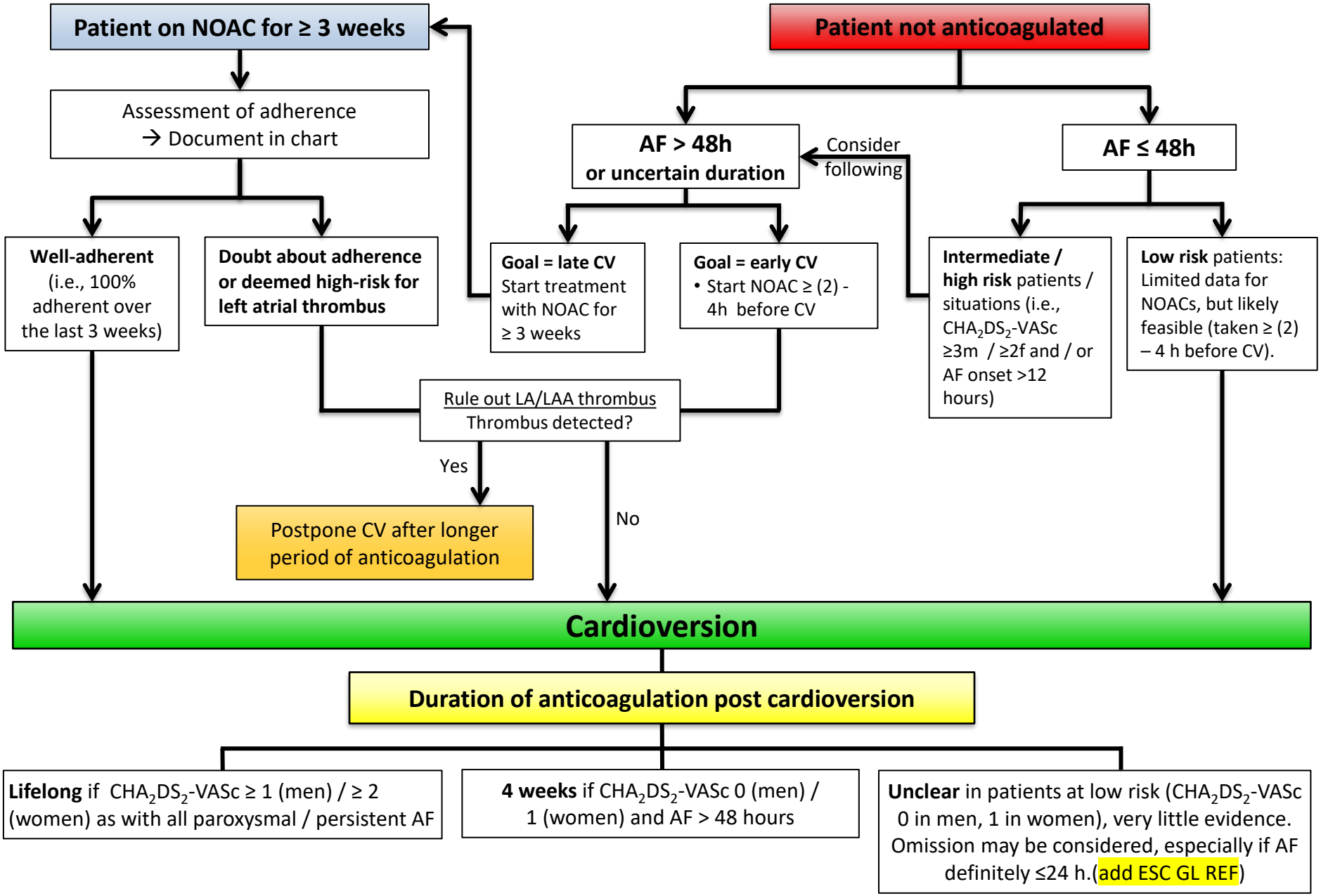


Fig. 20: Management of acute ischemic stroke with relevant neurological deficit on NOAC therapy

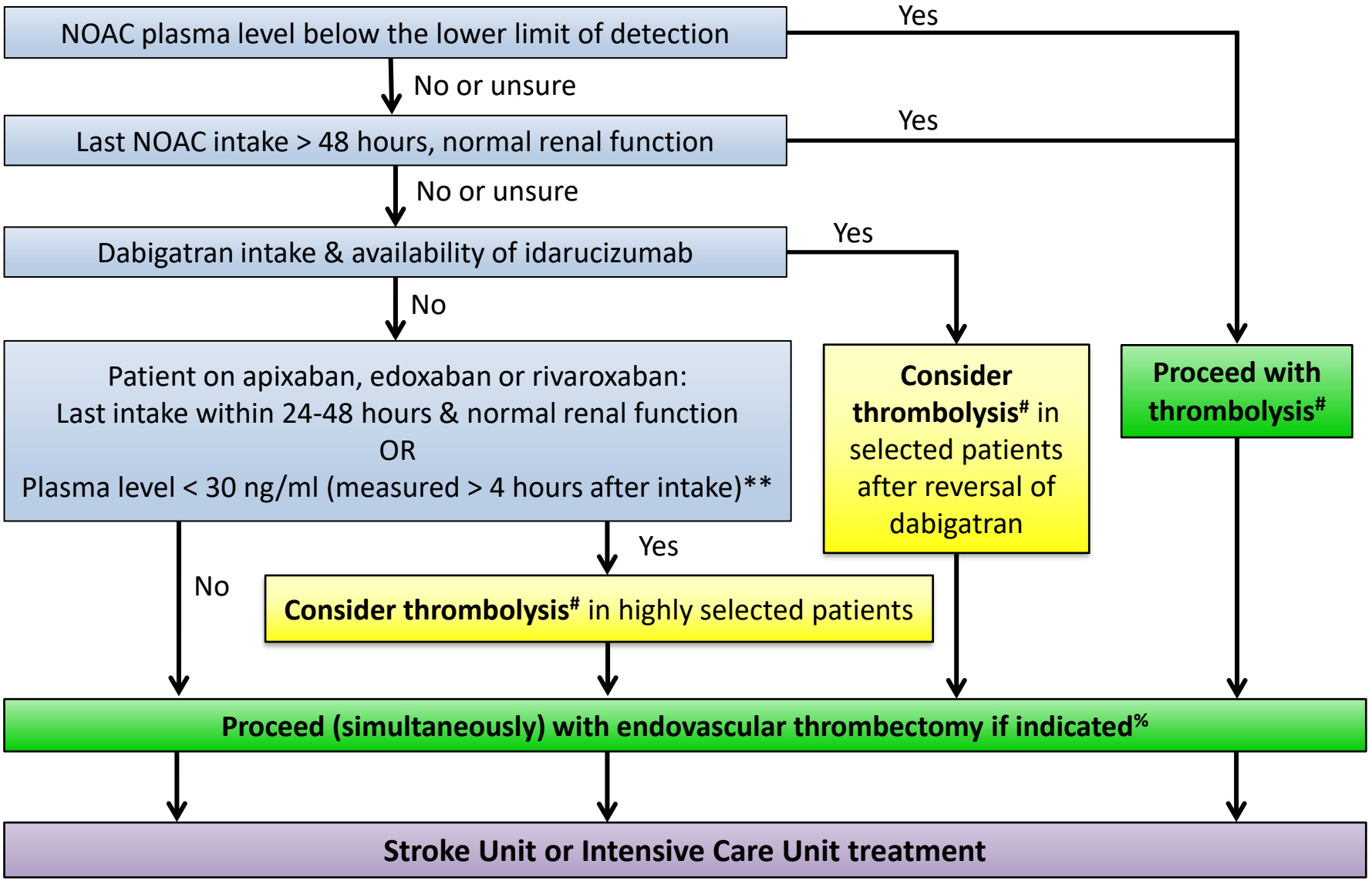
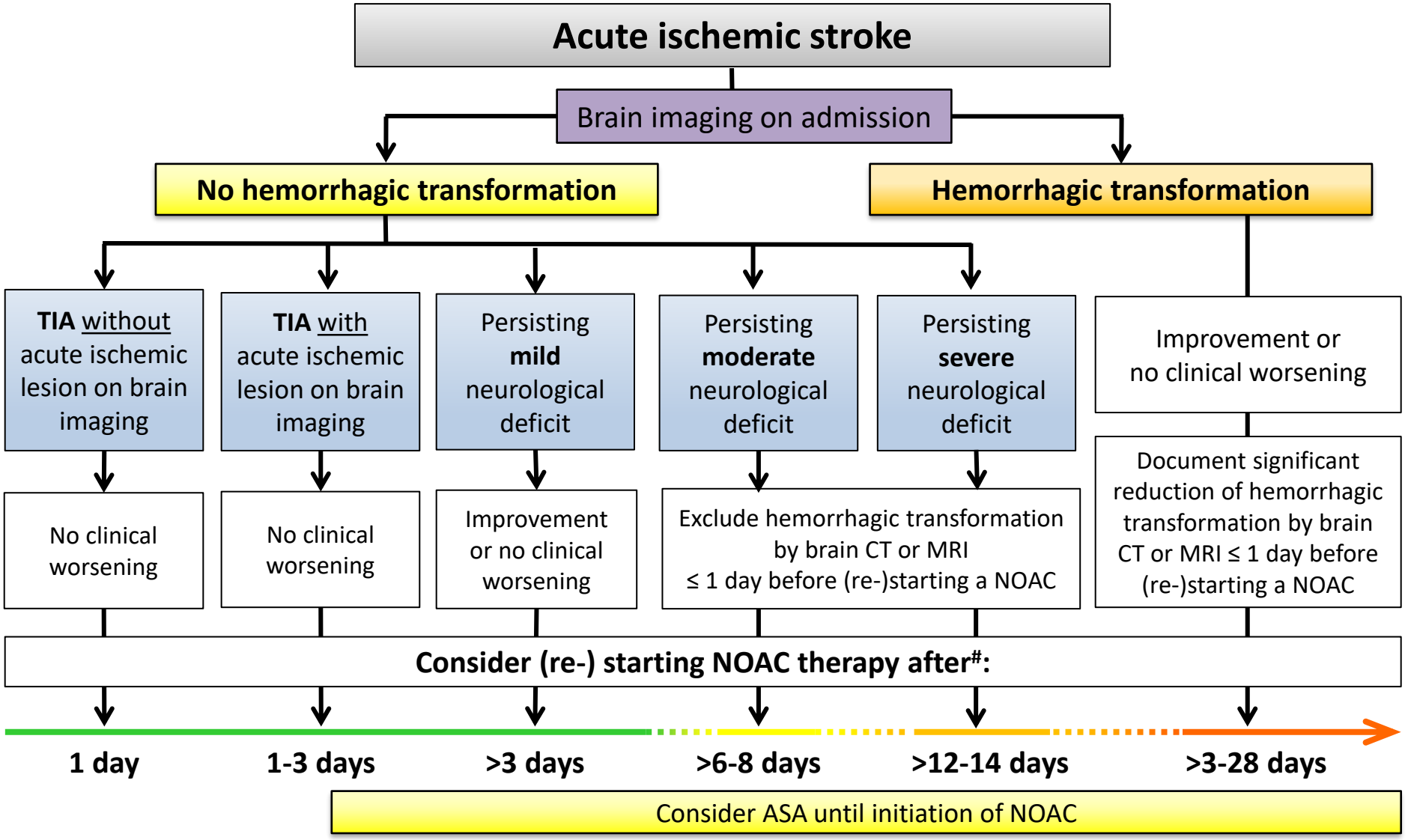


Fig. 21: (Re-)starting NOAC after acute ischemic stroke



Based on expert opinion! No RCT data available yet

Fig. 22: Patient post intracerebral haemorrhage

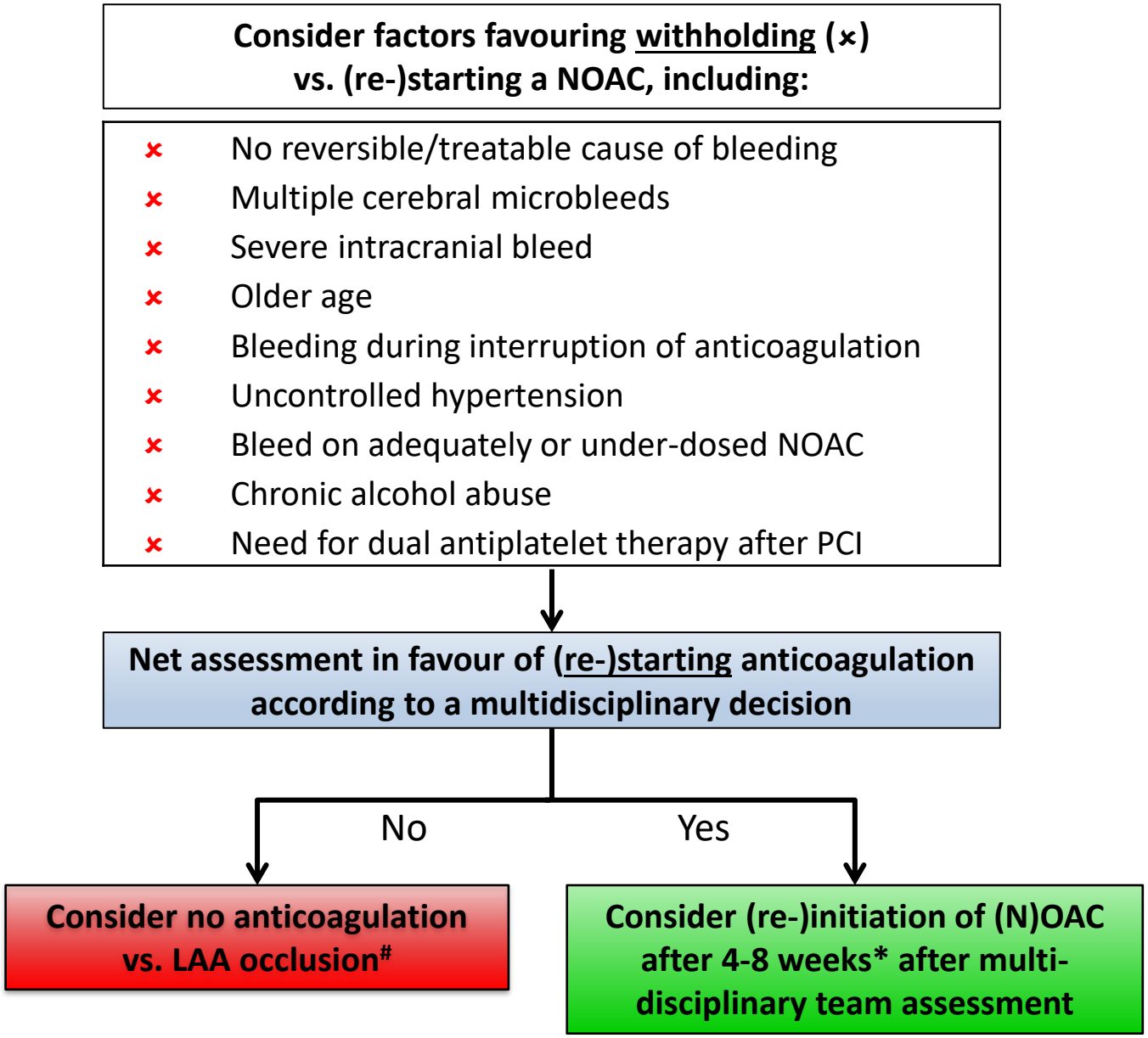


Fig. 23: NOACs in under- and overweight patients

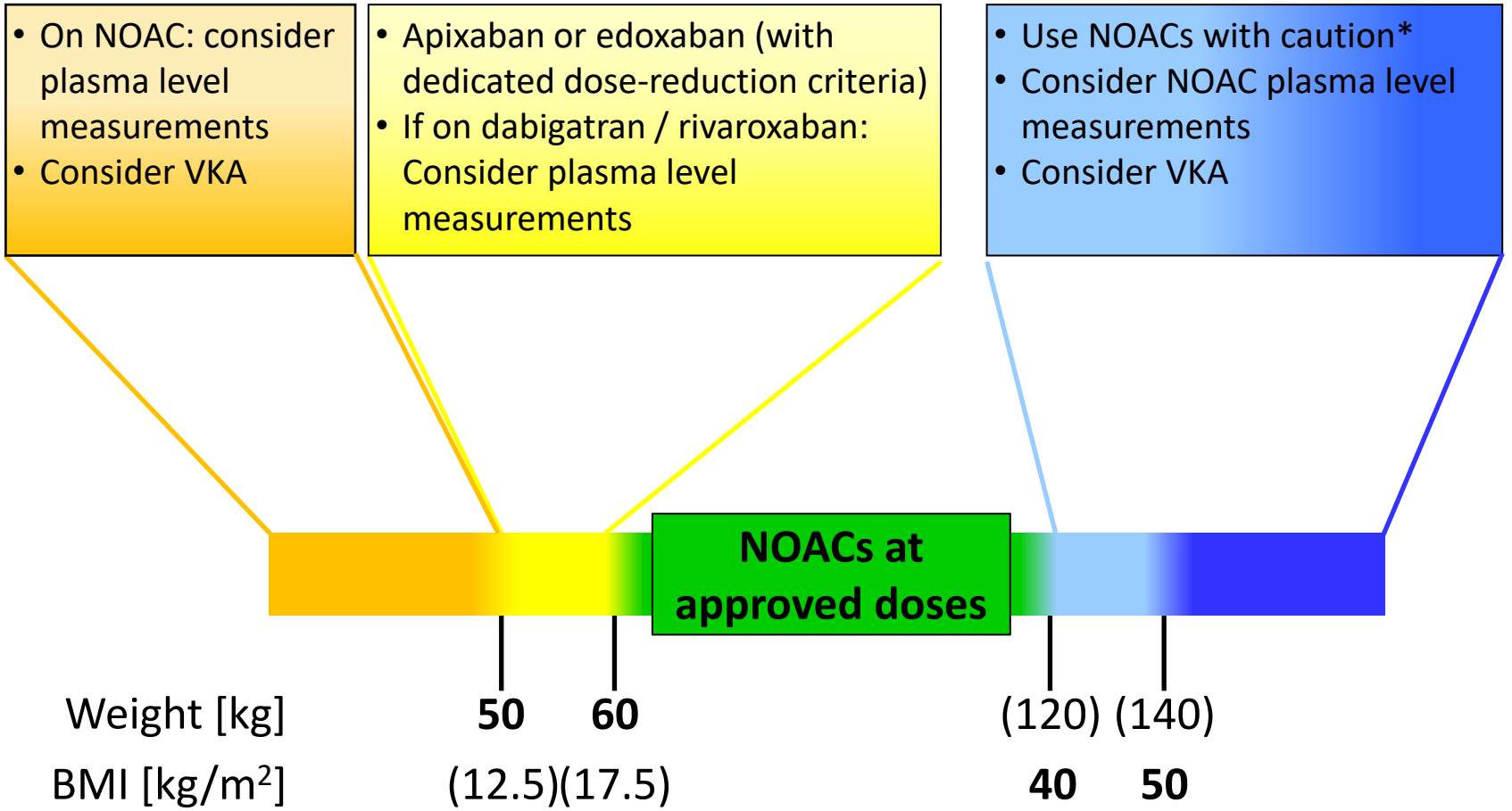


Fig. 24: NOACs in thrombocytopenia

1. Reason for thrombocytopenia?

- Decreased production (bone marrow disorder, liver disease)
- Chronic liver disease +/- hypersplenism
- Drug-induced (incl. HIT / HITT)
- Immune thrombocytopenia (ITP)
- Autoimmune disorders
- Others (incl. infection, alcohol, malignancy, pregnancy)

2. Platelet count and dynamics?

3. Bleeding risk?

- Recent major bleeding
- H/o hematopoietic stem cell transplant
- Coagulation abnormalities
- Platelet function defects
- General bleeding risk factors (e.g., HAS-BLED score)

< 20'000 / µl

- Avoid (N)OAC therapy
- Risk of spontaneous bleeding

20'000-50'000 / µl

- Proceed with great caution
- Very close clinical + platelet count monitoring
- Consider half-dose NOAC, esp. if ≥1 bleeding risk factor
- Multidisciplinary team evaluation

> 50'000 / µl

- Proceed with caution
- Close clinical + platelet count monitoring

Fig. 25: AF patient with a malignancy requiring OAC

Safety evaluation

- **AF-related** bleeding risk factors (e.g., by HAS-BLED or other bleeding scores)
- **Cancer-related** risk factors (actively bleeding/high-risk cancer, intracranial/liver metastases)
- **Treatment-related** risk factors (surgery, radiation, central lines, severe thrombocytopenia, etc.)

↓

Choice of anticoagulant

1. **NOAC** (unless opted against by multidisciplinary team, e.g., active GI cancer)
2. **LMWH**
3. **VKA**

↓

Patient protection

- **Close clinical follow-up**
- **Practical issues** (regular food intake? Correct dose? etc.)
- **Potential drug-drug interactions** (Table 6)
- **Gastric protection** (PPI/H_2-blockers)
- **Assess necessity for treatment interruption** (e.g., if platelet count <20k, severe renal impairment, active bleeding etc.)

Interdisciplinary teamwork

Cardiologist – Oncologist – Haematologist/Radiologist – Other specialties

Abbreviations

ACS	Acute Coronary Syndrome
ACT	Activated Clotting Time
AED	Antiepileptic drugs
AF	Atrial fibrillation
AFIRE	Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease
AMPLIFY	Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy
ANNEXA-4	Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors 4
aPCC	Activated Prothrombin Complex Concentrates
aPTT	Activated Prothrombin Time
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ATLANTIS	Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis
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
AUB	Abnormal uterine bleeding
AUC	Area under the curve
AUGUSTUS	Apixaban Versus Vitamin K Antagonist in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention,
AXADIA	A Safety Study Assessing Oral Anticoagulation With Apixaban Versus Vitamin-K Antagonists in Patients With Atrial Fibrillation (AF) and End-Stage Kidney Disease (ESKD) on Chronic Hemodialysis Treatment
AXAFA-AFNET	Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy – Atrial Fibrillation Network
BCRP	Breast cancer resistance protein
BID	twice daily
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
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCS	Chronic Coronary Syndrome
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease - Epidemiology Collaboration
CMB	Cerebral microbleeds
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies,
CORIDA	COncentration of RIvaroxaban, Dabigatran and Apixaban
COVID-19	Coronavirus Disease of 2019
CrCl	Creatinine clearance
CRNM	Clinically relevant non-major bleeding
CT	Computer tomography
CV	Cardiovascular
CYP	Cytochrome P (CYP)
DAPT	Dual antiplatelet therapy
DDI	Drug-drug interaction
DES	Drug-eluting stent
DOAC	Direct oral anticoagulant
dTT	Diluted thrombin time
EACTS	European Association for Cardio-Thoracic Surgery
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
EMA	European Medicines Agency
EMANATE	Eliquis evaluated in acute cardioversion compared to usual treatments for anticoagulation in subjects with NVAF
ENAVLE	Efficacy and Safety of edoxabaN in Patients After Heart Valve Repair or Bioprosthetic vaLve Replacement
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
ENVISAGE-TAVI	EdoxabaN Versus standard of care and theIr effectS on clinical outcomes in pAtients havinG undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation
ESO	European Stroke Organization
ESC	European Society of Cardiology
FFP	Fresh Frozen Plasma
GFR	Glomerular filtration rate
GI	Gastro-intestinal
GP	General Practitioner
GRACE	Global Registry of Acute Coronary Events
HCM	Hypertrophic cardiomyopathy
HCP	Healthcare provider
HIT / HITT	Heparin-induced thrombocytopenia +/- thrombosis
HMS	Heavy menstrual bleeding
HPLC/MS	High Performance Liquid Chromatography / mass spectrometry
ICB	Intracerebral bleeding,
INR	International Normalized Ratio
ISTH	International Society of Thrombosis and Hemostasis
ITP	Immune thrombocytopenia
J-ROCKET	Japanese ROCKET AF
LAA	Left atrial appendage
LMWH	Low molecular weight heparin,
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
MRI	Magnet resonance imaging
NOAC	Non-Vitamin K Antagonist Oral Anticoagulant
NSAID	Non-steroidal anti-inflammatory drug
NSTE-ACS	Non- ST-elevation acute coronary syndrome
OAC	Oral anticoagulation

PAUSE	Perioperative Anticoagulant Use for Surgery Evaluation
PCC	Prothrombin Complex Concentrates
PCI	Percutaneous Coronary Intervention
PD	Pharmacodynamic
PK	Pharmacokinetic
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
POISE-2	Perioperative Ischemic Evaluation 2
PPI	Proton pump inhibitor
PT	Prothrombin time
QD	Once daily
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
RENAL-AF	RENal Hemodialysis Patients ALlocated Apixaban Versus Warfarin in Atrial Fibrillation
RE-VERSE AD	Reversal Effects of Idarucizumab in Patients on Active Dabigatran,
RIVER	Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation
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
ROTEM	Rotational thromboelastometry
rt-PA	Recombinant tissue-type plasminogen activator
SAH	Subarachnoid hemorrhage
SDH	Subdural hematoma
SEE	Systemic embolic event
SmPC	Summary of product characteristics

STEMI	ST-elevation myocardial infarction
TAVI	Trans-catheter aortic valve implantation
TEE	Transesophageal echocardiogram
TEG	Thromboelastography
TIA	Transient ischaemic attack
TSP	Transseptal puncture
TT	Thrombin time
TTR	Time in therapeutic range
UFH	Unfractionated heparin
ULN	Upper limit of normal
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

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[3] Andrade JG, Verma A, Mitchell LB, Parkash R, Leblanc K, Atzema C, et al. 2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. *The Canadian journal of cardiology* 2018; **34**: 1371-92.

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2021 European Heart Rhythm Association Practical Guide on the use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

Online Supplement

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Practical considerations regarding adherence and persistence

Ensuring adherence and persistence to prescribed oral anticoagulant intake

Strict adherence to NOAC intake is crucial as its anticoagulant effect wanes within 12–24 hours after the last intake.[1, 2] NOAC plasma level measurements as well as general coagulation tests cannot be considered as tools to monitor adherence since they only reflect intake over the last 24 (-48) hours and the measured level is heavily dependent on the time between last intake and sampling (Chapter 5). Importantly, 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, a regular follow-up assessment for patients on NOACs is strongly advised, particularly in case of relevant comorbidities such as renal failure, older age, multiple comorbidities, frailty, or cognitive decline.

Although there is evidence for significantly lower discontinuation rates with NOACs than with VKAs, discontinuation is still a relevant issue.[3-21] Available observational data suggest variable adherence to NOAC intake from 38% to 99% depending on the setting and definition, which may severely diminish the benefit of treatment.[2, 5, 11, 16, 19, 21-36] Discontinuation of NOACs is associated with younger age, impaired renal function, high alcohol intake, lower CHA_2DS_2-VASc scores, and cost of treatment.[20]

It is important to have a system in place to check for adherence and persistence (e.g. follow- up phone calls, booklets, mobile apps and websites). This should prompt an assessment of the reasons for discontinuation and possible solutions thereof. Some of these concerns have been alleviated by recent implementation data which mostly confirm the improved risk/benefit profile in patients treated with NOACs vs. VKAs as

observed in the RCTs suggesting adequate adherence also in daily clinical practice.[9, 15, 25, 30, 37-54]

Practical considerations (Figure 1)

(1) **Patient education** on the need for oral anticoagulation therapy and the importance of strict adherence is important.[22, 55-61] Many simultaneous approaches can be employed to provide education including leaflets and instructions at initiation of therapy, a patient anticoagulation card, and group sessions. Reinforcing education is important 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), or StopAfib.org (https://www.stopafib.org), which variably include interactive formats such as online forums. 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 or apps.[23, 59, 62] It is critically important to educate patients at each visit about the modalities of intake (including once daily (QD) or twice a day (BID); intake with food in case of rivaroxaban, etc.), 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 (Figure 2). Education sessions can be further facilitated using specific checklists.[56, 58, 63, 64] Delivery of a uniform message by all parties involved in the patient pathway is critical, as delivery of conflicting information from healthcare providers has been associated with suboptimal adherence.[65]

(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 (particularly in frail and older patients).

(3) There should be a **pre-specified follow-up schedule** for the NOAC patient (as suggested in Figure 3) 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 and persistence. Nurse-coordinated AF centers may be helpful in coordinating patient follow-up and checking on adherence.[66-70]

(4) Although NOACs may have a day-marked blister pack format, **pill organizers or medication boxes** (conventional or with electronic verification of intake) are an easy way to optimize adherence. Even a simple calendar reminder can be helpful to increase adherence.[71]

(5) Many **technological aids** are available to enhance adherence: smartphone applications[72] with reminders and/or SMS messages to alert the patient about the next intake some even requiring confirmation that the dose has been taken. Various apps for both Android and iOS devices are available.[73] The long-term effects of such tools are unknown, and one tool may not suit all patients.

(6) In cases where suboptimal adherence is suspected, (remote) **electronic monitoring** may help educate patients 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.[74, 75] The health-economic validity of such an approach needs further study.

(7) Once daily (QD) **dosing regimens** generally result in greater adherence vs. twice daily (BID) regimens in cardiovascular patients.[21, 36, 76-78] Most, but not all studies evaluating adherence for NOACs indicate that a QD dosing regimen is superior from a total tablet count perspective.[5, 9, 25, 28-32, 62, 79-81] However, it is still uncertain whether any dosing regimen is superior in guaranteeing the clinical thromboembolic preventive effects and safety profile as seen in the RCTs.[9, 15, 31, 41-43, 47-51, 82, 83] Although there are modelling data suggesting that there is potentially a larger fluctuation in the anticoagulant activity when a single dose is omitted from a QD dosing regimen compared with when a single or even two doses are omitted from a BID regimen,[84] the clinical relevance of these fluctuations is unknown.[85] Therefore, it is essential to ensure that drugs are taken according to the prescribed regimen.

(8) 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 may 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.[86]

(9) 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 and guideline recommendations,[55, 58] and common misperceptions regarding the efficacy and safety of ("unmonitored") NOAC therapy need to be solved.

(10) In NOAC-treated patients in whom low adherence is documented 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 worse outcomes.

(11) The incremental **cost** and possibly necessary **co-payment** for NOACs may slow their uptake and use in spite of patients' and HCPs' preference of NOACs over VKA.[87] This needs to be discussed upfront with patients in order to avoid later adherence issues due to affordability. Cost-effectiveness analyses for individual healthcare setting are desirable in order to analyze overall cost (including hospitalization etc.) and benefit of different treatments

strategies and to implement medically useful and affordable treatment plans.[88, 89]

An anticoagulation card for NOACs and the importance of education (Figure 2).

Just like patients taking a VKA, those taking a NOAC are also advised to carry information about their anticoagulant therapy to alert any healthcare provider about their treatment. Ideally, they should carry details of all other therapy, too, in case of an emergency. Each manufacturer provides proprietary information cards to be completed by physicians and carried by patients; however, ideally, a uniform card should be used instead. The proposed EHRA NOAC card is available for download in various languages at www.NOACforAF.eu. In addition, use of medical ID jewelry may be an option.[90]

Organization of follow-up and continued care

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. Treatment requires vigilance to prevent and detect potentially severe complications, particularly as a large proportion of the patient population tends to be of older age and frail. Patients' treatments should be reviewed on a regular basis; preferably after 1 month initially and about every 3-12 months thereafter, depending on the individual patient's characteristics, comorbidities and co-medications (Figure 3). For example, an otherwise healthy young person with normal renal function, no relevant comorbidities who adheres well to treatment requires less close follow-up compared to older patients with relevant comorbidities (e.g. renal dysfunction), frail patients,[91, 92] or those with active cancer. Importantly, bleeding- and particularly stroke risk factors are dynamic over time and need to be re-assessed at every patient visit.[63, 93]

While coordinated by a cardiologist/AF specialist,[63] patient follow-up may be led by general practitioners with experience in this field and/or by appropriate secondary care physicians. Growing evidence shows that nurse-coordinated AF clinics or other integrated care strategies may have a very helpful complemental role in this regard.[66-70, 94-96] Each caregiver, including specially trained nurses and pharmacists, should clearly indicate all relevant findings, treatment adaptations, and when and where the next follow-up is due. As indicated above, alignment of all healthcare providers involved in the patient's care and delivery of a uniform message is critical, as delivery of conflicting information as well as suboptimal shared decision making has been associated with suboptimal adherence.[65] The ABC pathway as recommended in the 2020 AF guidelines can serve as a useful scaffold for this purpose:[63 63]

- A - Avoid stroke with anticoagulation
- B - Better symptom management with patient-centered, symptom directed decisions on rate or rhythm control
- C - Cardiovascular risk, comorbidity, and lifestyle factor optimization.[97]

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.

VKA to NOAC

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 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)). At that time, a new INR measurement can be scheduled. The proposed scheme (Figure 4, top panel) tries to unify different specifications from the SmPCs, which state that the NOAC can be started when INR is <3 for rivaroxaban, ≤2.5 for edoxaban, and <2.0 for apixaban and dabigatran. Once a NOAC is initiated any further INR monitoring needs to be discontinued.

NOAC to VKA

Owing to 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 (Chapter 16). Therefore, the NOAC and VKA should be administered concomitantly until the INR is in a range that is considered appropriate (Figure 4, lower panel) - similar to the situation when LMWHs are administered during VKA initiation. A loading dose is not advised for acenocoumarol and warfarin but may be appropriate with phenprocoumon (Chapter 16).

As NOACs may have an impact on INR measurements it is important that the INR is measured just before the next intake of the NOAC during concomitant administration, and is re-measured 2-3 days after stopping the NOAC (i.e. reflecting solely VKA therapy) to ensure adequate anticoagulation. It is also advisable to closely monitor INRs within the first month until stable values have been attained (i.e., three consecutive measurements yield 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 half a dose of the NOAC until the INR was within range, in combination with the above intensive INR testing strategy.[98] Switching according to this scheme has proven to minimize the risks of stroke and bleeding for edoxaban[98] while, conversely, inadequate transitioning was associated with increased stroke rates.[99, 100] 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 VKA therapy is not deemed appropriate, initiation of the VKA can be performed after switching the NOAC to LMWH (see below), which may be an option especially in patients with a high thromboembolic risk.

NOAC to parenteral or subcutaneous anticoagulants

The parenteral anticoagulant (UFH and LMWH) can be initiated when the next dose of the NOAC is due. If clinically necessary, this interval can be (substantially) shortened, e.g. in the setting of an acute coronary syndrome (see Chapter 9).

Parenteral anticoagulant to NOAC

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

Low-molecular-weight heparin (LMWH): 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.

NOAC to NOAC

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 may be advisable.

Aspirin or clopidogrel to NOAC

The NOAC can be started immediately and aspirin or clopidogrel stopped unless combination therapy is deemed necessary (see Chapter 9).

Pharmacokinetics and drug-drug interactions of NOACs

Rate and rhythm control drugs

Possible drug-drug interactions are listed in Tables 5-9.

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 of 23% increase in dabigatran levels in patients taking verapamil.[101] It is advisable to use the lower dose dabigatran (110 mg BID) when combined with verapamil ('purple', Table 5). A similar interaction had initially been noted for edoxaban.[102] 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 5). 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 with verapamil. Concurrent use of rivaroxaban and verapamil showed an 1.4 fold increase in rivaroxaban AUC in 27 subjects but combined use does not seem to result in higher bleeding rates.[103, 104] Caution might be warranted in combination with other factors ('yellow', Table 5). Diltiazem has a lower inhibitory potency of P-gp, resulting in non-relevant interactions,[101] although there is a 40% increase in plasma concentrations of apixaban ('yellow'; Table 5).[105]

For edoxaban a 40% increase in AUC was observed in patients on **amiodarone** with normal renal function.[106] 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.[107] Nevertheless, dose reduction is not recommended according to the SmPc in case of concomitant administration.

There is a strong effect of **dronedarone** on dabigatran plasma levels, which constitutes a contraindication for all concomitant use according to the EMA SmPC. The interaction potential is considered moderate for edoxaban ('purple'), and dronedarone intake was a dose reduction criterion in the ENGAGE-AF protocol.[108] 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). An analysis of NOAC plasma levels before surgical intervention demonstrated that concomitant intake of verapamil, dronedarone or amiodarone was significantly associated with higher pre-operative plasma levels.[109]

Other drugs

Tables 5-9 also list 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 hours after 110 mg dabigatran etexilate, the increase of dabigatran C_{max} and AUC was reduced to +24% 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 PCI as studied in the RE-DUAL PCI study is discussed in detail in Chapter 9.[110, 111]

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).[112] Due to the relevant decrease in NOAC levels, the concomitant use of St. John's wort is not advisable. For most other potential interactions with herbal products, no direct evidence is available yet. Additionally, because of the inherent variation in composition of herbal products, the effect of potential interactions may greatly differ between different products. Table 8 includes potential effects of ten common herbal products. Several herbal products have the potential to cause or increase bleeding due to their anticoagulant or antiplatelet properties.[113, 114] CYP3A4 and P-gp interactions are also possible,[114, 115] but the clinical relevance of these interactions is not always clear. As a result, the advice for most of these potential interactions is that caution is needed, especially in case of polypharmacy or in the presence of other bleeding risk factors.

Polypharmacy

Polypharmacy is a well-established risk factor and marker for adverse events due to drug-drug interactions and the higher prevalence of comorbidities, respectively.[116-118] In ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48, patients concomitantly taking several (≥ 5 or ≥ 9) medications experienced similar outcomes and consistent treatment effects of either NOAC relative to warfarin, while conceivably absolute event rates (particularly for bleeding and all-cause mortality) were higher with more co-medications.[117-119] Although reassuring, these findings are derived from post hoc analyses with several 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. These data indicate that polypharmacy in itself should not be a contraindication for the use of NOACs but special care needs to be taken when treating these vulnerable patients.

NOACs in patients with chronic kidney disease or advanced liver disease

Atrial fibrillation and chronic kidney disease

Not only are AF and CKD mutually potentiating their negative effects, recent reports also indicate that OAC can further aggravate CKD, possibly by inducing micro-bleeds in the kidneys and promoting vascular calcifications; this appears to occur to a lesser extent with NOACs compared to VKA.[120-123]

Several equations are available to gauge a patient's renal function, all with inherent strengths and limitations (Table 10).[124] In the context of NOAC treatment**, renal function should preferably be estimated by calculating the creatinine clearance (CrCl) using the Cockcroft–Gault method**, because this was used in most NOAC trials and is therefore also used for this *Practical Guide*. Indeed, use of other formulas including MDRD and CKD-EPI may overestimate kidney function particularly in older patients and in those with low body weights.[125]

Importantly, CKD can only be assessed by equations in stable situations. Dosage of NOACs must be reconsidered in acute renal failure or in worsening chronic renal failure. In acute renal failure, serum creatinine levels may only indicate mildly reduced (or even normal) renal function when in reality it is severely impaired. In such situations NOACs need to be stopped and, depending on the clinical situation, switched to unfractionated heparin before resumption after stabilization. In patients on NOACs renal function needs to be monitored carefully, at least yearly, to detect changes in renal function and adapt the dose accordingly. If renal function is impaired (i.e., CrCl ≤ 60 mL/min), a more frequent evaluation is advisable (e.g., by dividing CrCl by 10 to obtain the minimum frequency of renal function testing in months). In patients with additional risk factors (e.g., older age, frailty, multi-morbidity etc.), renal function may be evaluated even more frequently, especially if on dabigatran. Since acute illnesses (like infections, acute heart failure, etc.) may transiently affect renal function, they should also trigger re-evaluation. This guidance is also presented in the updated NOAC Card (Figure 2).

Of note, a possibly decreased efficacy of edoxaban 60 mg QD compared to warfarin was observed in patients with a CrCl of >95 mL/min in a non-prespecified subgroup analysis of the ENGAGE-AF trial.[108] Interestingly, as a result of these findings, further post-hoc analyses revealed a similar directional signal for rivaroxaban[126] and apixaban,[127-129] but not dabigatran. The most recent EMA SmPc advises that edoxaban should be used in "high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk".[130] A post-hoc analysis of the ENGAGE AF data showed that despite the apparent decrease in relative efficacy of edoxaban 60 mg QD in the upper range of CrCl, the safety and net clinical benefit of edoxaban compared with warfarin were consistent across the spectrum of renal function.[131] Moreover, both prospective observational as well as retrospective analyses found no evidence for a reduced effectiveness or any clinical relevance of this observation.[132] A dedicated comparison of edoxaban 60mg vs. 75mg QD in 607 patients with AF and high CrCl revealed a low (and similar) event rate for stroke (n=2 vs. n=3, respectively) and major bleeding (n=2 vs. n=3, respectively).[133] Taken together, the observed effects in patients with supra-normal renal function are unlikely to be of critical clinical relevance, also in view of the overall lower absolute event rate in these patients.

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

Benefits of VKAs in terms of reduced stroke and mortality are well studied in AF patients with *mild to moderate* CKD.[134-137] Compared with warfarin, all four NOACs showed consistent efficacy in the respective sub-group analyses of pivotal NOAC trials.[129, 131, 138-141] In addition, analyses from the ARISTOTLE trial data suggest that the bleeding benefit with apixaban compared to warfarin becomes significantly more prominent at lower CrCl values, while the stroke reduction benefit is maintained.[140, 142] In contrast, the reduction in major and life-threatening bleeding

with 110 mg dabigatran vs. warfarin is no longer present (trend / significant interaction) in patients with CrCl < 50 ml/min while maintaining a similar stroke risk reduction compared to VKA.[138]
A recent meta-analysis of 15 randomized and retrospective trials comprising about 78,000 patients with CKD (CrCl ranging from 15-89 ml/min) found that NOACs in comparison to VKA were associated with significant reductions of intracranial hemorrhages, stroke and systemic embolism, and mortality.[143]
In patients with CKD, adequate dosing is an essential issue to be addressed when using NOACs (Figure 7). While rivaroxaban, apixaban and edoxaban doses were reduced according to renal function in their respective RCTs, patients in the RE-LY trial were randomized to dabigatran 150mg BID or 110mg BID without dose reduction in patients with chronic kidney disease. Per SmPc, a reduction of dabigatran to 110 BID can be considered in patients with CrCl < 50 ml/min at high risk of bleeding according to the European SmPc,[144] and dabigatran is contra-indicated if CrCl drops below 30mL/min. Importantly, underdosing of NOACs in patients with normal or only mildly reduced renal function was found to be associated with less effectiveness (i.e., higher stroke rates) and no additional safety benefit in a large 'real-world' AF cohort as shown for apixaban.[145]

NOACs in liver disease

Advanced liver disease is associated with increased bleeding risk, but is also a prothrombotic disorder.[146] In addition, significant liver disease can profoundly affect hepatic clearance and drug metabolism, and altered functionality of liver enzymes and transporters may affect drug response and facilitate drug-induced liver injury.[147]
The use of VKAs in patients with advanced liver disease and coagulopathy is challenging due to intrinsically elevated INR values and difficulties in selecting appropriate VKA dosing.[148-150]
Patients with significant active liver disease including cirrhosis, or those with persistent (as confirmed by repeated assessment ≥1 week apart) elevation of liver enzymes or bilirubin (i.e., alanine transaminase or aspartate transaminase ≥2 times the upper limit of normal (ULN) or total bilirubin ≥1.5 times the ULN) were excluded from the landmark NOAC trials in AF.[108, 151-153] Consequently, all four NOACs are contraindicated in patients with hepatic disease associated with clinically manifest coagulopathy and clinically relevant bleeding risk including Child-Turcotte-Pugh C cirrhosis (Figure 8). Rivaroxaban should also not be used in AF patients with Child B liver cirrhosis due to a >2-fold increase in drug exposure in these patients.[154] Dabigatran, apixaban and edoxaban may be used with caution in patients with Child B cirrhosis (Figure 8).[155, 156] Recent registry data indicate that even in patients with AF and various degrees of accompanying liver disease NOACs may be associated with a lower incidence of bleeds and overall mortality.[157-160] Initiation and follow-up at a specialized center in a multidisciplinary team (including a hepatologist and a hematologist) is advisable (Figure 8).[161]
Since the withdrawal of the direct thrombin inhibitor ximelagatran as a result of its hepatotoxic side effects in 2006[162] there had been some concern regarding the potential of NOACs to cause drug-induced liver injury. However, no signal for an elevated risk of hepatotoxicity has been observed with the direct thrombin inhibitor dabigatran[151] or the FXa-inhibitors in a meta-analysis of 29 RCTs evaluating 152,116 patients.[163] In fact, the risk of liver injury may even be lower than with VKA.[164, 165 166]

Management of bleeding under NOAC therapy

Nuisance and minor bleeding

The clinical relevance of both nuisance and minor bleeds under NOAC therapy should not be underestimated as they are frequent causes of treatment interruptions. Patients need to be made aware of the signs and symptoms of such bleeding events and instructed to alert their healthcare provider in case of such an event (see Chapter 2); conversely, HCP need to inquire about nuisance bleedings (as well as treatment adherence) at every patient visit. Cessation or temporary interruption without consultation of the HCP primarily responsible for the patient's follow up (Figure 2) is strongly 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 bleeds 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 often be treated with local anti-fibrinolytics, improved oral hygiene, or cautery.
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 3, Figure 6).
Any suspected or documented occult bleeding should trigger a work-up to uncover the underlying cause (including, importantly, gastrointestinal cancer in the case of occult gastrointestinal bleeding)[167, 168] and the treatment thereof whenever possible.

Non-life-threatening major bleeding

Causal therapy to stop the bleed and standard supportive measures (such as mechanical compression, endoscopic or surgical hemostasis, fluid replacement, transfusion and other hemodynamic 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 due to the relatively short elimination half-lives of all NOACs (see Table 4).[169]
The use of systemic antifibrinolytics (e.g. tranexamic acid, 1g i.v., repeated every 6 hours 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 hemostasis, particularly in trauma-induced bleeding with a

favourable safety profile.[170, 171] Even when not yet supported by clinical data its use can therefore be considered for bleeds under NOACs, especially in situations of severe bleeding where frequently many factors of the coagulation cascade are deficient. Red blood cell transfusion is generally recommended at a hemoglobin level ≤ 7g/dl, or ≤ 8g/dl in case of coronary artery disease.[172, 173] Maintenance of a platelet count of ≥ 50.000 / ul is generally recommended.[174] Securing adequate diuresis appears important for all NOACs, but particularly in case of dabigatran (given the large degree of renal elimination of the drug).
In cases of major bleeding that is not immediately life- or organ-threatening but may lead to severe complications, anticoagulant reversal can be considered (Figures 9 and 10). Dialysis may be an option in this case for dabigatran particularly if idarucizumab is not available.[175, 176] 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.[177, 178]

Patients requiring an urgent surgical intervention

1) Acute emergency procedures (immediate life-, limb- or organ-saving intervention, typically cardiac, vascular, neurosurgical emergency procedures) need to be performed within minutes of the decision to operate and cannot be delayed (Figure 12). In these cases, reversal with idarucizumab (for dabigatran)[179] is advisable, especially in moderate- to high hemorrhagic risk procedures.[180] While the REVERSE-AD trial with idarucizumab enrolled both bleeding patients as well as those requiring urgent surgery, the ANNEXA-4 trial with andexanet alfa only enrolled patients experiencing an acute major bleed under therapy but not patients requiring urgent surgical interventions.[181] In view of the results it is conceivable that andexanet alpha (off-label) use may also be considered in life-threatening situations requiring an immediate intervention when available. It needs to be kept in mind that in contrast to idarucizumab, andexanet alpha inhibits all FXa inhibitors non-specifically which may have important implications for further downstream therapy (including unfractionated heparin administration).[182, 183]
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 6).[184-186] 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 hematoma.

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 an intervention should be deferred, if possible, until at least 12 h and ideally 24 h after the last dose of NOAC (Figure 12). In selected cases where delaying the procedure is likely to be associated with worse outcomes than an immediate procedure, administration of idarucizumab in patients treated with dabigatran may be considered. Also, coagulation test results (see below) can be awaited in this situation to gauge the necessity for reversal or, potentially, 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 8).

Patients undergoing a planned invasive procedure, surgery, or ablation

Interruption times based on bleeding risk

There is no universal definition of bleeding risk in interventional or surgical procedures. The current classification is derived from various different guidelines, trials and society recommendations.[187-190] Importantly, the risk category of operations and interventions reflects both the risk *of* bleeding, and the risk of adverse outcomes *in case of* bleeding. This list is not inclusive, and classifications need to be viewed in the context of relevant patient factors and specific procedural circumstances (Figure 13). For example, ≥ 48 hours interruption time prior to cardiac lead extraction may be advisable in a young patient with ICD leads implanted for 15 years, whereas extraction of a single pacemaker lead implanted for 1.5 years in an 80 years-old patient may be considered a low-bleeding risk procedure (in a patient with a high stroke risk).

Minor risk procedures

Most minor surgical procedures and those procedures where bleeding is easily controllable can usually be managed without interrupting oral anticoagulation (Table 12, Figures 14 and 15). In general, these procedures can be performed 12 to 24 hours after the last NOAC intake. It may be useful to have the intervention scheduled 18-24 hours after the last NOAC intake, and then restart 6 hours later (i.e., skipping one dose of dabigatran or apixaban and no dose of edoxaban or rivaroxaban). Patients may only leave the ambulatory practice/outpatient clinic/hospital if any peri-interventional bleeding has completely stopped. Moreover, they need 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) needs to be accessible in such a case.

Low risk procedures

For invasive procedures with a low risk (i.e. low frequency of bleeding and/or minor impact of bleeding; Table 12), the last dose of a NOAC should be taken 24 hours or more before the elective procedure in patients with normal kidney function (Figures 14 and 15). 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 hours or more before surgery (Figure 14).

High risk procedures

In case of invasive procedures or operations that carry a high risk for major bleeding or in which bleeding will have an important clinical impact, it is advisable to take the last NOAC dose 48 hours or longer before surgery. Again, the decision to pause therapy for longer should take into account all relevant patient- and procedure-related factors (Figure 13). In patients with impaired renal function even longer interruption of the NOAC intake is required, especially for dabigatran (Figures 14 and 15). In selected cases, measurement of NOAC plasma levels may be considered (see main text for details).

Special considerations for selected procedures

Regional anaesthesia and pain medicine

Invasive procedures such as spinal anaesthesia, epidural anaesthesia, and lumbar puncture require normal hemostatic function, and fall under the 'high 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 5 half-lives (corresponding to an interruption of 3 days in FXa-inhibitors and 4-5 days for dabigatran).[184, 191] NOAC therapy can usually be resumed 24h 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., 2 half-lives).[192]

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.[193] However, recommendations are often based on a low quality of evidence and mainly rely on available pharmacological information.[194] Dental extractions can generally be performed safely in an outpatient facility by applying local haemostatic measures, without interrupting anticoagulation and performing the intervention at trough level or by just skipping the morning dose of the NOAC.[195-199] 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 (some of which are currently being studied).[200]

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, without any bridging.[201] For NOAC- treated patients, the BRUISE-CONTROL 2 trial demonstrated similar bleeding and embolic rates in patients with a last intake 2 days before the implantation for rivaroxaban, apixaban, and (based on glomerular filtration rate) dabigatran vs. continued NOAC until the morning of the procedure.[202] Data from this trial confirm the available (limited) evidence from subgroup analyses from the pivotal Phase III trials.[203-206] Therefore, a standard strategy as for "minor bleeding risk" procedures with intake of the last dose the day before the procedure are advisable in most cases (Figure 14 and15).[207] Resumption of NOAC intake on the first (latest second) postoperative day is usually feasible.

Patient with atrial fibrillation and coronary artery disease

Elective coronary intervention (chronic coronary artery disease)

The NOAC should be discontinued before patients are taken to the cardiac catheterization lab and the NOAC effect should have disappeared (i.e. 24 h or longer after last intake; see Chapter 8). Peri-procedural anticoagulation should be used per local practice. Unfractionated heparin (70 IU/kg) rather than enoxaparin is preferred.[208] Unfractionated heparin should be administered to target ACT or aPTT levels per standard clinical practice.

Non-ST-elevation acute coronary syndrome

In the absence of contraindications, all NOAC patients developing Non-ST-elevation acute coronary syndrome (NSTE-ACS) should receive low-dose aspirin (150 – 300 mg loading dose) immediately after diagnosis.[209] After discontinuing the NOAC and waning of its effect (12 h or longer after last intake; see Chapter 8), fondaparinux (preferred) or enoxaparin can be initiated. The use of upstream P_2Y_{12} inhibitors should be avoided, especially in patients undergoing early invasive therapy. To reduce the risk of access site bleeding, a radial approach is preferred.[210]

ST-elevation myocardial infarction

In the absence of contraindications, all NOAC patients developing ST-elevation myocardial infarction (STEMI) should receive low-dose aspirin (150 – 300 mg loading dose) and a P_2Y_{12} inhibitor immediately at admission.[211] In frail patients at high bleeding risk, aspirin only might be a safer initial therapy awaiting invasive management, when indicated. Primary PCI (via a radial[210] approach) is the therapy of choice.[211] It is recommended to use additional parenteral anticoagulation (i.e. UFH or enoxaparin but not fondaparinux), regardless of the timing of the last dose of NOAC.[211] Unless for bail-out situations, routine glycoprotein IIb/IIIa inhibitors should generally be avoided.

Presentation on oral anticoagulation constitutes a relative contraindication for fibrinolysis,[211] and transfer to a center with

primary PCI capacity should be initiated as soon as possible.[211, 212] If fibrinolysis is the only available reperfusion therapy, it has to be carefully weighed against the inherently increased risk of bleeding, particularly if NOAC plasma levels are unknown or above the reference range. 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).

Post-procedural resumption of anticoagulation

In stabilized patients (i.e. no recurrent ischemia or need for other invasive treatments), the NOAC can be (re-)started as soon as parenteral anticoagulation has been stopped. Restarting or initiating the NOAC too early post-procedurally (on the day of the PCI) might temporarily increase bleeding risk.[213] The combination of antiplatelet agent(s) and NOAC, the dose of the NOAC and the subsequent duration of aspirin or/and P_2Y_{12} inhibitor treatment need to be individualized, based on a careful assessment of coronary thrombotic- versus bleeding risk (see Chapter 9). It is of paramount importance that the patient is discharged with a prespecified planned downgrade schedule of antithrombotic agents to reduce the longer-term risk of bleeding while protecting against coronary events.[63]

Cardioversion in a NOAC-treated patient

Cardioverting an AF patient treated for ≥3 weeks with a NOAC

Post-hoc analyses from RE-LY (dabigatran), ROCKET-AF (rivaroxaban), ARISTOTLE (apixaban) and ENGAGE-AF (edoxaban) suggest that electrical cardioversion in patients treated with NOACs has a similar (and very low) thromboembolic risk as under VKA.[151-153] Later prospective trials with rivaroxaban,[214] edoxaban,[215] and apixaban[216] as well as in various meta-analyses and observational studies have confirmed the low peri-cardioversion stroke risk in patients treated with a NOAC for ≥3 weeks compared to warfarin.[217-219] Hence, the cumulative evidence indicates that cardioversion is feasible without TEE in patients with regular and continued NOAC intake for ≥3 weeks.[63] Importantly, however, the patient needs to be inquired about strict adherence over the last 3 weeks and his/her answer should be documented in their file. If in doubt about perfect adherence, a left atrial / left atrial appendage thrombus needs to be excluded prior to cardioversion. 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: a TEE prior to AF ablation revealed thrombi or sludge in the left atrium in 1.6 – 2.1% of therapeutically anticoagulated patients, with the incidence of thrombus correlating with the $CHADS_2$ score (≤0.3% in $CHADS_2$ 0-1 vs. 0.5% in $CHADS_2$ ≥2 patients).[220-222] Therefore, it remains an individualized decision whether to perform a pre-cardioversion TEE for thrombus exclusion, even when considered effectively anticoagulated. Of note, not all strokes in patients with AF are due to thrombi in the LA/LAA which may explain (rare) ischemic events post-cardioversion even in patients on adequate anticoagulation and/or negative TEE.[223]

Cardioverting atrial fibrillation of >48 h in a patient not on NOAC

For the scenario of cardioversion in an AF patient who is not on a NOAC, prospective trial data with rivaroxaban,[214] edoxaban[215] and apixaban[216] studies offer important data since they included 57%, 27% and 100% of OAC-naïve patients, respectively. The cardioversion strategy was either early (with TEE) or delayed (i.e. with 3 – 8 weeks anticoagulation before cardioversion, without TEE). 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 treated patients (except for lower ischaemic events with apixaban in the 'Eliquis evaluated in acute cardioversion compared to usual treatments for anticoagulation in subjects with NVAF' (EMANATE) trial), and between the early and delayed strategy, although none of the trials were powered for non-inferiority. In EMANATE, 45% of the patients in the apixaban-group received an initial loading dose (of 10 mg, or 5 mg if dose-reduction criteria were met) to expedite cardioversion (allowed from 2h after this loading dose); also these patients did not show a higher bleeding tendency. Taken together, a strategy with at least a single NOAC dose 2-4 h before cardioversion appears safe and effective in patients with AF of >48 h duration, provided that a TEE is performed prior to cardioversion. The alternative involves starting anticoagulation with a NOAC for at least 3 weeks, followed by cardioversion (without TEE unless high risk patient or deemed non-adherent, see above).

Cardioverting AF of ≤48 h in an anticoagulation-naive patient

The 2020 ESC AF Guidelines indicated that early cardioversion can be performed without TEE when AF has a definite duration of ≤48h.[63] Different observational studies have shown a lower thromboembolic incidence rate with vs. without anticoagulation in patients with recent onset AF of ≤48 h, especially in those with a CHA_2DS_2-VASc ≥2 and AF duration ≥12h.[224-227] None of the dedicated randomized NOAC cardioversion trials provided information on whether intake of at least 1 dose of a NOAC is a feasible strategy in patients with AF of ≤48 h duration, who are currently often cardioverted after a single dose of LMWH. In EMANATE, all patients were OAC-naïve and 67% had AF ≤48h, but the outcomes of these subgroups have not been reported.

Given the consistent efficacy and safety of NOACs in patients with AF > 48h combined with the similar pharmacodynamic and pharmacokinetic properties of NOACs and LMWH, the use of a single dose of a NOAC (2)-4 h before cardioversion to replace LMWH may be justified in patients with AF definitely ≤48h without the need for a TEE. Nevertheless, in intermediate / high risk patients and situations (i.e., CHA_2DS_2-VASc ≥3 in males, ≥2 in females and/or AF onset >12 hours) or those in whom there is

any doubt about the onset of AF, a strategy with longer term anticoagulation (at least for 3 weeks before cardioversion) or a TEE strategy may be preferable. Indeed, it needs to be kept in mind that the 48h cut-off is not binary. As adequate absorption of rivaroxaban is only possible if taken with food, rivaroxaban may not represent the best option in a situation where patients need to be 'nil by mouth' prior to electrical cardioversion.

AF patients presenting with acute stroke while on NOACs

Management of NOAC treated AF patients in the acute phase of stroke

AF patients on NOACs with acute ischaemic stroke

There are no randomized trials on therapeutic management in NOAC treated AF patients with acute ischaemic stroke.

Thrombolysis

According to current guidelines and official labelling, thrombolytic therapy with intravenous recombinant tissue-type plasminogen activator (rt-PA) is approved within 4.5 hours of onset of stroke symptoms, but contraindicated in patients on full anticoagulation.[228, 229] rt-PA cannot be given (according to label) within 24 hours after last intake of NOAC due to their plasma half-lives (Table 4), which may be prolonged in chronic kidney disease (Chapter 4), older patients (Chapter 12) and other situations. A rapidly acting specific reversal agent, idarucizumab (Chapter 6) is available for dabigatran; as such, intravenous thrombolysis within 4.5 hours of onset of moderate to severe stroke may be feasible after reversal and assessment of coagulation (Figure 20).[230-232] In the absence of RCTs demonstrating efficacy and safety of this approach, balancing anticipated benefit vs. risks is important. It is unknown whether reversal of FXa inhibitors by administration of andexanet alfa followed by thrombolytic therapy in stroke patients is safe and effective.[233]

Published case series suggest that intravenous thrombolysis may be safe in patients with low plasma concentrations of NOACs[234] but reliable and rapid (point-of-care) tests for individual NOACs are not widely available.[235-237] However, the use of rt-PA may be considered in highly selected patients on NOACs where rapid, reliable agent-specific coagulation assessment (see Chapter 5) is available demonstrating a concentration <30 ng/ml for rivaroxaban, apixaban or edoxaban (if measured > 4 hours after drug administration), a reference value based on expert consensus only.[229] This strategy needs further evaluation in clinical studies and we urge development and implementation of easy-to-use point-of-care testing for emergency settings.[235, 238]

The use of rt-PA where anticoagulation status is unclear (e.g., AF patients with aphasia, time of last NOAC dose unknown, rapid assessment of plasma levels unavailable) is not advisable. Normal aPTT and INR results do not exclude relevant NOAC concentrations (see Chapter 5) and should not be used to guide thrombolysis decisions.[229]

Thrombectomy

There is a proven benefit of endovascular thrombectomy (EVT) initiated up to 6 hours after stroke onset in selected non-anticoagulated patients with a distal occlusion of the internal carotid artery, middle cerebral artery or proximal M2 divisions of the middle cerebral artery. EVT may also be beneficial in highly selected patients within 6 to up to 24 hours of last seen normal.[228, 239-242] A consensus statement from the European Stroke Organization (ESO) – Karolinska Stroke Update Conference recommends EVT in patients under NOAC or VKA treatment with large vessel occlusion without specifying a time window after stroke onset/last known normal.[229] Whether or not the results of endovascular thrombectomy trials hold true for anticoagulated patients remains to be established, as these trials either excluded or only contained few patients on VKA or NOACs. Available data suggest that EVT may be safe in selected anticoagulated patients,[243] and appears safer for patients on NOAC than VKA,[244] but the potential impact of (residual) NOAC levels on reperfusion-related bleeding risk has to be taken into account. A recent meta-analysis of case series and prospective multicentre registries suggests an increased intracranial bleeding incidence in VKA- but not NOAC-treated patients undergoing EVT.[245, 246] In the absence of study data, the application of idarucizumab/andexanet alfa for the purpose of reducing EVT-related bleeding complications is not advisable.

AF patients with acute intracranial bleeding (ICH)

All patients with acute ICH on OAC (VKA or NOAC) should have OAC withheld and urgent blood pressure management implemented. Immediate reversal of anticoagulation to limit haematoma enlargement is required. A neurologist/stroke physician should assess all such patients and neurosurgical opinion sought as appropriate.[247, 248]

Recommendations for the treatment of ICB under NOAC therapy are published,[229, 247] but the available level of evidence is low and based on expert consensus. A European Stroke Organization (ESO) consensus statement recommends reversal of anticoagulation without waiting for results of coagulation tests (Grade C), and to account for incomplete reversal by serial measurement of NOAC plasma concentrations (Grade C).[229] In dabigatran-related ICB, idarucizumab should be administered for immediate reversal (Grade C).[229, 249, 250] In factor Xa-inhibitors-related ICB, immediate administration of andexanet alfa is recommended (Grade C). If andexanet alfa is unavailable, administration of high-dose 4-factor PCC (50 IU/kg) is recommended (Grade C).[229] However, whether the use of PCC is helpful in factor Xa-inhibitor-related ICB is uncertain.

In the absence of high-level evidence the efficacy of specific reversal treatment strategies in NOAC-related ICH requires further clinical studies.[179, 181] Whether administration of the anti-fibrinolytic drug tranexamic acid may limit haematoma expansion in NOAC-associated ICB is currently being investigated in a small randomized trial (TICH-NOAC; NCT02866838).

NOACs in other special populations

NOACs in athletes

AF is the most common arrhythmia in athletes. Anticoagulation of athletes with AF is warranted according to current guidelines if the CHA_2DS_2-VASc score is ≥1 in men and ≥2 in women.[63] Usual advice to athletes on OAC for VTE has been to avoid contact- and higher injury-risk sports (e.g., equine and motor sports, rugby, martial arts etc.) while on treatment. There is little published evidence on the use of NOACs in AF in such populations. The use of an evening once daily agent may be preferable to avoid high levels of the drugs during daytime exercise, but no data is available to support this. All athletes presenting with AF should have a full cardiological assessment.

NOACs in women of reproductive age

Oral anticoagulants need to be considered with great caution in women of reproductive age. Two distinct situations require special consideration: Pregnancy and breastfeeding (where NOACs are generally contraindicated) and NOACs in the setting of menstrual / abnormal uterine bleeding (AUB).

NOACs in pregnancy and during breastfeeding

VKA therapy is associated with fetal harm / malformations.[251] Animal data equally support a potential for fetal harm for NOACs as they readily cross the blood-placenta barrier,[130, 252-254] and high rates of miscarriage (31%) and fetal abnormality (4-8%) were found in several patient series.[255-257] NOACs are hence contraindicated in pregnancy. A test to out-rule pregnancy and contraception counselling (including explicit warnings of fetal harm in the event of pregnancy on NOAC therapy) needs to be arranged before any treatment in women of reproductive age. Pregnancy on a NOAC should involve urgent multidisciplinary decision making with the patient including a switch to LMWH in case of requirement of continued anticoagulation.[258]

All NOACs are secreted into the breast milk although the effects on the newborn are unknown.[130, 259-261] In the absence of adequately powered studies and data, NOACs should not be used in breastfeeding women, and LMWH should be used instead.

NOACs and menstrual / abnormal uterine bleeding

Menses typically lasts 7 days with normal blood loss of < 80ml (with large intra- and interindividual variation). Abnormal uterine bleeding (AUB) or heavy menstrual bleeding (HMB), formerly termed *menorrhagia*, occurs in 9-14 % of women of reproductive age.[262] OAC use is an important iatrogenic cause of AUB/HMB, which was reported in 46% women on VKA; moreover, higher rates of AUB/HMB and an increased incidence of anemia was reported after initiation of OAC.[263]

The incidence of AF in women of reproductive age is low. Most evidence in this age group regarding AUB on NOAC therapy is derived from trials and registry data of NOACs in VTE treatment and secondary prevention. A registry of factor Xa inhibitor use in women of reproductive age (n=178) reported a 32% incidence of AUB/HMB.[264] Most cases were managed successfully with change of hormonal or anticoagulation medication (reduction, temporary interruption, or discontinuation of direct oral factor Xa inhibitor) but 14% of AUB/HMB required surgery. Importantly, 89% of patients had underlying anatomical abnormalities. Dabigatran has been associated with less AUB/HMB than VKA (5.9% versus 9.6%; OR 0.59; 95%CI 0.39–0.90; P = 0.015) with 0.5% and 0.8% major bleedings, respectively (HR, 0.65; 95% CI, 0.15–2.72). None of the bleeding events were fatal.[265]

Rivaroxaban was associated with prolonged menses (27 % vs. 8.3%, P=0.017), increased 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 to VKA in a single center observational study.[266] In the pooled EINSTEIN-DVT and PE trials, AUB was observed more frequently with rivaroxaban than with enoxaparin/VKA (HR 2.13; 95% CI, 1.57-2.89).[267] A small case series has reported resolution in 5/7 cases switching from rivaroxaban to apixaban.[268] The 'Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy' (AMPLIFY) trial reported clinically relevant non-major (CRNM) vaginal bleeding in 2.5 % and 2.1 % in apixaban- versus enoxaparin/warfarin users (OR 1.2, 95 % CI 0.7-2.0). 45 % and 20 % of all CRNM bleeding on apixaban and enoxaparin/warfarin, respectively, was vaginal in origin and was longer without significant differences in outcomes with apixaban.[269] In the Hokusai-VTE trial, rates of AUB/HMB was 15/100 person years (95% CI 11–19) versus 9/100 (95% CI 6–12) on edoxaban and LMWH/VKA, respectively (HR: 1.7, 95% CI 1.1–2.5). AUB occurred in 1.3% and 0.9% [OR 2.8; 95% CI 0.8–10.8] while CRNM vaginal bleeding occurred in 8.4% and 5.6% (OR 1.6, 95% CI 1.0–2.4), each on edoxaban vs. LMWH/VKA, respectively.[270]

In summary, there is a lack of robust data to reliably guide NOAC use in women of reproductive age with AF.[271] Although AUB/HMB seems less likely with dabigatran than with FXa inhibitors the quality of data does not seem to allow for a preference of one agent over the others. All cases of AUB/HMB on NOACs need gynecological assessment for underlying structural problems and consideration of local (hormone-loaded IUCD) or systemic (combined oral contraceptive) hormonal treatments and/or surgical procedures to reduce risk of recurrence. The use of anti-fibrinolytic agents (tranexamic acid 1 to 4g per days orally) or NOAC dose-reduction during menses can be considered in NOAC-associated AUB with important impact on the quality of life. A "test" of NOAC therapy may be advisable in women of reproductive age planned to undergo AF ablation since problems with AUB *after* the ablation may be more difficult to handle due to the presence of potentially prothrombogenic left atrial lesions and the inherent risk of thromboembolism in case of even short periods of OAC interruption.

NOACs in patients with atrial fibrillation and malignancy

The scope of the problem

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 tumor 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).[272-275] The increasing survival of cancer patients may additionally increase the incidence of AF among patients with active and past malignancies.

The risk of venous thromboembolism (VTE) is increased in the presence of cancer through a host of possible mechanisms.[276] Brain, pancreatic, ovarian, lung or hematological malignancies, as well as many cancer treatments (e.g., cisplatin, gemcitabine, 5-fluorouracil, erythropoietin, granulocyte colony stimulating factors) are associated with a particularly increased thromboembolic risk.[277]

Conversely, cancers may cause infiltrative liver failure resulting in thrombocytopenia or coagulopathy and increased risk of bleeding. Tumors may erode into blood vessels directly, and many gastro-intestinal and solid tumors such as intracranial tumors, renal cell carcinoma, or metastatic melanoma are very vascular and prone to bleeding. Hematologic 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 the platelet count and function (e.g., chemotherapy, some forms of irradiation).

Optimizing dose adjustments of Vitamin-K Antagonists

In spite of the preferred use of NOACs for stroke prevention in eligible patients with AF,[63] 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[278, 279] 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 of management approach. Conversely, a change in the approach to these patients needs to be considered if a low TTR is consistently observed. The 2020 ESC Guidelines give a class IIa recommendation to improve TTR and a class I recommendation to switch to a NOAC in patients with a TTR < 70%.[63]

Dosing during initiation of therapy

Automated dosing calculators are available that help in the determination of the 'optimal' starting regimen for warfarin (e.g., http://www.warfarindosing.org). Various factors play in favor of using a low vs. high starting dose, including older age, frailty, and chronic kidney disease. No strong advice can be provided for routinely using either strategy and individualization of the approach based on patient characteristics is required. In view of the lack of evidence supporting genotype-based dosing the latter is not advisable on a general basis.[279, 280] Use of a loading dose of warfarin is not recommended and may even be counterproductive.[281] For acenocoumarol, typical loading dose regimens include 2-3mg on day one, two and three (followed by INR assessment), but treatment may also be initiated using the anticipated maintenance dose.[282] In contrast, 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.[282] Typical loading dose regimens of phenprocoumon include 6 (-9) mg on day 1, followed by 6 mg on day 2 and 3-6mg on day 3, with subsequent dosing based on the a first INR measurement in the morning of day 4.

Dosing during maintenance therapy

Interpatient variability of optimal VKA 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 centers, data have emerged indicating the usefulness of using dosing algorithms to optimize VKA dosing and, ultimately, the time in therapeutic range (TTR).[283-285] One such algorithm is presented in Table 15, 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 with its shorter half-life more short-term based adjustment may be feasible.

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[286, 287] as well as self-monitoring and self-management[288] 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 intracranial bleeding increases at an INR > 3.0 (and clearly >4.0-5.0), the vast majority of events in absolute numbers occurs at a therapeutic INR level.[289] 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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