

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

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The current manuscript is the Executive Summary of the second update to the original Practical Guide, published in 2013. Non-vitamin K antagonist oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with atrial fibrillation (AF), and have emerged as the preferred choice, particularly in patients newly started on anticoagulation. Both physicians and patients are becoming more accustomed to the use of these drugs in clinical practice. However, many unresolved questions on how to optimally use these agents in specific clinical situations remain. The European Heart Rhythm Association (EHRA) set out to co-ordinate a unified way of informing physicians on the use of the different NOACs. A writing group identified 20 topics of concrete clinical scenarios for which practical answers were formulated, based on available evidence. The 20 topics are (i) eligibility for NOACs; (ii) practical start-up and follow-up scheme for patients on NOACs; (iii) ensuring adherence to prescribed oral anticoagulant intake; (iv) switching between anticoagulant regimens; (v) pharmacokinetics and drug–drug interactions of NOACs; (vi) NOACs in patients with chronic kidney or advanced liver disease; (vii) how to measure the anticoagulant effect of NOACs; (viii) NOAC plasma level measurement: rare indications,

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precautions, and potential pitfalls; (ix) how to deal with dosing errors; (x) what to do if there is a (suspected) overdose without bleeding, or a clotting test is indicating a potential risk of bleeding; (xi) management of bleeding under NOAC therapy; (xii) patients undergoing a planned invasive procedure, surgery or ablation; (xiii) patients requiring an urgent surgical intervention; (xiv) patients with AF and coronary artery disease; (xv) avoiding confusion with NOAC dosing across indications; (xvi) cardioversion in a NOAC-treated patient; (xvii) AF patients presenting with acute stroke while on NOACs; (xviii) NOACs in special situations; (xix) anticoagulation in AF patients with a malignancy; and (xx) optimizing dose adjustments of VKA. Additional information and downloads of the text and anticoagulation cards in different languages can be found on an EHRA web site ([www.NOACforAF.eu](http://www.NOACforAF.eu)).

## Keywords

Non-vitamin K antagonist oral anticoagulants • Vitamin K antagonist • Atrial fibrillation • Stroke

## Introduction

The proper use of non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) for stroke prevention in patients with atrial fibrillation (AF) requires a diligent approach in various settings of daily clinical practice.<sup>1</sup> This Practical Guide, as its predecessors from 2013 and 2015, supplements the Guidelines, providing guidance on how to use NOACs in specific clinical situations.<sup>1–3</sup> In some instances, the authors opted to make recommendations that do not fully align with all SmPCs, with the goal to provide more uniform and simple practical advice. The main pointers of the 2018 version of the European Heart Rhythm Association (EHRA) Practical Guide are summarized in this Executive Summary. The full text of the Update is published in the *European Heart Journal*.<sup>4</sup> The 2018 EHRA Practical Guide will also be presented in a new version of the slide kit (downloadable for free by EHRA members) and a Key Message booklet, which can be obtained through EHRA and the European Society of Cardiology (ESC). The reader is referred to visit [www.NOACforAF.eu](http://www.NOACforAF.eu) for up-to-date information, where also feedback can be provided.

## Eligibility for non-vitamin K antagonist oral anticoagulants

Strictly, 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).<sup>5–9</sup> The term 'non-valvular' has been eliminated in the 2016 ESC guidelines on the management of patients with AF and is also not used anymore in this practical guide.<sup>5,7</sup> Indeed, all other native valvular stenoses and insufficiencies as well as a moderately sized group of patients after mitral valve repair and bioprosthetic valve replacements were included in the pivotal NOAC trials in which they demonstrated a comparable relative efficacy and safety vs. warfarin in patients with vs. without valvular disease (except for a higher risk of bleeding with rivaroxaban vs. warfarin in patients with valvular heart disease in a *post hoc* analysis of the ROCKET-AF trial).<sup>7,10–15</sup> Non-vitamin K antagonist oral anticoagulants may therefore be used in such patients.<sup>5,7,16</sup> One exception may be AF in the presence of a biological mitral prosthesis implanted for rheumatic mitral stenosis. Although mitral valve flow is normalized post-mitral valve replacement in these patients, their atria usually remain large and severely diseased. As such, VKA may be the preferred option over NOACs in these patients, but more data are

needed. In hypertrophic (obstructive) cardiomyopathy, there is limited experience with NOACs but from a pathophysiological perspective NOACs can be used in these patients.<sup>17,18</sup>

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

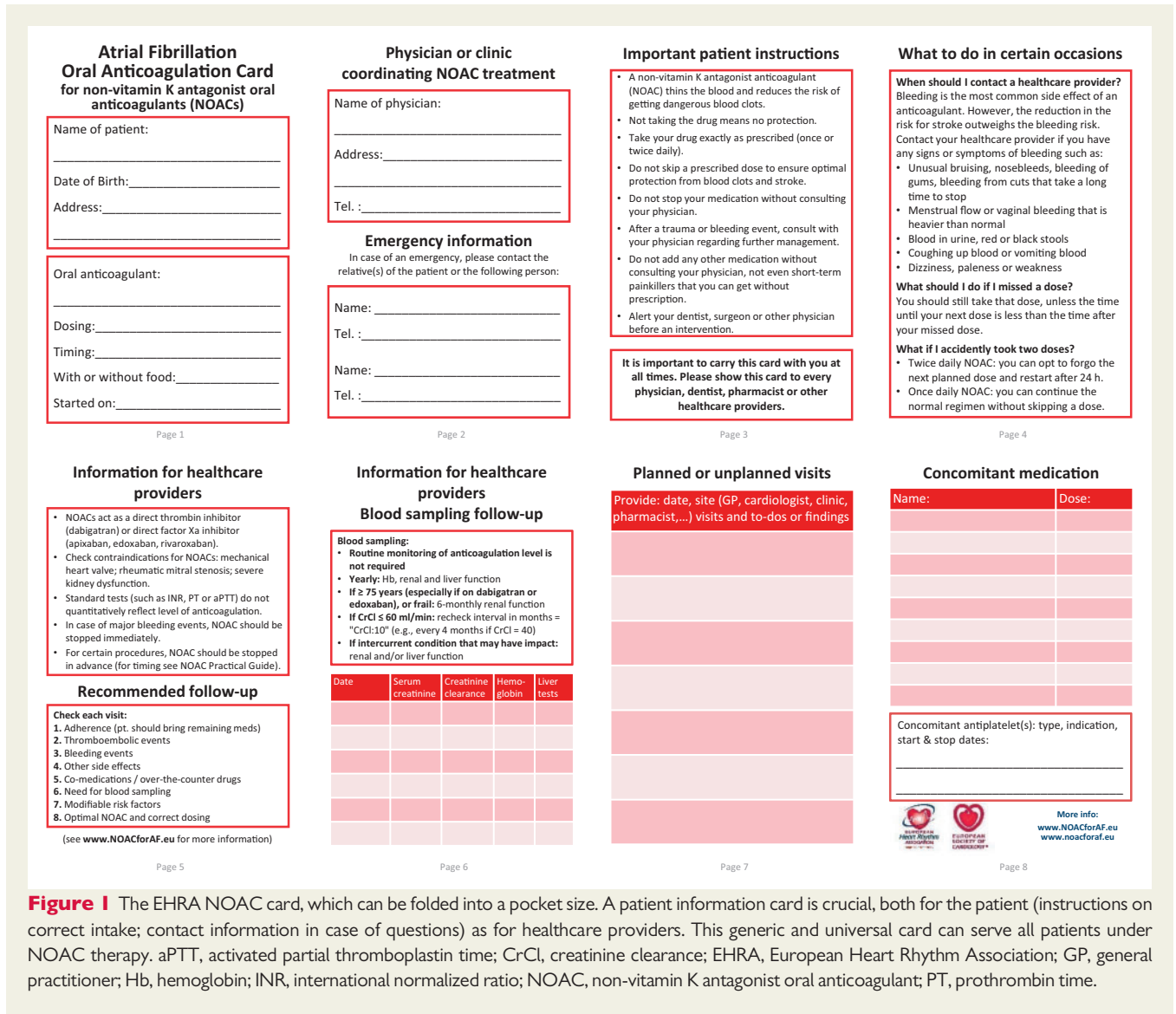
With four NOACs available in different dosages for different indications and with different dose-reduction criteria, identification of the correct dose has become more complicated and is one of the key challenges in the daily use and individualization of treatment.<sup>19–23</sup> Dose reduction of NOACs is primarily recommended only according to the dose-reduction criteria investigated in the large phase III trials. Whenever possible, the tested standard dose of NOACs should be used. Also, patient age, weight, renal function, co-medications, and other comorbidities influence the choice.

Bleeding risk should be systematically assessed, e.g. by the HAS-BLED or other bleeding risk scores.<sup>24,25</sup> Importantly, however, a high bleeding risk in itself should not automatically result in decision not to anticoagulate as stroke risk tracks along with the bleeding risk.<sup>5,26</sup> For the practical management, correcting and minimizing modifiable risk factors is of critical importance in order to minimize the risk of bleeding while on treatment with a NOAC.<sup>5</sup>

The proposed NOAC card (*Figure 1*) presented in this version of the Practical Guide has been updated and will be available for download in various languages at [www.NOACforAF.eu](http://www.NOACforAF.eu). Critical elements in the follow-up of patients (and in the assurance of optimal adherence) are summarized in *Figure 2*.

## Importance of drug–drug interactions of non-vitamin K antagonist oral anticoagulants

Despite fewer interactions with NOACs compared to VKA, physicians need to consider the pharmacokinetic interactions of accompanying drugs and comorbidities when prescribing NOACs.<sup>2</sup> The use of plasma level monitoring for NOAC dose-adjustment is discouraged for the vast majority of patients due to the lack of outcome data



**Figure 1** The EHRA NOAC card, which can be folded into a pocket size. 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 can serve all patients under NOAC therapy. aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; EHRA, European Heart Rhythm Association; GP, general practitioner; Hb, hemoglobin; INR, international normalized ratio; NOAC, non-vitamin K antagonist oral anticoagulant; PT, prothrombin time.

to support such an approach. Only in very 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. 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.

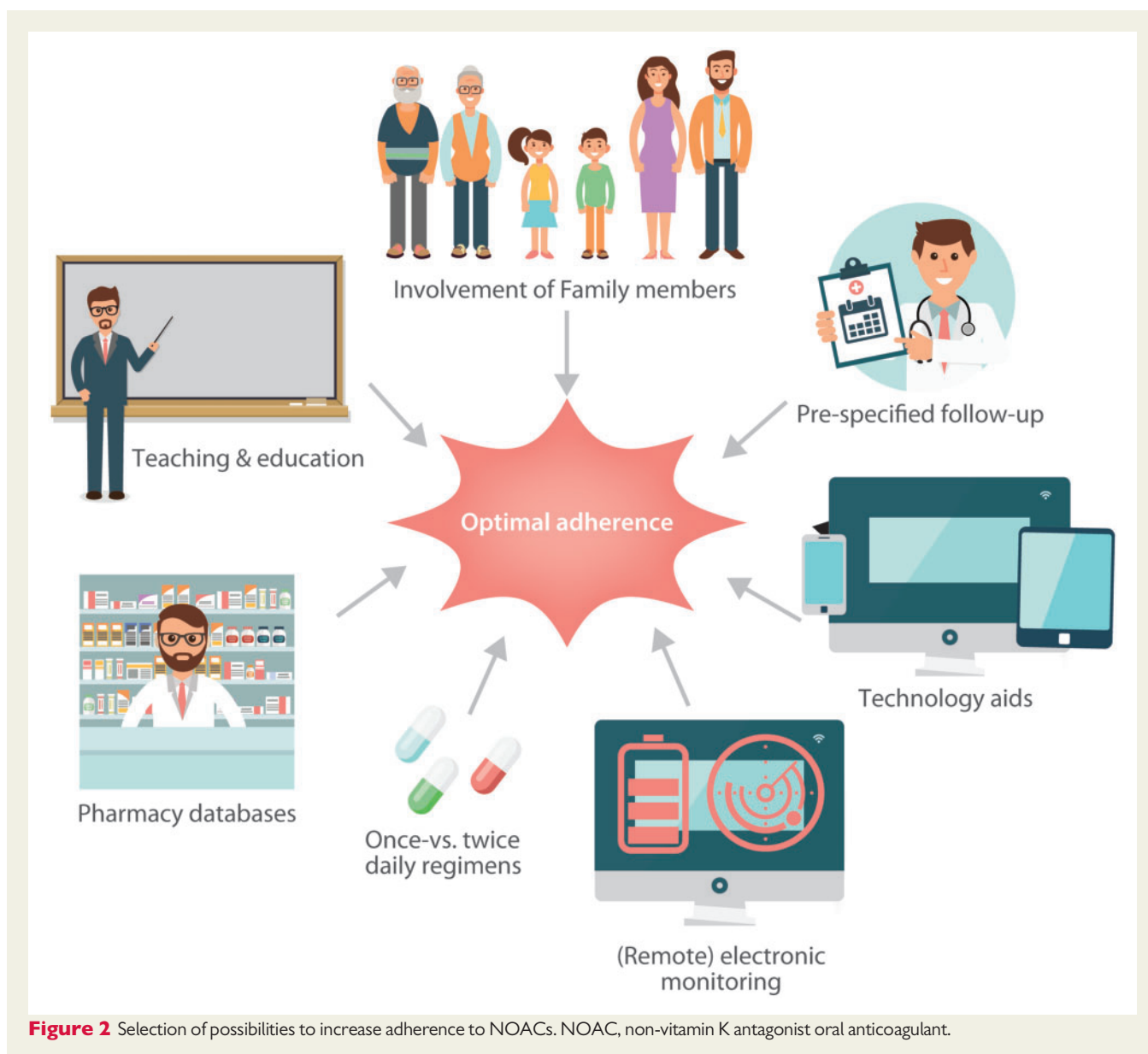
## Non-vitamin K antagonist oral anticoagulants in patients with chronic kidney disease or advanced liver disease

In the context of NOAC treatment, renal function should preferably be estimated by calculating the creatinine clearance (CrCl) using the Cockcroft–Gault method, which was used in most NOAC trials. In

patients on NOACs, renal function needs to be monitored diligently, at least yearly, to detect changes in renal function and adapt the dose accordingly. If renal function is impaired (i.e. CrCl ≤ 60 mL/min), a more frequent evaluation is recommended (e.g. by dividing CrCl by 10 to obtain the minimum frequency of renal function testing in months).

Compared with warfarin, all four NOACs showed consistent efficacy and safety in patients with *mild to moderate* chronic kidney disease (CKD) compared with non-CKD patients in the respective subgroup analyses of pivotal NOAC trials.<sup>27–32</sup> In addition, the ARISTOTLE trial data analysis suggests that the bleeding benefit with apixaban compared to warfarin becomes significantly more prominent at lower CrCl values, while the stroke reduction benefit is maintained.<sup>29–33</sup> In contrast, the bleeding benefit of 110 mg dabigatran over warfarin is lost in patients with CrCl < 50 mL/min while maintaining a similar stroke risk reduction compared to VKA.<sup>27</sup>

There are no randomized clinical trial (RCT) data on the use of NOACs or warfarin for stroke prevention in AF patients with



severe CKD or on renal replacement therapy (RRT). The efficacy and safety of NOACs in patients with end-stage renal dysfunction and on dialysis is unclear and subject to ongoing studies (e.g. NCT02942407 and NCT02933697). Given the lack of strong evidence also for VKA in this patient population, the decision to anticoagulate remains a very individualized one requiring a multidisciplinary approach considering and respecting patients' preferences.<sup>34–36</sup>

The use of VKAs in patients with *advanced liver disease* and coagulopathy is challenging due to intrinsically elevated International Normalized Ratio (INR) values and difficulties in selecting appropriate VKA dosing.<sup>37–41</sup> Also all four NOACs are contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Turcotte-Pugh C cirrhosis. Rivaroxaban should also not be used in AF patients with Child B liver cirrhosis.<sup>42</sup>

## How and when to measure the anticoagulant effect of non-vitamin K antagonist oral anticoagulants?

Non-vitamin K antagonist oral anticoagulants do not require monitoring of coagulation. However, laboratory assessment of drug exposure and anticoagulant effect may help clinicians in emergencies such as bleeding, urgent procedures, suspected overdose, or acute stroke. It can also be considered to guide long-term treatment in exceptional patients with special characteristics. This, however, should only be done under the guidance of a coagulation expert and in the knowledge that hard clinical outcome data do not exist for such a strategy.

Routine coagulation tests (PT and aPTT) generally do not provide an accurate assessment of NOAC anticoagulant effects. Conversely,



the latter can be measured via specific coagulation assays developed for the quantification of NOAC plasma levels.<sup>43–45</sup> The use of appropriate calibrators allows for the determination of plasma concentrations of all NOACs. It is recommended that labs should be experienced with these measurements. Moreover, emergency situations will require 24/7 availability of the specific assays, which is currently only possible in a minority of labs.

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

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

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

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

- (1) *Waiting* until the anticoagulant activity of the NOAC effect wanes as a result of spontaneous clearance of the drug.
- (2) *Specific reversal*. A specific reversal agent is available for dabigatran (idarucizumab, a humanized antibody fragment that specifically binds dabigatran).<sup>46</sup> Specific agents for FXa inhibitors are undergoing clinical testing, including andexanet alfa<sup>47</sup> and ciraparantag (PER 977).<sup>48</sup>
- (3) *Non-specific support of haemostasis* using coagulation factors concentrates. There is increasing information about the effects of (activated) prothrombin complex concentrates in cohorts of NOAC-treated patients with bleeding.<sup>49</sup> In contrast, the use of fresh frozen plasma is not considered a useful reversal strategy.<sup>50</sup> The use of antifibrinolytics (e.g. tranexamic acid, 1 g i.v., repeated every 6 h if needed) or desmopressin 0.3 µg/kg i.v. infusion (with a maximal dosing of 20 µg)—especially in special situations with associated coagulopathy or thrombopathy—may be considered.

*Nuisance bleeds* can usually be managed by delaying intake or withholding the NOAC for a maximum of one dose. *Minor bleedings* may require more aggressive therapy with a focus aimed at treating the cause of the bleeding (e.g. PPI for gastric ulcers, antibiotics for urinary tract infection, etc.). Epistaxis and gum bleeds can be treated with local anti-fibrinolytics. In case of recurrent minor bleeding events without causal therapeutic options, an alternative NOAC with a potentially different bleeding profile should be considered while maintaining effective stroke prevention. A suspected or documented occult bleeding should trigger a workup to uncover the underlying cause and the treatment thereof whenever possible. Cessation or temporary interruption without consultation needs to be discouraged due to the subsequently increased thromboembolic risk. *Major and/or life-threatening bleeding* needs to be

aggressively managed including the use of specific as well as non-specific reversal strategies.

## Patients undergoing a planned invasive procedure, surgery, or ablation

Awaiting the results of the ongoing Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE; NCT02228798), few prospective data on the management of NOACs are available.<sup>51</sup>

It is recommended not to interrupt oral anticoagulation for most *minor surgical* procedures, and those procedures where bleeding is easily controllable. In general, these procedures can be performed 12–24 h after the last NOAC intake, with NOAC restart 6 h later.

For invasive procedures with a *low bleeding risk* (including cardiac device implantations), it is recommended to take the last dose of a NOAC 24 h before the elective procedure in patients with normal kidney function.<sup>52</sup> For patients on dabigatran and a CrCl <80 mL/min, a graded interruption should be considered.

In case of invasive procedures that carry a *high risk for major bleeding*, it is recommended to take the last NOAC dose 48 h or longer before surgery. In cases with combined factors that make prediction of NOAC clearance unclear, measurement of NOAC plasma levels may be considered, and only go ahead with the planned surgical intervention when the level is considered low enough. However, such an approach is without evidence base, including the determination of 'safe' NOAC levels in this setting as well as waiting for levels to drop into that range whilst accepting the inherent risk of thromboembolism during that time.

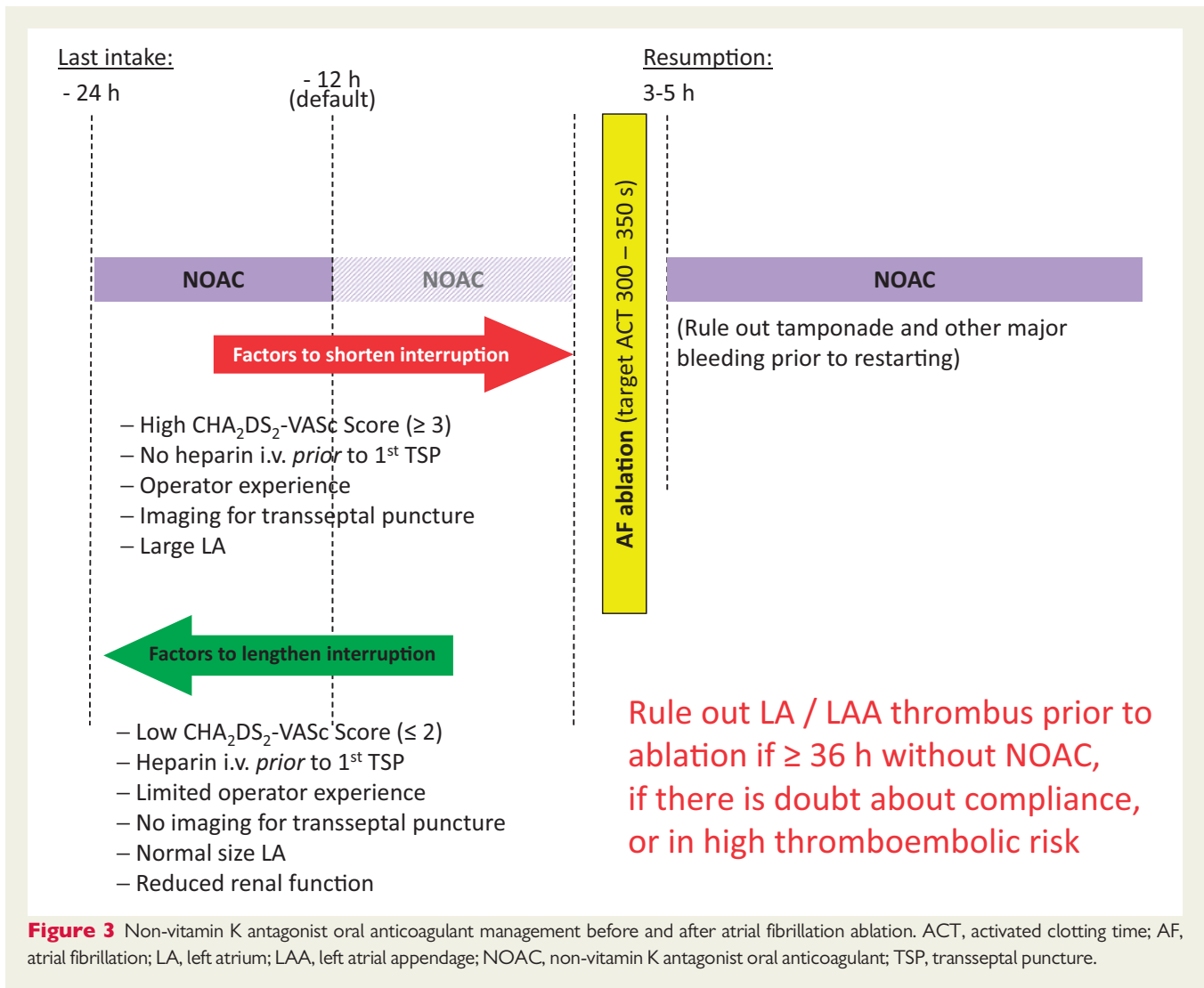
Preoperative bridging with low molecular weight heparin (LMWH) or heparin is *not* recommended in NOAC-treated patients.

*After a procedure* with immediate and complete haemostasis, NOACs can generally be resumed 6–8 h after the end of the intervention. In surgical interventions for which resuming full dose anticoagulation within the first 48–72 h after the procedure carries a bleeding risk that may outweigh the risk of AF-related embolism, initiation of post-operative thromboprophylaxis 6–8 h after surgery and restarting the NOAC 48–72 h postoperatively, but as soon as possible, can be considered.

Whether opting to administer the last NOAC dose shortly before an *AF ablation procedure* (i.e. 'truly uninterrupted') or to go for a short cessation period (last NOAC dose on the day before the procedure), may depend on a number of factors (Figure 3).<sup>2,53–58</sup> It is reasonable to administer a last dose of NOAC 12 h before the start of the intervention, especially if transseptal puncture is performed without periprocedural imaging (as is mostly the case in Europe).<sup>53</sup>

## Patients requiring an urgent surgical intervention

If an emergency intervention is required, the NOAC should be discontinued immediately. Specific management will then depend on the level or urgency.<sup>59</sup>



*Immediate 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. In these cases, reversal with idarucizumab (for dabigatran)<sup>46</sup> should be considered, especially in moderate-to high-haemorrhagic risk procedures.<sup>60</sup> If specific reversal agents are not available, prothrombin complex concentrate (PCC) or activated PCC (aPCC) should be considered despite the clinical lack of evidence for efficacy and safety (only animal data).<sup>61–63</sup>

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

*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.

## Patient with atrial fibrillation and coronary artery disease

The combination of AF and coronary artery disease is not only a common and complex clinical setting to deal with regarding anticoagulation and antiplatelet therapy, it is also associated with significantly higher morbidity and mortality.<sup>64,65</sup> The practice of adding aspirin or a P2Y<sub>12</sub> inhibitor to a (N)OAC is referred to as 'dual therapy', while adding both aspirin and a P2Y<sub>12</sub> inhibitor to a (N)OAC is called 'triple therapy'. Dual antiplatelet therapy is referred to as 'DAPT'.

Recent randomized clinical trials (WOEST, PIONEER AF, RE-DUAL PCI) have revealed an almost halved risk for clinically relevant bleeding in patients with AF treated with dual therapy compared to triple therapy after PCI. Albeit those studies were individually underpowered for efficacy, a meta-analysis suggests that the likelihood of an excess of

thrombo-embolic events during dual therapy vs. triple therapy is low.<sup>66</sup> Two ongoing trials, AUGUSTUS (NCT02415400) and ENTRUST-AF PCI (NCT02866175)<sup>67</sup> will add further information on how and how long (if at all) triple anticoagulation should be administered.

In general, the bleeding risk seems to be lower with a NOAC plus antiplatelet combination than with a VKA plus antiplatelet combination.<sup>68–70</sup> The length of DAPT/triple therapy no longer depends on the type of stent [i.e. Drug-eluting stent (DES) or bare metal stent (BMS)] but on the clinical presentation of the patient.<sup>5,71</sup> Today, the 'default' duration of triple therapy may be as short as 3 months after ACS and 1 month after elective stenting; however, both the duration of aspirin and/or P2Y<sub>12</sub> inhibitor as well as the choice of NOAC need to be individualized, based on a careful assessment of ischaemic- vs. bleeding risk. In the setting of dual therapy it may be feasible to use one of the newer P2Y<sub>12</sub> inhibitors with a (N)OAC under certain circumstances such as perceived high-thrombotic risk, ACS, or prior stent thrombosis.

The 2017 ESC DAPT and 2016 AF guidelines recommend discontinuing any antiplatelet agent at 12 months after a PCI or ACS and to only consider keeping one antiplatelet plus a (N)OAC beyond 12 months in patients at very high risk of coronary events.<sup>5,71</sup>

## Cardioversion in a non-vitamin K antagonist oral anticoagulant treated patient

Based on current ESC guidelines,<sup>5</sup> in patients with AF of  $\geq 48$  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 transoesophageal echocardiography (TOE) performed to rule out left atrial thrombi. After cardioversion, continuous oral anticoagulation is mandatory for at least another 4 weeks, irrespective of CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>5,72</sup>

A strategy with at least a single NOAC dose  $\geq 4$  h before cardioversion ( $\geq 2$  h after apixaban loading dose) appears safe and effective in patients with AF of  $\geq 48$  h duration, provided that a TOE is performed prior to cardioversion. The alternative is starting anticoagulation with a NOAC first, and delaying cardioversion for at least 3 weeks.<sup>73–77</sup> A similar strategy of starting the NOAC before cardioversion, with a TOE dependent on institutional policy or patient-elevated stroke risk, is applicable to those with AF of  $< 48$  h duration.

Patients in whom TOE identifies a left atrial thrombus should not undergo cardioversion. Treatment with VKA is standard in these situations but NOACs may also be an option, particularly in patients where a VKA is not well tolerated or adequate INR control cannot be obtained.

## Atrial fibrillation patients presenting with acute stroke while on non-vitamin K antagonist oral anticoagulant

According to current guidelines and official labelling, thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) is

approved within 4.5 h of onset of stroke symptoms but should not be administered in patients on full anticoagulation. Therefore, thrombolytic therapy cannot be given within 24 h after the last intake of a NOAC due to their plasma half-lives. The case is different for dabigatran due to the availability of the rapid acting specific reversal agent, idarucizumab. After reversal and assessment of coagulation status, intravenous thrombolysis within 4.5 h of onset of moderate to severe stroke seems feasible and safe according to case series.<sup>78–80</sup> Based on expert consensus, the use of rt-PA may be considered in selected patients on a NOAC in cases in which a reliable and NOAC specific coagulation assessment is available without long delay and demonstrating a concentration  $< 30$  ng/mL for rivaroxaban, apixaban, or edoxaban (see main document for detailed discussion).<sup>81,82</sup>

There is a proven benefit of endovascular thrombectomy up to 7.3 h after stroke onset in selected non-anticoagulated patients with a distal occlusion of the internal carotid artery or the proximal middle cerebral artery,<sup>83</sup> and thrombectomy also seems to be beneficial in highly selected stroke patients within 6–24 h of last seen normal.<sup>84,85</sup> Endovascular thrombectomy is now mentioned as 'first-line treatment' in patients with contraindication for intravenous thrombolysis, while the AHA guidelines provide no specific recommendation in this regard.<sup>86,87</sup> Although the trials underlying these recommendations either excluded or contained just a few patients on VKA or NOAC, the small amount of data available suggests that endovascular thrombectomy may be safe also in these individuals but an impact of present anticoagulation on reperfusion-related bleeding risk has to be taken into account.<sup>88</sup>

In AF patients after ischaemic stroke, NOACs should be (re-) initiated in analogy to clinical practice with VKAs. Recommendations on (re-) starting of oral anticoagulation after ischaemic stroke must outweigh (recurrent) stroke risk vs. secondary haemorrhagic transformation.<sup>5,89–91</sup>

In analogy to patients with *acute intracranial bleeding (ICB)* being treated with warfarin, discontinuation of the drug, urgent blood pressure management, and rapid correction of the coagulation status (ideally with a direct reversal agent) is needed to limit haematoma enlargement in patients under NOACs.<sup>92–94</sup>

In the absence of randomized controlled trials, a case-by-case consideration is needed whether or not to reintroduce anticoagulation of any type in patients who have experienced an anticoagulation-related ICB.<sup>5,94–96</sup> Left atrial appendage occlusion may be considered, but also here randomized evidence is missing, which is why, ideally, treatment should occur in the framework of a randomized trial to contribute to evidence.<sup>97</sup>

## Non-vitamin K antagonist oral anticoagulants in special situations

Meta-analyses of NOAC trial data suggest no interaction of age for safety and efficacy (except for an increased risk of extracranial bleeding in patients  $\geq 75$  vs  $< 75$  years with both doses of dabigatran as compared to Warfarin).<sup>98,99</sup> Importantly, the higher absolute stroke 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 (see Table 1).<sup>100</sup>

**Table 1** Summary of age profile and interaction of age on bleeding in NOAC trials

Trial	≥75 subgroup overall % (number of patients)	Major bleeding (%/pt years NOAC vs VKA per age group P interaction for age)	Intracranial bleeding
<b>RE-LY</b>	41% (n = 7258)		
Dabigatran 110 mg BID		≥75: 4.43% vs. 4.37% < 75: 1.89% vs 3.04%	≥75: 0.37% vs 1.00% < 75: 0.14% vs 0.61%
		<b>P for interaction &lt;0.001</b>	<i>P for interaction = 0.28</i>
Dabigatran 150 mg BID		≥ 75: 5.10% vs 4.37% < 75: 2.12% vs 3.04%	≥ 75: 0.41% vs 1.0% < 75: 0.26% vs 0.61%
		<b>P for interaction &lt;0.001</b>	<i>P for interaction =0.91</i>
<b>ROCKET-AF</b>	44% (n = 6229)		
Rivaroxaban 20 mg OD (per protocol dose reduction to 15 mg in 20%)		≥ 75: 4.86% vs 4.40% < 75: 2.69% vs 2.79%	≥ 75: 0.34% vs 0.49% < 75: 0.20% vs 0.41%
		<i>P for interaction =0.336</i>	<i>P for interaction =0.365</i>
<b>ARISTOTLE</b>	31% (n = 5678)		
Apixaban 5 mg BID(per protocol dose reduction to 2.5 mg BID in 4.7%)		≥ 75: 3.3% vs 5.2% 65-74: 2.0% vs 2.8% < 65: 1.17% vs 1.51%	≥ 75: 0.43 vs% 1.29% 65-74: 0.28% vs 0.81% < 65: 0.31% vs 0.35%
		<i>P for interaction = 0.63 (continuous)</i>	<i>P for interaction = 0.20 (continuous)</i>
<b>ENGAGE-AF TIMI 48</b>	40% (n = 8474)		
<i>Higher dose edoxaban regimen</i>		≥ 75: 4.0% vs 4.8% < 75: 2.0% vs 2.6%	≥ 75: 0.5% vs 1.2% < 75: 0.3% vs 0.6%
Edoxaban 60 mg OD (28.6% < 75 and 41% ≥ 75 dose reduced to 30 mg)		<i>P for interaction = 0.57</i>	<i>P for interaction =0.34</i>
<i>Lower dose edoxaban regimen*</i>		≥ 75: 2.3% vs 4.8% < 75: 1.2% vs 2.6%	≥ 75: 0.4% vs 1.2% < 75: 0.2% vs 0.6%
Edoxaban 30 mg OD (28.6% < 75 and 41% ≥ 75 dose reduced to 15 mg)		<i>P for interaction = 0.95</i>	<i>P for interaction =0.99</i>

\*Not licensed.

Falls and risk of subdural haemorrhage in particular are often considered by physicians as a contraindication to OAC.<sup>101,102</sup> However, frailty and a (perceived) increased risk of falling *per se* should not be an exclusion criterion to anticoagulate since frail and older patients are at an increased risk of stroke and have been shown to benefit from NOAC therapy (best shown for edoxaban and apixaban).<sup>103–108</sup>

Dementia should not be viewed as a general contraindication to anticoagulation either, especially if well managed from a logistical point of view. Paradoxically, the fact that others take care of providing medication to dementia patients may guarantee higher adherence.

Overall, NOACs appear to be similarly safe and effective in patients with *moderate obesity* (up to 120 kg) or *moderate underweight* (down to 50 kg).<sup>41,109–123</sup> For patients with low body weight (<60 kg) specific dose-reduction criteria were employed in the trials for edoxaban and apixaban possibly making those drugs the preferred choice in these patients. Because of limited data in extremes of body weight, the use of VKA in patients with a body mass index  $\geq 40$  kg/m<sup>2</sup> (or weight > 120 kg) as well as in those weighting <50 kg should be considered (in line with recommendations from the International Society on Thrombosis and Haemostasis).<sup>116</sup> In rare case when a NOAC is needed in such circumstances, specific measurements of drug trough levels should be considered. This, however, should only be done under the guidance of a coagulation expert and in the

knowledge that hard clinical outcome data do not exist for such an approach.

All OAC use should be considered with caution in *women of child-bearing age* and an appropriate test to rule out pregnancy and contraceptive counselling advice arranged before initiation of any agent. Abnormal uterine bleeding (AUB; formerly called *menorrhagia*), occurs in 9–14% of the general female population of reproductive age,<sup>124</sup> which may be exacerbated by oral anticoagulants.<sup>125</sup> All cases of AUB on OAC need to have gynaecological assessment. Importantly, NOACs are contraindicated in pregnancy as well as during breastfeeding.

In patients with *epilepsy*, anticoagulation is affected by antiepileptic drugs via various potential interactions.<sup>126</sup> The significance of these drug–drug interactions is still largely unknown with only occasional case reports available.

## Anticoagulation in atrial fibrillation patients with a malignancy

So far, the only published RCT specifically targeting cancer patients stems from the HOKUSAI-VTE Cancer trial comparing edoxaban



with LMWH in patients with VTE (but not AF).<sup>127</sup> In line with these findings, several meta-analyses of the small subgroup of cancer patients in VTE trials reported similar or better efficacy of NOACs in comparison to VKA or LMWH for VTE prevention, although major bleeding rates were higher.<sup>128,129</sup> In how far these findings apply to AF patients with cancer requires further data. Indeed, much is still unknown about drug–drug interactions between NOACs and specific chemotherapeutic agents, urging further caution.<sup>130</sup>

## Optimizing dose adjustments of vitamin K antagonists

Automated dosing calculators are available that help in the determination of the 'optimal' starting regimen for VKA (e.g. <http://www.warfarindosing.org>). During maintenance therapy, using dosing algorithms to optimize VKA dosing and, ultimately, the time in therapeutic range (TTR) has been shown to be useful.<sup>131–133</sup> Importantly from a conceptual point of view, dosing is optimized not using daily dose adjustments but adjustments based on the weekly intake in warfarin. Receiving care at a dedicated anticoagulation clinic<sup>134,135</sup> as well as self-monitoring and self-management<sup>136</sup> has been shown to improve INR control in well-selected patients.

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