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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 specific 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,
Introduction

The proper use of non-vitamin K antagonist (VKA) oral anticoagu-

lants (NOACs) for stroke prevention in patients with atrial fibrilla-
tion (AF) requires a diligent approach in various settings of daily clinical practice.1 This Practical Guide, as its predecessors from 2013 and
2015, supplements the Guidelines, providing guidance on how to use
NOACs in specific clinical situations.1,3 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.4 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 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).5–9 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.5,7 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 piv-
otal NOAC trials in which they demonstrated a comparable relative
efficacy and safety vs. warfarin in patients with vs. without valvular dis-
ease (except for a higher risk of bleeding with rivaroxaban vs. war-
farin in patients with valvular heart disease in a post hoc analysis of
the ROCKET-AF trial).7,10–15 Non-vitamin K antagonist oral anticoagu-
lants may therefore be used in such patients.5,7,16 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 pre-
ferred option over NOACs in these patients, but more data are
needed. In hypertrophic (obstructive) cardiomyopathy, there is a
limited experience with NOACs but from a pathophysiological perspec-
tive NOACs can be used in these patients.17,18

Practical start-up and follow-up scheme for patients on non-vita-
mín K antagonist oral anticoagulants

With four NOACs available in different dosages for different indica-
tions 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.19–23
Dose reduction of NOACs is primarily recommended only accord-
ing to the dose-reduction criteria investigated in the large phase III tri-
als. 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.24,25 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.5,26
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.5

The proposed NOAC card (Figure 1) presented in this version of
the Practical Guide has been updated and will be available for down-
load in various languages at www.NOACforAF.eu. Critical elements
in the follow-up of patients (and in the assurance of optimal adher-
ence) 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, physi-
cians need to consider the pharmacokinetic interactions of accompa-
nying drugs and comorbidities when prescribing NOACs.5 The use
of plasma level monitoring for NOAC dose-adjustment is discour-
aged for the vast majority of patients due to the lack of outcome data
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: | | |

Information for healthcare providers

- NOACs act as a direct thrombin inhibitor (apixaban, edoxaban, rivaroxaban).
- Check creatinine clearances for NOACs: mechanical heart valve, thrombotic mitral stenosis, severe kidney dysfunction.
- Standard tests (such as INR, PT or aPTT) do not quantitatively reflect level of anticoagulation.
- In case of major bleeding events, NOAC should be stopped immediately.
- For certain procedures, NOAC should be stopped in advance (for timing see NOAC Pracical Guide).

Recommended follow-up

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

Important patient instructions

- A non-vitamin K antagonist anticoagulant (NOAC) thins the blood and reduces the risk of getting dangerous blood clots.
- Not taking the drug means no protection.
- Take your drug exactly as prescribed (once or twice daily).
- Do not skip a prescribed dose to ensure optimal protection from blood clots and stroke.
- Do not stop your medication without consulting your physician.
- After a trauma or bleeding event, consult with your physician regarding further management.
- Do not add any other medication without consulting your physician, not even short-term painkillers that you can get without prescription.
- Alert your dentist, surgeon or other physician before an intervention.

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 occasions

When should I contact a healthcare provider?
Bleeding is the most common side effect of an anticoagulant. However, the reduction in the risk for stroke outweighs the bleeding risk.
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?
You should still take that dose, unless the time until your next dose is less than the time after your missed dose.

What if I accidentally took two doses?
- Twice daily NOAC: you can opt to forget the next planned dose and restart after 24 h.
- Once daily NOAC: you can continue the normal regimen without skipping a dose.

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.: | | |

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. 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.

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. 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.34–36

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.37–41 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.42

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. 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 antplatelet 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). Specific agents for FXa inhibitors are undergoing clinical testing, including andexanet alfa and ciraparantag (PER 977).
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. In contrast, the use of fresh frozen plasma is not considered a useful reversal strategy. The use of antifibrinolytics (e.g. tranexamic acid, 1 g i.v., repeated every 6 h if needed) or desmopressin 0.3 mg/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 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 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. 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. 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 uncertain, 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). 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 peri-procedural imaging (as is mostly the case in Europe).

Patients requiring an urgent surgical intervention

If an emergency intervention is required, the NOAC should be discontinued immediately. Specific management will then depend on the level or urgency.
Immediate 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) should be considered, especially in moderate- to high-haemorrhagic risk procedures.

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).

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. The practice of adding aspirin or a P2Y₁₂ inhibitor to a (N)OAC is referred to as ‘dual therapy’, while adding both aspirin and a P2Y₁₂ 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...
Cardioversion in a non-vitamin K antagonist oral anticoagulant treated patient

Based on current ESC guidelines,5 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 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 CHA2DS2-VASc score.5,72

A strategy with at least a single NOAC dose ≥4 h before cardioversion (≥2 h after apixaban loading dose) appears safe and effective in patients with AF of ≥48 h duration, provided that a TOE is performed prior to cardioversion. The alternative is starting anticoagulation with a NOAC first, and delaying cardioversion for at least 3 weeks.73–77 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. 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.78–80 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).81,82

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,83 and thrombectomy also seems to be beneficial in highly selected stroke patients within 6–24 h of last seen normal.84,85 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.86,87 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.88

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.5,89–91

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.92–94

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.94–96 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.97

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 ≥75 vs <75 years with both doses of dabigatran as compared to Warfarin).98,99 Importantly, the higher absolute stroke risk resulted in a lower 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).100
Falls and risk of subdural haemorrhage in particular are often considered by physicians as a contraindication to OAC. 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).

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). 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 >40 kg/m² (or weight >120 kg) as well as in those weighing <50 kg should be considered (in line with recommendations from the International Society on Thrombosis and Haemostasis).

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 childbearing age and an appropriate test to rule out pregnancy and contraceptive counselling advice arranged before initiation of any agent. Abnormal uterine bleeding (AUB; formerly called menorrhagia), occurs in 9-14% of the general female population of reproductive age, which may be exacerbated by oral anticoagulants. 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. 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

| 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** |
| RE-LY | 41% (n = 7258) | ≥75: 4.43% vs. 4.37% | ≥75: 0.37% vs 1.00% |
| | | < 75: 1.89% vs 3.04% | < 75: 0.14% vs 0.61% |
| | | **P for interaction <0.001** | **P for interaction = 0.28** |
| | | ≥75: 5.10% vs 4.37% | ≥75: 0.41% vs 1.0% |
| | | < 75: 2.12% vs 3.04% | < 75: 0.26% vs 0.61% |
| | | **P for interaction <0.001** | **P for interaction = 0.91** |
| ROCKET-AF | 44% (n = 6229) | ≥75: 4.86% vs 4.40% | ≥75: 0.34% vs 0.49% |
| | | < 75: 2.69% vs 2.79% | < 75: 0.20% vs 0.41% |
| | | **P for interaction = 0.336** | **P for interaction = 0.365** |
| ARISTOTLE | 31% (n = 5678) | ≥75: 3.3% vs 5.2% | ≥75: 0.43% vs 1.29% |
| | | 65-74: 2.0% vs 2.8% | 65-74: 0.28% vs 0.81% |
| | | < 65: 1.17% vs 1.51% | < 65: 0.31% vs 0.35% |
| | | **P for interaction = 0.63 (continuous)** | **P for interaction = 0.20 (continuous)** |
| ENGAGE-AF TIMI 48 | 40% (n = 8474) | ≥75: 4.0% vs 4.8% | ≥75: 0.5% vs 1.2% |
| | | < 75: 2.0% vs 2.6% | < 75: 0.3% vs 0.6% |
| | | **P for interaction = 0.57** | **P for interaction = 0.34** |
| | Higher dose edoxaban regimen | ≥75: 2.3% vs 4.8% | ≥75: 0.4% vs 1.2% |
| | Edoxaban 60 mg OD (28.6% < 75 and 41% ≥ 75 dose reduced to 30 mg) | < 75: 1.2% vs 2.6% | < 75: 0.2% vs 0.6% |
| | | **P for interaction = 0.95** | **P for interaction = 0.99** |

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with LMWH in patients with VTE (but not AF). \textsuperscript{127} 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. \textsuperscript{128,129} 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. \textsuperscript{130}

### 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](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. \textsuperscript{131–133} 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 \textsuperscript{134,135} as well as from the weekly intake in warfarin.

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