The European Heart Rhythm Association Practical Guide on the Use of New Oral Anticoagulants in Patients with Non-valvular Atrial Fibrillation – A Brief Summary

Katrina Mountfort, Medical Writer, Radcliffe Cardiology

Reviewed by Paulus Kirchhof

University of Birmingham Centre for Cardiovascular Sciences, Birmingham, UK

Abstract

New oral anticoagulants (NOACs) are an alternative to vitamin K antagonists (VKAs) in the prevention of stroke in patients with non-valvular atrial fibrillation (AF). The European Heart Rhythm Association (EHRA) has produced a practical guide to detail the use of NOACs in clinical practice. The guide includes a practical start-up and follow-up scheme, emphasising the importance of strict adherence to the regimen – the anticoagulant effect drops rapidly after 12–24 hours. There is also guidance on how to measure the anticoagulant effect of NOACs, switching between anticoagulant regimes and dealing with dosing errors. Physicians will have to consider the pharmacokinetic effect of drugs and co-morbidities when prescribing NOACs – plasma levels of NOACs may be affected by P-glycoprotein (P-gp) substrates, as well as cytochrome P450 (CYP3A4) inducers or inhibitors. In patients with chronic kidney disease, reduced doses of NOACs may be indicated. Guidance is also given on the management of bleeding complications, and the cessation and reinitiation of NOACs in patients undergoing surgical interventions. Finally, the use of NOACs in specific clinical situations is considered; these include patients with AF and coronary artery disease (CAD), patients presenting with acute stroke while taking NOACs and patients with cancer.

Keywords

Atrial fibrillation, new oral anticoagulants, dabigatran, apixaban, rivaroxaban, edoxaban

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New oral anticoagulants (NOACs), including dabigatran[1] (a direct thrombin inhibitor), apixaban,[2] rivaroxaban[3] and edoxaban[4] (activated factor Xa inhibitors, not yet approved) have become alternatives to vitamin K antagonists (VKAs) for thromboembolic prevention in patients with non-valvular atrial fibrillation (AF), as a result of their numerous clinical advantages. However, there is a need for a practical guide detailing their use in specific clinical situations, which cannot be provided by practice guidelines due to lack of evidence and supporting data.[5] For similar reasons, the summary of product characteristics (SmPC) supplied by the manufacturer cannot provide such information. Furthermore, SmPCs are written for each individual agent, while the NOACs can often be treated as a group in practical terms. The European Heart Rhythm Association (EHRA) has therefore produced a practical guide to help with the use of the NOACs in clinical practice until more 'real life' data are available.[6] This article aims to provide a brief summary of this guide.

Practical Start-up and Follow-up Scheme for Patients on New Oral Anticoagulants

Before prescribing NOACs to patients with AF, a risk–benefit analysis should be carried out. When choosing a NOAC, the possibility of drug–drug interactions (DDIs) with co-medications should be considered. At the time of prescribing NOACS, patient education is crucial. The concomitant use of proton pump inhibitors (PPIs) is also recommended to reduce the risk of gastrointestinal bleeding. Patients should carry details about their therapy; a generic information card could serve for all NOACs. Most importantly, at start-up, it is vital to educate the patient on the importance of strict adherence to regimen, stressing the dangers of discontinuation or missing a dose.

A structured follow-up procedure for patients taking NOACs is essential, preferably every three months. Follow-ups can be undertaken by general practitioners (GPs), appropriate secondary care physicians, or nurse co-ordinated AF clinics.[7] During each visit, the following should be checked:

- compliance, including inspecting remaining medication;
- signals of thromboembolism;
- adverse effects (AEs), particularly bleeding; and
- use of co-medications.

Monitoring haemoglobin, renal and hepatic function should be performed yearly; more frequently in patients receiving dabigatran, in elderly and/or frail patients and those with compromised renal function.[5]

How to Measure the Anticoagulant Effect of New Oral Anticoagulants

Routine monitoring of coagulation is not required, although quantitative assessment of drug exposure may be useful in some emergency situations. In the absence of good data, a history of drug intake is probably the best available information on the anticoagulant effect.

Table 1: Absorption and Metabolism of New Oral Anticoagulants

	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Bioavailability	3–7 %	50 %	62 %	66 % (without food) ~100 % with food
Prodrug	yes	no	no	no
Clearance: non-renal/renal of adsorbed dose if normal renal function	20 %/80 %	73 %/27 %	50 %/50 %	65 %/35 %
Liver metabolism: CYP3A4	no	yes (elimination; minor CYP3A4)	minimal (<4 % of elimination)	yes (elimination)
Absorption with food	no effect	no effect	6–22 % more	+39 %
Intake with food?	no	no	no official recommendation yet	mandatory
Absorption with H2B/PPI	plasma level -12 to -30 %	no effect	no effect	no effect
Asian ethnicity	plasma level +25 %	no effect	no effect	no effect
GI tolerability	dyspepsia 5–10 %	no problem	no problem	no problem
Elimination half-life	12–17 hours	12 hours	9–11 hours	5–9 hours (young)/ 11–13 hours (elderly)

*GI = gastrointestinal; PPI = proton pump inhibitors. * = Not yet approved.*

Table 2: Potential Drug–Drug Interactions – Effects on New Oral Anticoagulant Plasma Levels

		Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Atorvastatin	P-gp/CYP3A4	+18 %	no data yet	no effect	no effect
Digoxin	P-gp	no effect	no data yet	no effect	no effect
Verapamil	P-gp/week CYP3A4	+12–180 %	no data yet	+53 % (slow release)	minor effect
Diltiazem	P-gp/week CYP3A4	no effect	+40 %	no data	minor effect
Quinidine	P-gp	+50 %	no data yet	+80 %	+50 %
Amiodarone	P-gp	+12–60 %	no data yet	no effect	minor effect
Dronedarone	P-gp/CYP3A4	+70–100 %	no data yet	+85 %	no data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP/CYP3A4	+140–150 %	+100 %	no data yet	up to +160 %
	Interaction	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fluconazole	CYP3A4	no data	no data	no data	+42 %
Cyclosporin; tacrolimus	P-gp	no data	no data	no data	+50 %
Clarithromycin; erythromycin	P-gp/CYP3A4	+15–20 %	no data	no data	+30–54 %
HIV protease inhibitors	P-gp and BCRP/CYP3A4	no data	strong increase	no data	up to +153 %
Rifampicin; St John's wort; carbamezepine; phenytoin; phenobarbital	P-gp and BCRP/ CYP3A4/CYP2J2	-66 %	-54 %	-35 %	up to -50 %
Antacids	GI absorption	-12–30 %	no data	no effect	no effect

*BCRP = breast cancer resistance protein; P-gp = P-glycoprotein. * = Not yet approved.*

When interpreting anticoagulation assays, it is important to know exactly when the NOAC was administered relative to the time of blood sampling. The maximum effect on clotting tests is gained around three hours after administration. For dabigatran, thrombin time (TT), ecarin clotting time (ECT),[8,9] activated thromboplastin time (aPTT)[8,9] and prothrombin test (PT)[9,10] may be used. Anti-factor Xa chromogenic assays are also commercially available; though their use has not been comprehensively validated.

Drug–Drug Interactions and Pharmacokinetics of New Oral Anticoagulants

The uptake, metabolism and elimination of NOACs are summarised in *Table 1*. Mechanisms underlying potential DDIs include the P-glycoprotein (P-gp) transporter involved in absorption and renal clearance.[11] Plasma levels of NOACs may be affected by P-gp substrates, which include many drugs used in AF patients (e.g. verapamil, dronedarone, quinidine). Cytochrome P450 (CYP3A4) is involved in the hepatic clearance of rivaroxaban,[12] but dabigatran is unaffected.[13] Plasma levels of rivaroxaban may therefore be affected by CYP3A4 inducers or inhibitors.

Dose reduction of NOACs is essential in patients treated with concomitant medications that increase the NOAC plasma level.[14,15] Therefore a system of levels of alert has been devised whereby red indicates a contraindication for use, orange indicates adaptation of the NOAC dose and yellow indicates dose maintenance, unless there are two concomitant yellow interactions, in which case dose reduction is recommended. A detailed table of potential DDIs is presented in *Table 2*.

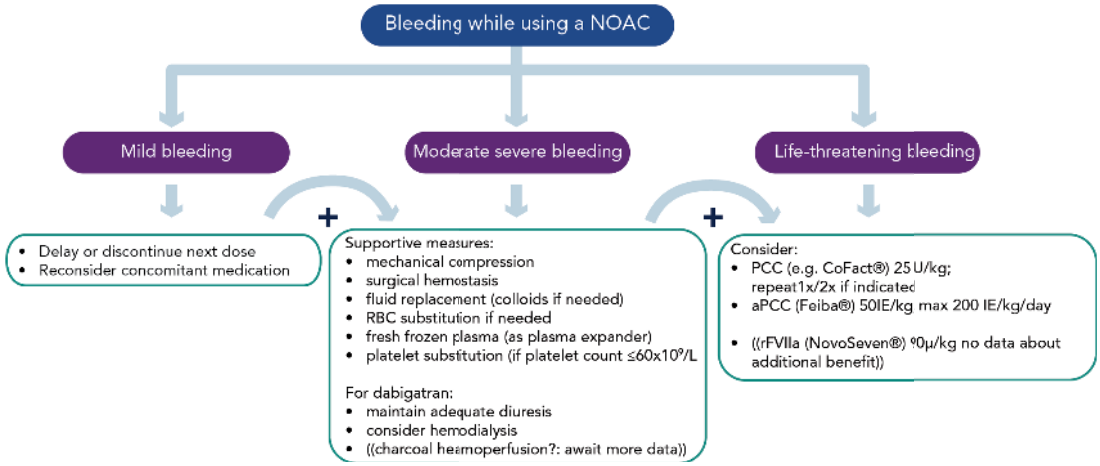
Switching Between Anticoagulant Regimens

When switching between anticoagulant regimes, anticoagulant efficacy must be maintained while minimising bleeding risk. Switching from VKAs to NOAC can be immediate if the international normalized ratio (INR) is less than 2.0. Due to the slow onset of action of VKAs, when switching from NOACs to VKAs, the two drugs should be administered concomitantly until the INR reaches an appropriate level.

Ensuring Compliance with New Oral Anticoagulant Intake

Ensuring compliance with NOAC intake is vital because the anticoagulant effect drops rapidly after 12–24 hours. Daily dosing

Figure 1: Management of Bleeding in Patients Taking New Oral Anticoagulants



NOAC = New Oral Anticoagulant; PCC = Prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate; RBC = red blood cell; rFVIIa = Recombinant Factor VIIa.

(QD) has been associated with better compliance than twice daily dosing (BID) in other drugs,[16] but there is insufficient data to instruct an optimum regime. Patient education may involve leaflets and instruction at initiation, patient safety cards and group sessions. Technological aids such as medication boxes may help. If low compliance persists, a therapy switch to VKAs may be appropriate.

How to Deal with Dosing Errors

Dosing errors must be dealt with promptly. In case of a missed dose on a BID regime, the missed dose can be taken up to six hours after the scheduled intake. If this is not possible, the dose should be skipped and the next scheduled dose taken. For QD, the missed dose can be taken up to 12 hours after scheduled intake. After a double dose, on BID, skip the next planned dose and restart BID after 24 hours. On QD, continue the normal regimen. Hospitalisation is advised in case of overdose.

Patients with Chronic Kidney Disease

Chronic kidney disease (CKD) confers the risk of thromboembolic events and bleeding in AF patients,[17,18] as well as being a risk factor for stroke and systemic embolism.[19] NOACs may be used in AF patients with mild or moderate CKD. Careful consideration should be given before administering dabigatran, which is primarily cleared renally, to patients with CKD. Individual risk–benefit analyses should be undertaken. Reduced doses of FXa inhibitors may be indicated in patients with reduced renal function (creatinine clearance [CrCl] 30–50 ml/min).[10] Dose reductions are indicated in patients with CrCl <50 ml/min for apixaban[2] and rivaroxaban.[20] NOACs should be avoided in AF patients with haemodialysis; VKAs may be preferable.

Renal function should be monitored at yearly intervals if CrCl exceeds 60 ml/min and the NOAC dose adapted in response to any change. If renal function is impaired (30–60 ml/min), six-monthly monitoring is recommended. In advanced CKD (CrCl ≤30 ml/min), monitoring should be carried out every three months. These are expert suggestions that are not supported by good data.

What To Do If There is a Suspected Overdose Without Bleeding, or a Clotting Test is Indicating a Risk of Bleeding

Doses of NOACs above those recommended are associated with increased bleeding risk. In cases of acute recent ingestion of overdose, activated charcoal should be given to reduce absorption. Coagulation tests can assess possible bleeding risks. However, given the short plasma half-life of NOACs, in the absence of bleeding, a 'wait-and-see' approach is recommended.

Management of Bleeding Complications

Recommendations on bleeding management are summarised in *Figure 1*.

Not Life-threatening Bleeding

In view of the short plasma half-life of NOACs, time is the most important antidote.[21] Restoration of haemostasis should occur within 12–24 hours after the last dose. It is therefore important to establish the exact time of last intake and factors influencing plasma concentration, such as co-medications and CKD. Dialysis is an option for removal of dabigatran,[22] but the risks of bleeding at the puncture site must be balanced against the risk of waiting.

Life-threatening Bleeding

In addition to the measures for not life-threatening bleeding, prothrombin complex concentrate (PCC) may be used.[23]

Patients Undergoing a Planned Surgical Intervention or Ablation

Surgical interventions that carry a bleeding risk[24] require temporary cessation of NOACs. When the intervention involves no significant bleeding risk (e.g. dental interventions, cataract, glaucoma intervention), the procedure can be carried out at the trough concentration of the NOAC (i.e. 12 or 24 hours after the last intake). If possible, the intervention should be scheduled 18–24 hours after the last intake, then NOACs restarted six hours later. For procedures with a minor bleeding risk, NOACs should be discontinued 24 hours before the procedure. For high-risk interventions such as pulmonary vein isolation (PVI) or thoracic surgery, the last NOAC should be taken 48 hours previously. In cases of impaired kidney function, earlier interruption of therapy may be indicated.

For procedures with immediate and complete haemostasis, NOACs can be resumed 6–8 hours after the intervention. However, for many surgical interventions, the risks of resuming NOACs within 48–72 hours after the procedure may outweigh the risk of cardioembolism.

Low molecular weight heparins (LMWH) may be used 6–8 hours after surgery if haemostasis has been achieved, restarting NOACs 48–72 hours after the procedure. Maximal anticoagulation effect will be achieved within two hours of ingestion. For AF patients undergoing PVI, a strategy of bridging with VKAs is preferred.[25]

Patients Undergoing an Urgent Surgical Intervention

In cases of emergency intervention, the NOAC should be discontinued, surgery deferred, if possible, for at least 12 hours and ideally 24 hours after the last dose.

Patient with Atrial Fibrillation and Coronary Artery Disease

The combination of AF and coronary artery disease (CAD) is relatively common, and is associated with significantly higher mortality rates.[26] Recommendations are based on three clinical scenarios.

Scenario 1 – Acute Coronary Syndrome Management in Atrial Fibrillation Patients on New Oral Anticoagulants

Risk scores for ischaemic and bleeding events may guide therapeutic decisions.[27] NOACs should be discontinued upon presentation with acute coronary syndrome (ACS). Unless contraindicated, low-dose aspirin should be given, as well as a $P2Y_{12}$ inhibitor. In cases of ST-elevation myocardial infarction (STEMI), additional parenteral anticoagulation should be used. In cases of non-ST elevation MI (NSTEMI), after discontinuing the NOAC and waning of its effect, fondaparinux (preferred), unfractionated heparin (UFH) or enoxaparin may be initiated. For percutaneous coronary intervention (PCI) in NSTEMI, the NOAC should be discontinued and the NOAC effect should have disappeared before the intervention. Periprocedural anticoagulation is recommended.

In the chronic setting (<1 year after ACS), anticoagulant therapy should be personalised, based on atherothrombotic, cardioembolic and bleeding risks. For therapy beyond the first year, treatment as in scenario 3 may be used.

Scenario 2 – Management of the Patient with a Recent Acute Coronary Syndrome (<1 Year) Who Develops New Onset Atrial Fibrillation

According to ACS guidelines, dual antiplatelet therapy should be given for up to one year. If AF develops, anticoagulants may be considered. In patients with low atherothrombotic risk, VKAs monotherapy may be considered after 1–3 months, especially if they have elevated bleeding risk.

Scenario 3 – A Stable Coronary Artery Disease Patient (Acute Coronary Syndrome >1 Year Ago) Develops Atrial Fibrillation

Stable CAD patients developing AF should receive anticoagulation. Any of the NOACs may be used in preference to VKAs, without increased risk of myocardial ischaemic events.[28]

Cardioversion in a New Oral Anticoagulant Treated Patient

In patients with AF >48 hours duration undergoing cardioversion, oral anticoagulants should be given for at least three weeks previously, and for four weeks afterwards. Clinical data show no significant additional risk in patients treated with NOACs and VKAs.[29] If NOAC compliance is assured, cardioversion should be safe. If in doubt about compliance, a prior transoesophageal echocardiogram (TOE) should be considered.

Patients Presenting with Acute Stroke While on New Oral Anticoagulants

Acute Phase

Patients with Acute Haemorrhagic Stroke

NOAC therapy should be discontinued. The use of procoagulants, as described above, may be considered.

Patients with Acute Ischaemic Stroke

Thrombolytic therapy cannot be given within 48 hours after the last dose of NOACs. In case of uncertainty regarding the last dose, a prolonged aPTT (dabigatran) or PT (FXa inhibitors) contraindicates the use of thrombolytics. If NOACs have been given within 48 hours and coagulation tests are not available or abnormal, recanalisation of the occluded vessels may be considered.

Post-acute Phase

Haemorrhagic Stroke

If the cardioembolic risk is high and risk of new haemorrhage low, NOACs may be restarted after 10–14 days. For patients with low cardioembolic risk and high bleeding risk, reinitiation of NOACs is contraindicated unless bleeding has been reversed.

Ischaemic Stroke

If the infarct size is not expected to increase the risk of secondary intracerebral bleeding, NOACs may be reinitiated in patients with transient ischaemic attack (TIA) after one day, in small, non-disabling infarcts after three days, moderate stroke after six days and large infarcts not before two weeks.

Transient Ischaemic Attack of Cardioembolic Origin

NOACs should be restarted as soon as possible; bridging with LMWH is not required.

Ischaemic Stroke of Cardioembolic Origin

Initiation of NAOCs depends on the infarct size and risk of new embolic stroke; bridging with LMWH is not required.

Patients with Atrial Fibrillation and Significant Carotid Stenosis

Carotid endarterectomy and not stenting is recommended to avoid triple therapy, which is associated with increased bleeding.

New Oral Anticoagulants Versus Vitamin K Antagonists in Atrial Fibrillation Patients with a Malignancy

Patients with malignancies are at increased risk for thromboembolic events – tumours may secrete prothrombotic factors or induce inflammatory responses. Cancer therapy also inflicts bleeding risks through surgery, tissue damage or myelosuppression. Many malignancies are associated with increased risk of mucosal bleeding. Furthermore, chemotherapy may interact with coagulation mechanisms.

Multidisciplinary care by cardiologists and oncologists is required. If anticoagulant therapy is needed, the greater clinical experience of, and reversal options with VKAs indicate that they should be chosen over NOACs. Established NOAC therapy should be continued where possible. Patients undergoing radiation therapy or chemotherapy without a marked myelosuppressive effect should continue NOACs,

adapting the dose if indicated. In patients undergoing myelosuppressive chemotherapy or radiation therapy, temporary dose reduction or cessation of NOACs should be considered, with monitoring of blood counts, bleeding signs, and liver and renal function. ■

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