GUIDELINES FOR THE NOVEL ORAL ANTICOAGULANTS (NOACs)

The Novel Oral Anticoagulants (NOACs) are a potential new alternative to Vitamin K antagonists (most commonly Warfarin) for nonvalvular atrial fibrillation and treatment of venous thromboembolism. Given the limited literature available at present and rapid advancement in our knowledge of NOACs these guidelines are subject to change.

Use of NOACS in Nonvalvular Atrial Fibrillation

The Royal Surrey County Hospital NHS Foundation Trust has chosen to adopt a similar anticoagulation policy to Guildford and Waverley CCG in order to maintain consistency between primary and secondary care:

Indications for NOACs in Nonvalvular AF

NOACs have been licensed for use in nonvalvular atrial fibrillation in patients with at least 1 risk factor for stroke. Local guidelines suggest that Warfarin should remain first-line therapy. Indications for the use of a NOAC include:

1. Warfarin allergy or absolute contraindication to Warfarin
2. Ischaemic stroke on Warfarin (having considered adjustment of target INR/antiplatelet therapy).
3. Poor INR control after a minimum 3-month trial.

NB Patient preference: when discussed at recent GP meetings there has been broad agreement that where a patient 'at risk' (with non rheumatic atrial fibrillation $CHA_2DS_2VASc \geq 2$) expresses strong patient preference ***against*** taking VKA and/or strong preference for NOACs, provided the patient has been properly informed about risks and benefits of NOAC, then patient reluctance/refusal to take VKA may be taken as an absolute contraindication to VKA (criteria 1 above) and a NOAC should be prescribed instead of VKA.

Choice of Oral Anticoagulant in AF

- 1st line therapy: Warfarin
- 2nd line therapy (if meets criteria above): Dabigatran or Rivaroxaban
- 3rd line therapy (if meets criteria above): Apixaban (if CrCl 15-30ml/min).

Doses of NOACs for stroke prevention in AF

Drug Name	Dosing schedule	Dosing in Renal Impairment
Dabigatran	150mg BD Reduce dose to 110mg BD in patients over age 80yrs, increased risk of bleeding or concomitant treatment with verapamil	CrCl 30-50 ml/min the recommended dose is 150 mg BD However, for patients with high risk of bleeding, a dose reduction to 110mg BD should be considered CrCl <30ml/min- DO NOT use
Rivaroxaban	20mg once daily	CrCl 15-49ml/min (*see below) reduce dose to 15mg once daily (in addition to this, use with caution in patients with concomitant drugs that may increase rivaroxaban levels) *****_Limited clinical data exists for patients with CrCl 15-29ml/min therefore_ ***caution*** _must be exercised in these patients_ CrCl <15ml/min–DO NOT use
Apixaban	5mg BD Reduce dose to 2.5 mg BD in patients over 80yrs with body weight ≤60kg)	Reduce dose to 2.5mg BD if CrCl 15-29ml/min, or if serum Cr ≥133micromol/L and age ≥ 80yrs or body weight ≤60kg If CrCl <15ml/min–DO NOT use

Refer to current BNF or SPC for full details on contra-indications and interactions.
Please note that calculated creatinine clearance (Cockcroft and Gault formula) is to be used for these drugs. Do **NOT** use eGFR.

Use of NOACS in treatment of Venous Thromboembolism

Choice of NOAC

Currently only rivaroxaban has a licence for this indication. The dose is 15mg bd for 3 weeks (21 days), followed by 20mg once daily.

Indications for rivaroxaban

Indications for choosing rivaroxaban over warfarin are as for atrial fibrillation above. Remember that rivaroxaban is contraindicated in those with significant liver disease and those with CrCl <15ml/min. For patients with CrCl 15-49ml/min (* see note below) dose is 15mg bd for 3 weeks (21 days), thereafter the dose is 20mg od. A reduction of the dose from 20mg od to 15mg od should be considered if the patient's assessed bleeding risk outweighs the risk of recurrent DVT/PE. This recommendation is based on PK modeling and has not been studied in a clinical setting.

*****_Limited clinical data exists for patients with CrCl 15-29ml/min therefore_ ***caution*** _must be exercised in these patients_ Also note that low molecular weight heparin (dalteparin) remains the anticoagulant of choice in cancer patients with VTE.

Refer to current BNF or SPC for full details on contra-indications and interactions.

NOACS before and after elective invasive procedures

NOACs should be discontinued in a similar fashion to Vitamin K Antagonists (VKAs) prior to invasive procedures where there is deemed to be a potential risk of bleeding. They should not be discontinued prior to low risk procedures (for example biopsy of non-vascular tissue).

Generally, because of the rapid onset and offset of NOACs, perioperative bridging with heparin / low molecular weight heparin is not required.

Patients with high thrombotic risk

Very high-risk patients (mechanical heart valves, high risk thrombophilia) are not suitable for NOACS. Consider delaying surgery or IVC filter for patients with stroke, TIA or venous thrombosis within the last 3 months. Complex patients and their anticoagulation management should be discussed on an individual basis with the appropriate Consultant.

Discontinuation of NOAC before an invasive procedure

NB: Calculated creatinine clearance using ideal body weight should be used (Cockcroft-Gault formula).

Rivaroxaban

Manufacturer advises withhold for "at least 24 hours" prior to surgery. However, it should be noted that clearance of rivaroxaban is affected by patient age, renal function and liver function, and all of these should be taken into account when determining when to stop rivaroxaban pre-surgery. One proposed scheme is as follows:

Renal function (CrCl, mL/min)	Rivaroxaban half-life	Minimum time-frame to withhold prior to surgery	Minimum time-frame to withhold prior to surgery
		Low bleeding risk	High bleeding risk

Greater than or equal to 50mL/min	5-9 hours (11-13 hours in elderly)	24 hours (2 days if elderly)	2 days (3 days if elderly)
Less than 50mL/min	> 9 hours	48 hours (3 days if elderly)	> 2 days (4 days if elderly)

(From Guideline for managing patients on Rivaroxaban, Medicines Regulation and Quality, Department of Health, Queensland Government, 2013)

Coagulation tests

Where haemostasis is critical, consider checking coagulation before surgery to ensure drug clearance. Prothrombin time (PT) is the most sensitive, easily available assay – prolongation suggests rivaroxaban not cleared.

Dabigatran

Renal function (CrCL ml/min)	**Dabigatran Half-life (estimated)**	**Minimum time-frame to withhold prior to surgery**	**Minimum time-frame to withhold prior to surgery**
		High risk of bleeding or major surgery	**Standard risk**
≥80	13 hours	2 days before	24 hours before
≥50 - 80	15 hours	2-3 days before	1-2 days before
≥30 - <50	18 hours	4 days before	2-3 days before

Coagulation tests

Where haemostasis is critical, consider checking coagulation before surgery to ensure drug clearance. APTT and thrombin time (TT) are the most sensitive, easily available assays – prolongation suggests dabigatran not cleared.

Apixaban

Low risk of bleeding	Discontinue at least 24 hours before procedure. This includes interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled.
Moderate or high risk of bleeding	Discontinue at least 48 hours before procedure

Recommencement of NOACs after invasive procedures

Low bleeding risk surgery	**High bleeding risk surgery**
Resume NOAC 24 hour after surgery once haemostasis achieved. Standard dose. Consider thromboprophylaxis (dalteparin 5000units) on the evening of surgery as per VTE risk assessment.	Resume NOAC 48-72 hours after surgery once haemostasis achieved. Standard dose. Consider post-operative thromboprophylaxis (dalteparin 5000units) as per VTE risk assessment prior to resuming NOAC.

NOACS before non-elective invasive procedures

If an urgent intervention is required all NOACs should be temporarily discontinued. If this cannot be delayed then the risk of bleeding may be increased.

NOACs are not reliably reversible - please see the section **'Reversal of Anticoagulant Drugs'.**

Dabigatran

If an acute intervention is required, dabigatran should be temporarily discontinued. Surgery / intervention should be delayed if possible until at least 12 hours after the last dose.

Rivaroxaban

If an acute intervention is required, rivaroxaban should be temporarily discontinued. Surgery / intervention should be delayed if possible until at least 24 hours after the last dose.

Apixaban

If an acute intervention is required appropriate caution should be exercised, taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Conversion to and from Vitamin K antagonists and Heparin to NOACS

Conversion from VKA to NOAC

	To dabigatran/apixaban	To rivaroxaban
From warfarin	Discontinue warfarin and start dabigatran/apixaban when INR <2.0.	Stroke prevention in AF: Discontinue warfarin and start rivaroxaban when INR ≤3.0. Treatment of VTE: Discontinue warfarin and start rivaroxaban when INR ≤ 2.5

Conversion from NOAC to VKA

Remember that all the NOACS can affect the INR, which may not reflect anticoagulant intensity accurately. INR measurement should therefore be timed so as to minimise the influence of the NOAC on the INR.

	To VKA
From dabigatran	CrCL ≥50 ml/min: start VKA 3 days before discontinuing dabigatran. CrCL ≥30-50 ml/min: start VKA 2 days before discontinuing dabigatran. INR testing should not be performed until dabigatran has been stopped for at least 2 days.
From rivaroxaban	Give rivaroxaban + VKA concurrently until INR ≥2.0. While patients are on both rivaroxaban and VKA the INR should not be tested earlier than 24 hours after a dose of rivaroxaban (ie just before the next scheduled dose is due). Once rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose.
From apixaban	Continue apixaban for at least 2 days after beginning VKA. After 2 days of coadministration of apixaban + VKA, obtain an INR immediately prior to the next scheduled dose of apixaban (12 hours after the previous dose). Continue coadministration of apixaban + VKA until INR ≥2.0.

Conversion from parenteral anticoagulants (eg LMWH) to NOACs

Dabigatran and Rivaroxaban

For patients already receiving a parenteral anticoagulant start NOAC 0-2 hours prior to the time the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g. intravenous unfractionated heparin).

Apixaban
For patients already receiving a parenteral anticoagulant start apixaban at the time of the next dose of the parenteral drug was to be given.

Conversion from NOACs to parenteral anticoagulants (eg LMWH)

Dabigatran- For patients currently taking dabigatran, wait 12 hours before initiating treatment with a parenteral anticoagulant.

Rivaroxaban- Give the first dose of parenteral anticoagulant at the time the next rivaroxaban dose would have been taken.

Apixaban- Give the first dose of parenteral anticoagulant at the time the next apixaban dose would have been (ie 12 hours after last apixaban dose).

References:

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The NOAC Steering group was formed by a group of clinicians and a Pharmacist in 2012 at the Royal Surrey County Hospital in order to provide guidance on use of a new anticoagulant drugs.

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