The Dudley Group NHS
NHS Foundation Trust

NOVEL ORAL ANTICOAGULANTS GUIDELINE

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CHANGE HISTORY

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A translation service is available for this document. The Interpretation/Translation Policy, Guidance for Staff is located on the intranet under Trust-wide Policies.

Contents

Section		Page Number
1	Statement of Purpose	4
2	Scope	4
3	Definitions	4
4	Duties	4
5	Process	4
5.1.1	Indications for NOAC	4
5.1.2	Rationale for recommending specific NOAC	5
5.1.3	Contraindications	6
5.1.4	Medications that interactwith NOAC	6
5.1.5	Relative contraindications	7
5.1.6	Switching from NOACs to VKAs	7
5.1.7	Monitoring of anticoagulation whilst on NOACs	8
5.2.1	NOACs peri procedural management	8
5.2.2	Novel oral anticoagulants	8
5.2.3	Elective Procedures	9
5.2.4	Emergency Procedures	10
6	Training / Support	11
7	Process for Monitoring Compliance	11
8	Equality Impact Assessment	11
9	References	11
10	Overview and Current Practice	14
11	Monitoring Compliance Checklist	15

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1. INTRODUCTION

Three large randomised studies have been published comparing a novel oral anticoagulant (NOAC) against warfarin in patients with non-valvular AF. The first to report was the RE-LY trial [1] which compared the oral Direct thrombin inhibitor Dabigatran (at two different doses) against warfarin. The ROCKET-AF trial[2] compared the oral direct FXa inhibitor Rivaroxaban against warfarin. The ARISTOTLE trial [3] compared the oral direct FXa inhibitor Apixaban against warfarin.

In these 3 studies dabigatran, rivaroxaban and apixaban, as compared with warfarin, all significantly reduced the risk of hemorrhagic stroke. In all 3 studies, the reductions in the primary efficacy end point — which included hemorrhagic as well as ischemic stroke — were greatly influenced by this dramatic reduction in the risk of hemorrhagic stroke [4]. The ARISTOTLE trial showed apixaban to be the first of the newer oral anticoagulants to show a significant reduction in the risk of death from any cause as compared with warfarin (hazard ratio, 0.89; 95% confidence interval [CI], 0.80 to 0.99; P = 0.047). Although this was notable, both dabigatran and rivaroxaban, as compared with warfarin, showed similar directional trends [4].

A fourth study ENGAGE AF-TIMI 48 [5] is currently still recruiting and yet to report its findings. This is comparing the oral direct FXa inhibitor Edoxaban (at two different doses) against warfarin.

Following these studies both Dabigatran and Rivaroxaban are licensed for use in Europe for the Prevention of Systemic Embolism in Non-Valavular AF. Apixaban is still awaiting approval in this setting based on the ARISTOTLE trial.

Both Dabigatran and Rivaroxaban have been appraised by NICE in this setting [6,7] (Apixabans NICE approval is expected in April 2013 at the earliest)[8]

Current Practice

The Vitamin K antagonist Warfarin has been the mainstay of anticoagulation for over half a century. Clinicians are intimately familiar with warfarin and there are clear guidelines for its use [9]. Monitoring for its anticoagulant effect is routinely available, and physicians and surgeons are aware of the need to interrupt warfarin for many interventional procedures [10]. There are established and highly effective treatment strategies for bleeding in patients receiving warfarin and for the management of unanticipated excess anticoagulant effect [11,12]. However warfarin has many undesired effects including interaction with a legion of other medications, foods and alcohol resulting in over or under coagulation which can result in an adverse clinical outcome [13,14]. In addition to this frequent monitoring of the INR whilst taking warfarin can be burdensome, inconvenient and costly [15].

Despite this well over 1% of the UK population is anticoagulated principally with warfarin with the indication for the significant majority of patients (>60%) being to prevent systemic embolism secondary to AF.

2. STATEMENT OF PURPOSE

In the Dudley area the anticoagulation services are based at Dudley Group NHS Foundation Trust, with warfarin clinics occurring at Russells Hall Hospital, Guest and Corbett (7 hospital clinics including 1 induction clinic) as well as a number of satellite clinics (14) and domiciliary services (greater than 1,000 patients). Over 6,600 patients are currently anticoagulated in the Dudley area managed by the anticoagulant services. For approximately 4,500 patients the principal indication for anticoagulation is for prevention of systemic embolism in Non-Valvular AF. Following recent randomised studies and NICE approvel (See Appendix 1) these guidelines have been produced to direct clinical staff in the initiation and subsequent management of the novel oral anticoagulants.

3. SCOPE

This document must be used as clinical guidance by all clinical staff caring for patients receiving novel oral anticoagulants

4. DEFINITIONS

NOAC's -Novel oral anticoagualants(New oral anticoagulants that do not require regular dose adjustment)
INR -International normalised ratio(Worldwide used measure of clotting time)
VKA's -Vitamin K antagonists(Oral anticoagulant which prolongs clotting time by inhibiting the action of Vitamin K on clotting factors eg. Warfarin)
LMWH- Low molecular weight heparin (Blood thinning injection)
AF- Atrial fibrillation (irregular heart beat)

5. DUTIES

All GPs, Consultants and nursing staff are responsible for ensuring the prescription and management of NOAC's.

The Thrombosis Group is responsible for development and implementation of guidance related to NOAC's.

6. PROCESS

6.1 INDICATIONS AND RATIONALE FOR NOVEL ORAL ANTICOAGULANTS

6.1.1 Following review and interpretation of the evidence base (including the principal trials as referenced above), the regulatory status and the issued NICE guidance where Warfarin not considered appropriate, in collaboration with our commissioners we are recommending Rivaroxaban 20mg od (eGFR >50) or 15mg od (eGFR 30-50) as a first line treatment option for the prevention of stroke and systemic embolism in newly diagnosed patients with AF who are suitable for anticoagulation with one or more of the following risk factors:

- Previous stroke, transient ischaemic attack or systemic embolism
- Left ventricular ejection fraction below 40%
- Symptomatic heart failure of New York Heart Association (NYHA) class 2 or above
- Age 75 years or older
- Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension

6.1.2 The following are reasons as to the rationale for recommending Rivaroxaban (Xarelto) as opposed to Dabigatran (Pradaxa) for anticoagulation in the setting of Non-Valvular AF:

- Rivaroxaban is once daily as opposed to twice daily (thus leading to greater compliance)
- Rivaroxaban is less reliant on renal excretion (30% with Rivaroxaban v 80% with Dabigatran)
- Dabigatran cannot be dosette boxed/removed from its packaging
- Rivaroxaban carries theoretically less risk in overdose(Due to Rivaroxaban having a limited absorption ceiling effect with no further increase in average plasma exposure expected at supratherapeutic doses of 50 mg Rivaroxaban or above).
- More *in vitro* data that Rivaroxaban is reversible with Prothrombin Complex Concentrate
- Higher rates of discontinuation than warfarin with Dabigatran in the RE-LY trial.
- Dabigatran interacts with Amiodarone and Verapamil

In respect to patients already taking warfarin the NICE guidance states[6,7]:

'For people who are taking warfarin, the potential risks and benefits of switching to rivaroxaban should be considered in light of their level of international normalised ratio (INR) control.'

In view of this the following criteria for consideration of switching patients from warfarin to Rivaroxaban have been agreed with Commissioners:

Laboratory Parameters:

- Poor INR control

- Any single INR > than 10
- Any two INRs > than 8
- Any three unexplained INRs > than 5 in a 6 month period

Clinical parameters:

- Polypharmacy especially if medications/antibiotics are likely to be started/stopped (eg bronchiectasis)
- Any clinically significant or major bleeding on warfarin
- Any embolic stroke or peripheral embolism on warfarin
- Patient preference

Please note if a patient has a well controlled INR on warfarin there will be limited benefit (and potential risk) by switching from warfarin to the NOACs

Practicalities of Switching From Warfarin to the NOACs

Although not evidence based, when switching from warfarin to rivaroxaban or dabigatran, we advocate starting the Novel Anticoagulant when the warfarin has been discontinued and the INR fallen to 2.5 or less. Point of care testing kits should **NOT** be used to check the INR at time of transition[16].

6.1.3 Contraindications to the Novel Oral AntiCoagulants (Applicable In All Settings):

- Other co-existing indications for anticoagulation (eg Mechanical heart valve, VTE)
- Pregnancy
- Breast feeding
- Renal failure with an eGFR <30 (caution/reduced dose eGFR 30-50)
- Liver failure (ALT > 2 the upper limit of normal &/or any evidence of chronic liver failure ie Child Pugh score B or above)
- Low platelets < 50
- Hypersensitivity to Rivaroxaban or Dabigatran
- Concurrent use of Ketaconazole

6.1.4 Medications That Interact With the NOACs and Should be Avoided:

Rivaroxaban is subject to interaction via P-glycoprotein as well as inducers and inhibitors of the microsomal enzyme CYP3A4, which is responsible for metabolism of rivaroxaban. Dabigatran is dependent on P-glycoprotein for its transport across the intestinal wall and thus interacts with inhibitors or inducers of this drug. Thus the following drugs should be avoided:

Rivaroxaban:

-Rifampicin (decreases levels) - AVOID
-St John's wort (not determined) - AVOID
-Clarithromycin (increases levels) - AVOID
-Ritonavir (increases levels) – AVOID

This list is not exhaustive, and the patient's medication should be checked regularly against the summary of product characteristics (SPC)

Dabigatran:

- Rifampicin (decreases levels) - AVOID

- St John's wort (not determined) - AVOID
- Quinidine (increases levels) – give at least 2 hours after dabigatran
- Amiodarone (increases levels) – AVOID
- Verapamil (increases levels – dependent on formulation) – give at least 2 hours after dabigatran

This list is not exhaustive, and the patient's medication should be checked regularly against the summary of product characteristics (SPC)

6.1.5 Relative Contraindications to Anticoagulation

The NOACs like warfarin and all the Vitamin K Antagonists (VKAs) can all cause bleeding due to their anticoagulant effect. Thus the following are relative contraindications to all anticoagulants whether the VKAs or NOACs:

- Falls
- Bleeding eg peptic ulceration
- Poor compliance
- Antiplatelet agents (aspirin, clopidogrel, dypridamole)

6.1.6 Switching from NOACs to VKAs

Please note some people will require switching from the novel oral anticoagulants to Vitamin K antagonist eg warfarin. For example if they are intolerant of novel oral agents, or develop renal failure, or develop another indication for anticoagulation not licensed for the novel oral anticoagulants.

Thus the following strategy should be used for converting from Rivaroxaban or Dabigatran to warfarin [16]:

Table 3. Suggested strategy for conversion from dabigatran or rivaroxaban to warfarin

Calculated creatinine clearance, mL/min	Dabigatran: start day with warfarin*	Rivaroxaban: start day with warfarin*
> 50	Day - 3	Day - 4
31-50	Day - 2	Day - 3
15-30	Day - 1	Day - 2

*Dabigatran/rivaroxaban is stopped on day 0. The longer overlap with rivaroxaban is justified by its half-life being shorter than that of dabigatran and by the concern about thromboembolic events shortly after transitioning from rivaroxaban to warfarin.

6.1.7 Monitoring of AntiCoagulation Whilst on NOACs

There should be no routine monitoring of baseline coagulation on these novel oral anticoagulants. This is because they do not give a reliable picture of the level of anticoagulation. Dabigatran is known to prolong the prothrombin time (PT) and the activated Partial Thromboplastin Time (APTT). Rivaroxaban can also prolong the PT and APTT. The degree of prolongation of these clotting tests is unreliable, and the results cannot be routinely interpreted [16,17]. Specific assays to monitor the degree of anticoagulation are being developed, though are not routinely available at present.

For management of reversal of Novel Oral AntiCoagulants and peri-procedural management, please see below.

6.2 NOVEL ORAL ANTICOAGULANTS- PERI PROCEDURAL MANAGEMENT

6.2.1 The novel anticoagulants dabigatran and rivaroxaban have recently been approved by NICE for the long-term anticoagulation of patients with non-valvular atrial fibrillation[6,7]. There will therefore be increasing numbers of patients circulating in this trust that will be on one of these agents. The pharmacodynamics, mode of action, monitoring and reversal of these agents are fundamentally different from those of warfarin..

6.2.2 The three important characteristics of the novel anticoagulants for peri-operative management (as compared to warfarin) are their relatively short half-lives, their short onset of action (two hours) and their reliance on renal function for their clearance. **Renal function must therefore be assessed when planning procedures in these patients. This should be done no more than one month before the procedure and repeated nearer the time of procedure if there is clinical concern.**

6.2.3 Novel oral anticoagulants- The following are on the formulary to prescribe

Rivaroxaban (*Xarelto*)

This is an oral direct factor Xa inhibitor. In the context of long-term anticoagulation for atrial fibrillation, it is given at a dose of 20mg once daily. In the event of renal failure (creatinine clearance of 30-49ml/min), the dose is 15mg once daily. Its half-life is 11-13 hours in patients with a creatinine clearance of more than 30ml/min, but unknown in patients with a creatinine clearance of less than 30ml/min [16,18]. It does not need monitoring routinely. There are other indications for rivaroxaban, which are not currently part of this trust's policy.

Dabigatran (*Pradaxa*)

Dabigatran etexilate is an oral pro-drug that is rapidly converted by a serum esterase to dabigatran, a direct, competitive inhibitor of thrombin. In the context of long-term anticoagulation for atrial fibrillation, it is given at a dose of 150mg twice daily (or 110mg twice daily in patients over 75. Its half-life varies according to the patient's creatinine clearance, being 14-17 hours if the clearance is more than 80ml/min, and 27 hours if the clearance is less than 30ml/min [16,19]. It does not require routine monitoring.

6.2.4 Elective procedures

If the patient is taking either Rivaroxaban or Dabigatran *exclusively* for AF there is no need to specifically bridge the short period of interruption for elective procedures with low molecular weight heparin or unfractionated heparin, though compliance with the Trusts guidance for VTE prophylaxis must be adhered too.

In patients with normal renal function who are to undergo a procedure with a low risk of bleeding (i.e. those procedures that would be safe with an INR of 1.5), both dabigatran and rivaroxaban should be interrupted for 24 hours[20]. Such procedures include cardiac catheterisation, diagnostic endoscopy, laparoscopic

cholecystectomy, colonoscopy and minor orthopaedic surgery. For procedures that are higher risk of bleeding, both agents should be interrupted for 48 hours [20].

With declining renal function, the periods of interruption should be increased (see below).

	Timing of last dose before surgery	
eGFR (ml/min)	Standard bleeding risk	High bleeding risk
DABIGATRAN		
>80	24 hours	2 days
51-80	24 hours	2 days
31-50	2 days	4 days
<31	4 days	6 days
RIVAROXABAN		
>30	24 hours	2 days
<30	2 days	4 days

The time of restarting the dabigatran or rivaroxaban depends on the risk of bleeding. For major abdominal or urological surgery with incomplete haemostasis, the drugs should not be started if there is evidence of active bleeding. For procedures with good haemostasis, the first dose should be given at least 4-6 hours post procedure. For dabigatran, the first dose should be halved (i.e. 75mg), and a similar approach is reasonable for rivaroxaban (i.e. 10mg). Normal dosing can be resumed from the second dose.

Patients with bowel paralysis may require bridging with parenteral anticoagulants given their inability to take their oral anticoagulant.[20]

There should be no routine monitoring of baseline coagulation on these novel anticoagulants. This is because they do not give a reliable picture of the level of anticoagulation. Dabigatran is known to prolong the prothrombin time (PT) and the APTT. Rivaroxaban can also prolong the PT and APTT.
The degree of prolongation of these clotting tests is unreliable, and the results cannot be routinely interpreted,[16],[21].

6.2.5 Emergency Procedures

Patients receiving dabigatran or rivaroxaban who need to undergo emergency procedures or surgery will either have to wait until the anticoagulant effect has diminished spontaneously, or undergo the procedure with the risk of increased bleeding present. There is some limited evidence that the novel oral anticoagulants can be reversed by 4-factor prothrombin complex concentrate (PCC) e.g. octaplex[16]. This will need to be discussed with the haematologist on-call. (Please refer to additional guidance on the reversal of novel oral anticoagulants below).

6. 4 GUIDELINE FOR THE REVERSAL OF NOVEL ORAL ANTICOAGULANTS (NOAC) DABIGATRAN AND RIVOROXIBAN

There is limited data/evidence for the reversal of the novel oral anticoagulants, particularly in the clinical setting [22,23,24,25]. Some data exists for reversal of the NOACs *in vitro/ex vivo* [16,23,24,25,26,27,28].

In the event of bleeding firstly an assessment regarding the degree of bleeding needs to be made by the clinician caring for the patient - if the bleeding is minor (eg epistaxis, menorrhagia) then simply withholding the NOAC is likely to be sufficient [16,25]

If the bleeding is significant/major (eg major GI bleeding, intracranial bleeding), stop the NOAC. If the patient presents within 2 hours of taking Dabigatran then activated charcoal can be administered.[28]

If the bleeding is considered to be ***ongoing and life threatening*** then consideration of administration of PCC (Octaplex) can be made at a dose of 25 IU/kg as a one off dose (max 3,000 IU/kg). This can only be obtained from blood bank **after discussion and approval of use with the Consultant Haematologist** on call. Please note there is a thrombotic risk with the use of PCC[16,22,23,24,25].

A FBC should be checked to exclude thrombocytopenia.

6.4.1 There is currently no reliable or validated way of using existing coagulation tests to determine the degree of anticoagulation with the NOACs[,16,21,25]. However the PT/INR is prolonged with rivaroxaban though this is not sensitive at low concentrations. Similarly the aPTT is prolonged with dabigatran (the aPTT is prolonged 2 fold compared to controls at peak drug levels during chronic treatment and 1.5 fold at 12hours) [16,21,25].

7. TRAINING

Training will be provided via Screen Savers, Posters, educational update through Mandatory and Induction VTE training, ad-hoc lectures and departmental meetings

8 PROCESS FOR MONITORING COMPLIANCE

The effective implementation of this guideline will be monitored using the tools on the comparison monitoring checklist (Appendix 2)

9. EQUALITY IMPACT ASSESSMENT

“The Dudley Group NHS Foundation Trust is committed to ensuring that, as far as is reasonably practicable, the way we provide services to the public and the way we treat our staff reflects their individual needs and does not discriminate against individuals or groups on any grounds.

This document has been assessed appropriately”.

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COMPLIANCE MONITORING CHECKLIST APPENDIX 1

	Lead	Tool	Frequency	Reporting arrangements	Acting on recommendations and Lead(s)	Change in practice and lessons to be shared
How many Patients referred to ANS treated with Novel oral anticoagulants	CNS Anticoagulation and Thrombosis	Cross reference with pharmacy all patients prescribed Novel oral anticoagulants	Monthly	Thrombosis Group Bi annual	If number of patients being treated on Novel oral anticoagulants exceed referral to ANS inform relevant medical teams of correct process of referral	Ensure all relevant clinical staff aware of guideline