Dartford and Gravesham NHS
NHS Trust

PROTOCOL FOR APPROPRIATE PRESCRIBING OF DIRECT ACTING ORAL ANTICOAGULANTS (DOACs) AND MANAGEMENT OF HAEMORRHAGE AND SURGICAL PATIENTS

Clinical Guideline	
Reference Number	PH035
Status	Approved
Version	3
Implementation Date	November 2013
Current/Last Review Dates	September 2015, December 2016
Next Formal Review	December 2019
Sponsor	Dr Raphael Ezekwesili, Thrombosis Committee Chairman
Sponsor Signature	
Authors	Chikondi Savieli, Cardiology Pharmacist, Dr Prasanna Aghoram Consultant Geriatrician/Clinical Stroke Lead, Dr Tariq Shafi, Lead Consultant Haematologist
Where available	ADAGIO, A&E, Acute Stroke Folder, Surgical Pre-Assessment Clinic
Target audience	All Trust clinical staff

Approval/Ratified Record		
Committee Name	**Chairperson**	**Date**
Thrombosis Committee	Dr R. Ezekwesili	Sep 2013
Medicines Management Committee	Dr M. Toth	May 2013
Prescribing and Formulary Group	Dr J Kwan	**Dec 2016**

Consultation	**Date**
Lead Consultant Haematologist	August 2013
Consultant Haematologists	June 2013
Emergency Medicine Consultants	September 2012
Clinical Director (Medicine)	September 2012
Clinical Director (Surgery)	September 2012
Anaesthetists	November 2012
Orthopaedics Consultants	November 2012
Medication and Safety Learning Group (Table 1)	August 2015
Surgical Pre-assessment Group Lead Dr Sanjay Parmar (Peri-op management)	November 2016

Regulators Requirements	
NICE guidelines	

Document Control / History	
Version No	**Reason for change**
1	New protocol implemented due to new oral anticoagulants recommended by NICE
2	Updated prescribing and switching anticoagulants and management of bleeding
3	Scheduled update

Contents

1. Introduction.

Vitamin K antagonist (VKA) oral anticoagulants, warfarin and other coumarins were the only oral anticoagulant agents available for prevention and treatment of thromboembolic disease for decades. Recently a number of Direct Acting oral anticoagulants (DOACs), including Dabigatran, Rivaroxaban Apixaban and Edoxaban, have been licensed in the United Kingdom. Dabigatran is a direct reversible competitive thrombin inhibitor whilst Rivaroxaban, Apixaban and Edoxaban are highly selective direct and reversible inhibitor of factor Xa.

The DOACs offer many advantages over VKA oral anticoagulants such as faster onset of action, predictable pharmacology, standard dosing, fewer drug and food interactions and no requirement for regular monitoring. However, lack of a standard test to determine the degree of anticoagulation and direct reversal agent in case of bleeding or emergency surgery, and recent reports of increased bleeding risk in a range of clinical conditions have heightened the need to increase awareness of the risks involved in prescribing these agent. Recently Idarucizumab (Praxibind®), a reversal agent specific for Dabigatran was launched in the UK. At the time of writing this protocol, Andexanet Alfa for the reversal of Factor Xa Inhibitor activity was still in development.

All DOACs are licensed for use in the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF), treatment of deep venous thrombosis (DVT) and Pulmonary Embolism (PE) and prophylaxis for recurrent DVT and PE. In addition Dabigatran, Rivaroxaban and Apixaban are licensed for prevention of venous thromboembolic events after knee and hip replacement. Rivaroxaban has an additional license for prevention of adverse outcomes after Acute Coronary Syndrome.

All DOACs have been reviewed by NICE and the Technology Appraisal guidelines are as follows:

- Prevention of stroke in adults with non-valvular AF TA275 (Apixaban) TA256 (Rivaroxaban) TA249 (Dabigatran) TA355 (Edoxaban)
- Treatment and prophylaxis for recurrent DVT and PE TA341 (Apixaban) TA287 TA261 (Rivaroxaban) TA327 (Dabigatran) TA354 (Edoxaban)
- Prevention of venous thromboembolism after elective hip or knee surgery TA245 (Apixaban) TA170 (Rivaroxaban) TA157 (Dabigatran)
- Prevention of adverse outcomes after acute management of acute coronary syndrome TA335 (Rivaroxaban)

2. Purpose.

This document aims to provide guidance for all clinical staff on:

- Appropriate prescribing of DOACs
- Management of haemorrhage in patients taking DOACs
- Peri-operative management of patients on DOACs

3. Appropriate prescribing of Direct Acting Oral Anticoagulants

Prescribing of these agents should be within there licensed indication(s) and in accordance to NICE Technology Appraisal guideline. Warfarin, Unfractionated Heparin and Low Molecular Heparins should continue to be used where indicated. In selecting DOACs following consideration should be given to:

- the relative lack of experience of long term use compared with warfarin
- the higher rates of gastrointestinal bleeding with dabigatran and rivaroxaban
- the limited data on use in patients at the extremes of body weight and those with renal and hepatic impairment.

Locally **first line** choices have been agreed to minimise risk of prescribing and administration errors. Where a DOAC is to be prescribed, Rivaroxaban should be used as first line choice for treatment of DVT and PE and Apixaban for Stroke Prevention in patients with AF. All DOACs are available on formulary and could be used at the discretion of a senior clinician. See Table 1 for dosing details for first line choices. Refer to the respective SPCs and BNF for dosing details for other DOACs and indications.

Prescribing Direct-Acting Oral Anticoagulants (DOACs)

1. Check **RENAL** function - Calculate **Creatinine Clearance (mL/min) = Factor x (140 - Age) x Ideal Body Weight (kg) / Serum Creatinine (micromol/L)** **Factor MALE = 1.23 FEMALE = 1.04**
2. DOACs are **CONTRAINDICATED** if Creatinine Clearance is **less than 15mL/min**
3. **STOP** Warfarin/Acenocoumarol (sinthrome), Dalteparin, Heparin, Fondaparinux
4. DOACs and other anticoagulants (e.g. Dalteparin, Fondaparinux) **CANNOT** be given concurrently
5. **SWITCHING** from another anticoagulant- DOAC should be started at least 22 - 24hours post last dose of Dalteparin/Fondaparinux OR at the time of discontinuation of Heparin infusion OR when INR is less than 2. Refer to product SPC for further details on switching
6. **INTERACTIONS** – e.g. other anticoagulants, rifampicin, antiepileptics, antifungals, antiretrovirals. Check BNF for a detailed list of drug interactions

DVT/PE

Treatment of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism and secondary VTE prevention

FIRST LINE

RIVAROXABAN

DOSE: 15mg BD for 21 days then 20mg OD thereafter

If Creatinine Clearance 15-49mL/min

Dose : 15mg BD for 21 days then consider reducing dose to 15mg OD if risk of bleeding outweighs risk of recurrent VTE

AF

Prophylaxis for Stroke and Systemic embolism in patients with non-valvular Atrial Fibrillation

FIRST LINE

APIXABAN

DOSE: 5mg BD

If Creatinine Clearance 15 – 29mL/min OR
at least TWO of the following characteristics present:

- ✓ Age ≥ 80 years
- ✓ Body weight ≤ 60 kg
- ✓ Serum creatinine ≥ 1.5 mg/dL (133 micromol/L)

REDUCE DOSE to 2.5mg BD

***NB: If the First-line choice is not suitable, rivaroxaban/apixaban may be considered as second line. Please refer to BNF for dosing**

References: BNF ed. 70, NICE TA 275 (AF), SPC (Apixaban) BNF ed. 70, NICE TA 261 (DVT), 287 (PE), SPC (Rivaroxaban)

4. Management of Haemorrhage in patients taking DOACs

The overall bleeding risk of both direct thrombin inhibitors (dabigatran) and factor Xa antagonists (rivaroxaban edoxaban and apixaban) was similar to warfarin in clinical studies.

The half-life of Dabigatran is 12-18 hours, Rivaroxaban 5-13 hours and Apixaban 12 hours. Dabigatran is renally eliminated so clearance is significantly influenced by renal function, and any deterioration in renal function will prolong the half-life. Approximately 2/3 of rivaroxaban undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. Apixaban has multiple routes of elimination. Renal excretion of apixaban accounts for approximately 27% of total clearance. Edoxaban half-life is 10 - 14 hours. Renal clearance accounts for approximately 35% of the administered dose and metabolism and biliary/intestinal excretion account for the remaining clearance.

Currently, therapeutic monitoring is not indicated. The INR is insensitive to dabigatran or rivaroxaban/apixaban/edoxaban activity and therefore is unsuitable as a primary measure of anticoagulant activity.

There are a few laboratory assays that may provide useful information in an emergency situation. Direct thrombin inhibitors and Factor Xa antagonist prolong prothrombin time (PT), (PT is more sensitive to rivaroxaban than to dabigatran), activated partial thromboplastin time (aPTT), thrombin time (TT) (Rivaroxaban has no effect on the TT). However, the degree of prolongation does NOT reliably predict plasma drug levels nor does it provide an accurate assessment of risk of surgical haemorrhage. The information provided by these assays is limited to whether there is residual drug effect or not. **Note:** A normal PT or aPTT does not exclude the possibility of residual anticoagulant effect. Measurement of fibrinogen in patients taking dabigatran can give falsely low results but, with marked variation with different reagents. D-dimer levels are suppressed by all anticoagulant drugs but these agents do not interfere with the D-dimer assay. For example, patients taking dabigatran or rivaroxaban could have a prolonged APTT and/or PT and those on dabigatran a falsely low fibrinogen and the results might wrongly be interpreted as suggesting disseminated intravascularcoagulation (DIC). However, dabigatran and rivaroxaban do not cause thrombocytopenia and the D-dimer level is likely to be low. For summary of the laboratory assays for each drug see **Table 2.**

Table 2: Laboratory Assays for ''emergency situation''

Test	Apixaban	Dabigatran	Rivaroxaban
Prothrombin Time (PT)	✓	-/+	✓
Activated Partial Thrompoplastin Time (aPTT)	-/+	✓	-/+
Thrombin Time (TT)	x	-/+	×
Anti-Factor Xa	*✓	×	*✓
Fibrinogen	-	Falsely low	-
D-dimer	Low	Low	Low

- **A normal PT or aPTT does not exclude the possibility of residual anticoagulant effect**
- **New oral anticoagulants do not cause thrombocytopenia and the D-dimer level is likely to be low**
- **TT not available locally**
- **-/+ Not ideal but widely available**
- ***✓ requires calibration with required drug Not locally available**

to determine the relative intensity of newer anticoagulants but cannot determine drug levels and at present there tests are either too sensitive or insensitive and NO definite lab tests yet available

Idarucizumab (Praxibind®), a reversal agent specific for Dabigatran is now available in the UK. Currently there is **no antidote** for edoxaban, rivaroxaban or apixaban for the reversal of their anticoagulation effect. There are limited options for management of bleeding. In cases of a bleeding event treatment with a DOAC should be stopped immediately and all measures to control bleeding and maintain haemostasis should be initiated. See **Flowchart 1**.

If the drug was consumed within two to three hours (up to 6hours for apixaban) of presentation, activated charcoal, at standard doses, should be given. Fresh frozen plasma infusion will **not** reverse the anticoagulation effect of Dabigatran, as the drug will inhibit thrombin in the transfused plasma. At the recommendation of the Haematologists use of procoagulant haemostatic agents such as recombinant Factor VIIa (rFVIIa) activated or non-activated prothrombin complex concentrates (PCC) could be considered. These have been shown to be of benefit in animal studies, however a recent small study in healthy subjects PCC immediately and completely reversed the anticoagulant effect of rivaroxaban but had no influence on the anticoagulant action of dabigatran at the PCC dose used in this study. A single dose of Beriplex 30-50units/kg is thought to be adequate, however if bleeding continues re-check PT, aPTT or TT and discuss with Haematologist if further doses can be given.

Haemodialysis may be used as a last resort for dabigatran. Only very limited reports on the use of these techniques in bleeding patients on dabigatran are available and the evidence for their support remains preliminary. Furthermore, their rapid deployment in settings outside intensive care units is likely to be challenging. Approximately 60% of dabigatran is removed after four hours dialysis. Rivaroxaban on the other hand is not expected to be dialysable due to the high plasma protein binding. See **Flowchart 1** for a summary on management of bleeding in patients taking new oral anticoagulants.

FLOW CHART 1 - MANAGEMENT OF BLEEDING IN PATIENTS TAKING DIRECT ACTING ORAL ANTICOUNGULANTS

There is No specific reversal agent for Edoxaban, Rivaroxaban or Apixaban. Idarucizumab a reversal agent specific for Dabigatran is available
Management of bleeding should be through cessation of treatment and general haemostatic measures

PATIENT RECEIVING NEWER ORAL ANTICOAGULANTS PRESENTS WITH A BLEED

STOP ORAL ANTICOAGULANT & any antiplatelets and parenteral anticoagulants

REQUEST
1. Coagulation screen to include aPTT, PT (and TT if available)
2. Full Blood Count
3. Renal function /eGFR

(Important: *document time of last dose of anticoagulant)*

CONTACT Haematologist

Clinically significant anticoagulant effect is less likely with normal aPTT, PT (and TT)

CONSIDER CHARCOAL IF INGESTION LESS THAN 2-3HOURS

MILD BLEED

- Mechanical compression/ wound packing
- Tranexamic Acid
  - Oral 500mg - 1g TDS **or**
  - IV 500mg – 1g (max 4g/24hrs)
- Delay next dose or discontinue therapy

Continues to bleed

MAJOR BLEED*

Maintain BP and Urine Output

- Give Oxygen
- Fluid Resuscitation
- Control Haemorrhage
  - Mechanical compression/wound packing
  - Surgical/radiological intervention
- Tranexamic Acid 2g IV(max 4g/24hrs)
- Discuss with Haematologist use of Prothrombin Complex Concentrate (Beriplex 30-50 Units/kg)
- Red cell transfusion
  - Aim Hb > 10g/dl
- Platelet transfusion
  - Aim Plt >50x 10^9/L or
  - If CNS bleed aim Plt >100x 10^9/l
- ♦ FFP/cryo if fibrinogen< 1.5 APTT>1.5
- ♦ **Consider initiation 'code red' major haemorrhage policy so RBC + FFP available**

***Major Bleed**: Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome (Schulman el al J Thromb Haemost 2010:3:692-694)

LIFE THREATENING BLEED including INTRACEREBRAL BLEED±

Discuss with Haematologist use of

- ♦ **Idarucizumab for Dabigatran**
- ♦ **Prothrombin Complex Concentrate (Beriplex 30-50 Units/kg)**
- ♦ **Factor VIIa**
- ♦ **FEIBAIf**

± For Intracranial Bleed also refer to separate protocol on management of Intracerebral Haemorrhage

5. Peri-operative management of patients on new oral anticoagulants

a) Elective invasive or surgical procedures in patients receiving new oral anticoagulants (See Flowchart 2)

DOACs should be discontinued prior to elective invasive or surgical procedures. The management needs to take into consideration of the thromboembolic risk balanced against the bleeding risk associated with the surgical procedure. Guidance on when to discontinue the DOAC can only be provided based on the elimination half-life of the drugs to ensure that procedures are undertaken at the time when there is minor or no anticoagulant effect.
Dabigatran clearance is depended on renal function, therefore patient's renal function, timing of surgery and risk of bleeding should be carefully considered to determine when to discontinue therapy. For patients with moderate renal impairment (CrCl < 50) anticoagulant effect may still be present 3-4 days after discontinuation of therapy and 2-3 days in mild renal impairment. It has been recommended that a normal or near-normal aPTT or thrombin clotting time be documented to ensure that dabigatran has been adequately cleared from the circulation prior to surgery
Apixaban, edoxaban and rivaroxaban must be discontinued 24 hours before surgery regardless of the patient's renal function. Where the surgical procedure carries a high risk of bleeding they should be stopped 48hours prior to the procedure.

See below guidance on estimating thromboembolic risk and surgical procedures with high bleeding risk. Please note that this is guidance only, risk assess each individual patient and use clinical judgement to ensure minimal risk to them or seek haematology advice if unsure.

Thromboembolic Risk

LOW

- No VTE in prior 12 months and no other risk factors
- Non-valvular AF with no other risk factors ($CHADS_2$ score of 1 or CHA_2DS_2-VASc Score < 2 and no previous stroke/TIA)
- Bi-leaflet aortic valve without AF/other stroke risk

MODERATE

- VTE within last 3-12 months
- Recurrent VTE
- AF with additional risk factors (CHADS2 ≥ 2 or CHA_2DS_2-VASc Score ≥3)
- Bi-leaflet aortic valve prosthesis with additional risk factors for stroke (AF, prior stroke, TIA, hypertension, diabetes, Congestive Heart Failure, age older than 75 years)
- Non severe thrombophilia (e.g. heterozygous factor V Leiden)
- Active cancer (treated within 6 months or palliative)

HIGH

- VTE within prior 3 months
- Any mitral mechanical heart valve prosthesis
- Aortic caged ball/tilting disk aortic heart valve prosthesis
- Any mechanical valve with stroke/TIA within last 6 months
- AF with additional risk factors ($CHADS_2$ ≥ 3 or CHA_2DS_2-VASc Score ≥ 4)
- AF with stroke or TIA within the last 3 months
- Rheumatic valvular heart disease
- Severe thrombophilia (e.g. protein C or S deficiency, Antithrombin antiphospholipid syndrome, multiple thrombophilia)

High Bleeding Risk Surgery

- Urologic surgery (transurethral prostate resection, bladder resection, or tumour ablation; nephrectomy; or kidney biopsy)
- Cardiac device implantation (e.g. Pacemaker or implantable cardioverter defibrillator)
- Colonic polyp resection
- Surgery and procedures in highly vascular organs, such as the kidney, liver, and spleen
- Bowel resection
- Major surgery with extensive tissue injury (e.g., cancer surgery, joint arthroplasty, reconstructive plastic surgery)
- Cardiac, intracranial, or spinal surgery

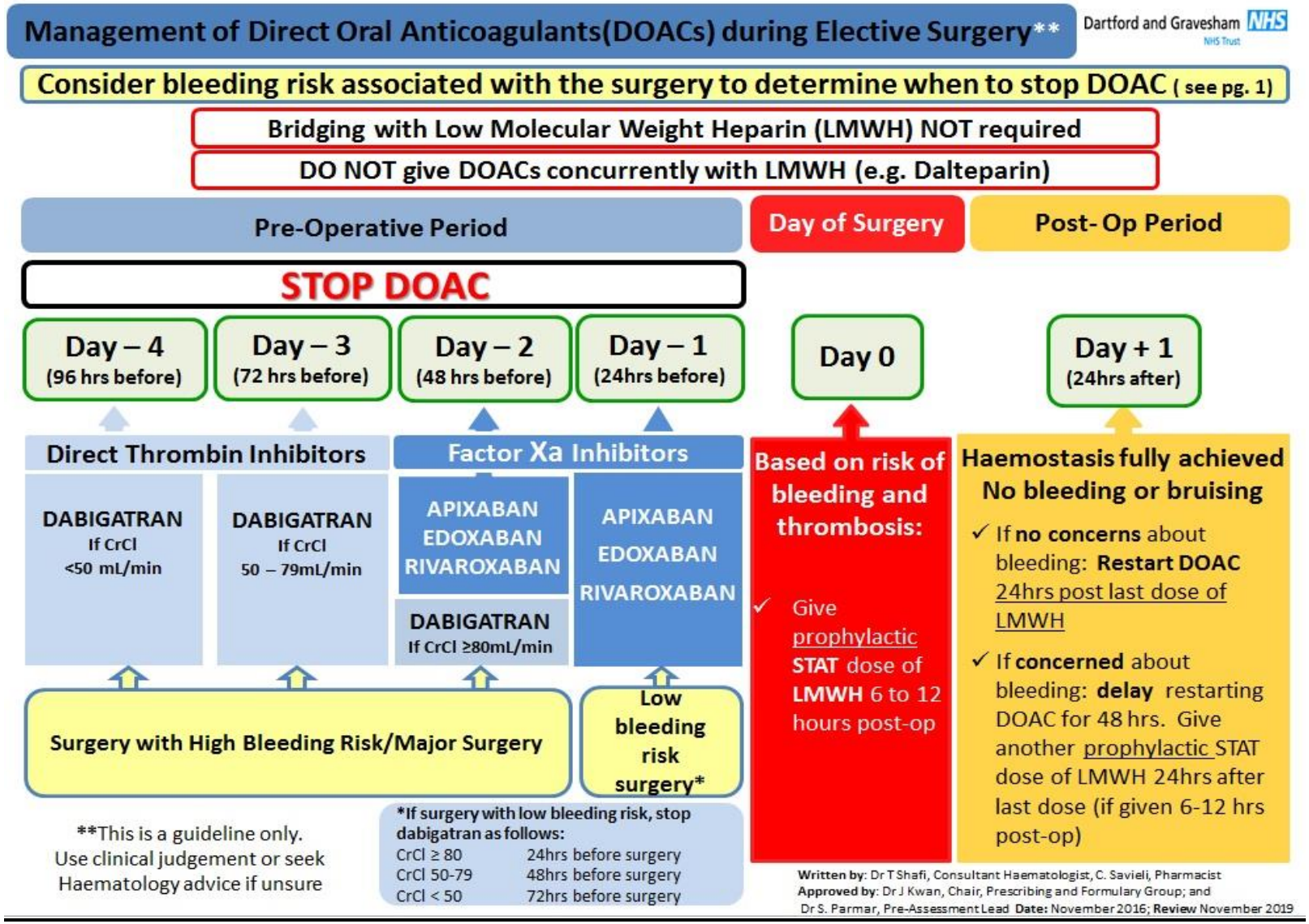
**This is a guideline only. Use clinical judgement or seek Haematology advice if unsure

b) Emergency surgery in patients receiving new oral anticoagulants (See Flowchart 3)

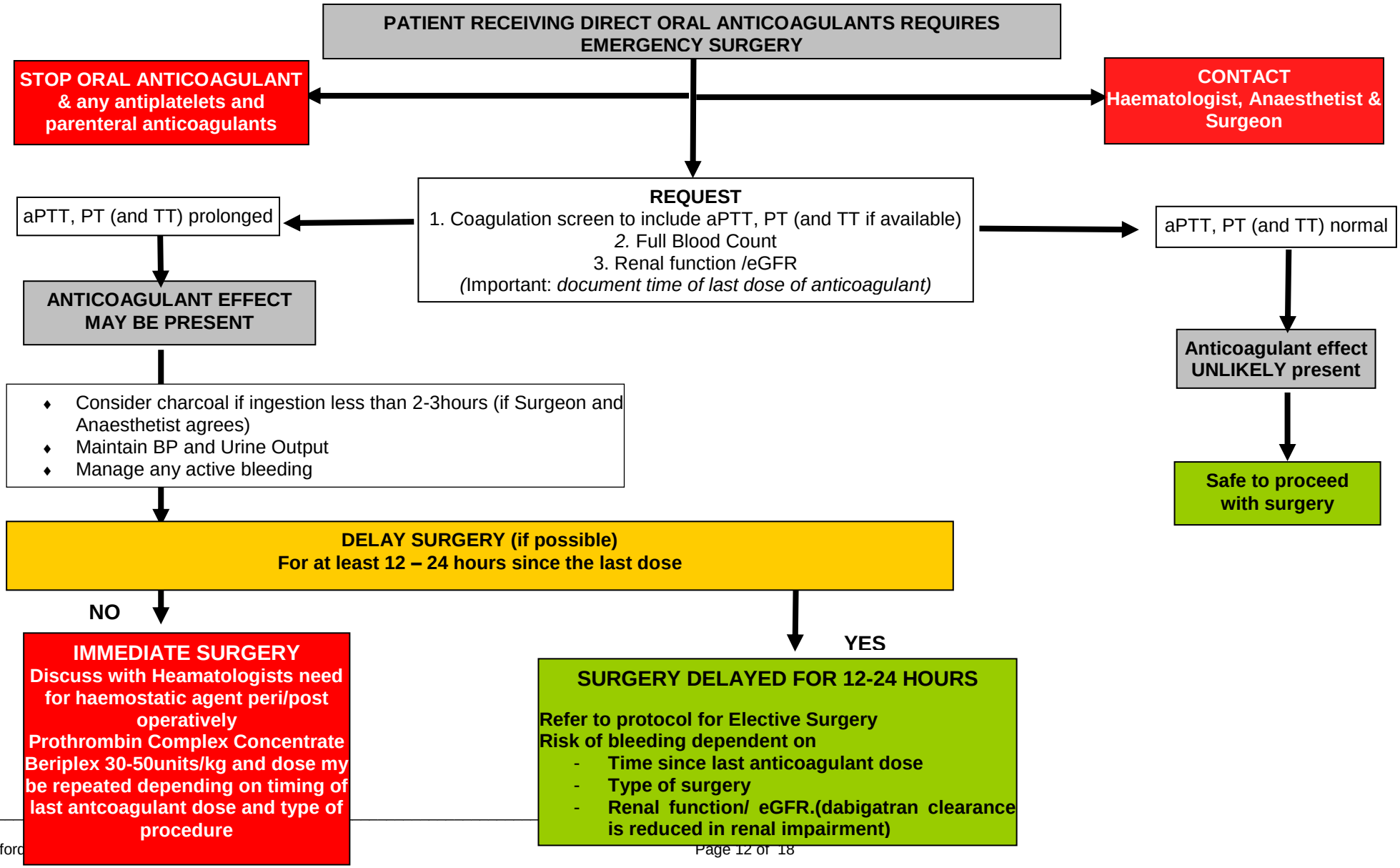
If an emergency invasive procedure or surgical intervention is required the anticoagulant should be temporarily discontinued. Currently there is a reversal agent specifically for dabigatran and not for the other DOACs. The procedure should be delayed if possible by at least 12-24 hours after the last dose was taken. If surgery cannot be delayed the risk of

bleeding may be increased. The risk of bleeding should be weighed against the urgency of the intervention. Where urgent life-saving surgery cannot be delayed contact the haematologist on call in relation to measures that can be taken to control bleeding prior to and during surgery.

Flowchart 2


Management of Direct Oral Anticoagulants(DOACs) during Elective Surgery**
Dartford and Gravesham NHS Trust
Consider bleeding risk associated with the surgery to determine when to stop DOAC (see pg. 1)
Bridging with Low Molecular Weight Heparin (LMWH) NOT required
DO NOT give DOACs concurrently with LMWH (e.g. Dalteparin)
Pre-Operative Period
Day of Surgery
Post- Op Period
STOP DOAC
Day – 4 (96 hrs before)
Day – 3 (72 hrs before)
Day – 2 (48 hrs before)
Day – 1 (24hrs before)
Day 0
Day + 1 (24hrs after)
Direct Thrombin Inhibitors
Factor Xa Inhibitors
DABIGATRAN If CrCl <50 mL/min
DABIGATRAN If CrCl 50 – 79mL/min
APIXABAN EDOXABAN RIVAROXABAN
DABIGATRAN If CrCl ≥80mL/min
APIXABAN EDOXABAN RIVAROXABAN
Surgery with High Bleeding Risk/Major Surgery
Low bleeding risk surgery*
Based on risk of bleeding and thrombosis:
✓ Give prophylactic STAT dose of LMWH 6 to 12 hours post-op
Haemostasis fully achieved No bleeding or bruising
✓ If no concerns about bleeding: Restart DOAC 24hrs post last dose of LMWH
✓ If concerned about bleeding: delay restarting DOAC for 48 hrs. Give another prophylactic STAT dose of LMWH 24hrs after last dose (if given 6-12 hrs post-op)
**This is a guideline only. Use clinical judgement or seek Haematology advice if unsure
*If surgery with low bleeding risk, stop dabigatran as follows:
CrCl ≥ 80 24hrs before surgery
CrCl 50-79 48hrs before surgery
CrCl < 50 72hrs before surgery
Written by: Dr T Shafi, Consultant Haematologist, C. Savieli, Pharmacist
Approved by: Dr J Kwan, Chair, Prescribing and Formulary Group; and Dr S. Parmar, Pre-Assessment Lead Date: November 2016; Review November 2019

FLOW CHART 3- MANAGEMENT OF PATIENTS TAKING DIRECT ORAL ANTICOAGULANTS WHO REQUIRE EMERGENCY SURGERY



c) Spinal/epidural anaesthesia or lumbar/epidural punctures

Prior to neuraxial intervention the physician/anaesthetist should carefully consider potential benefit versus the risk in anticoagulated patients or in patients who will be anticoagulated for thromboprophylaxis

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis.

Table 4 Spinal/epidural anaesthesia or lumbar punctures

Dabigatran	Rivaroxaban	Apixaban	Edoxaban
The use of Dabigatran is NOT recommended in patients undergoing anaesthesia with post-operative indwelling epidural catheters	An epidural catheter is NOT to be removed earlier than 18 hours after last administration of Rivaroxaban.	No information available	Discontinue edoxaban for at least 24 hours before the procedure
Administration of first dose of Dabigatran should occur a minimum of 2 hours after the catheter is removed.	The next rivaroxaban dose is to be administered NO earlier than 6 hours after removal of the catheter	No information available	Discontinue edoxaban for at least 24 hours before the procedure
Patients MUST be frequently monitored for signs and symptoms of neurological impairment			

6. Restarting oral anticoagulants after surgery

Apixaban, rivaroxaban, edoxaban and dabigatran are all rapidly absorbed, rapid onset of action, with peak anticoagulant activity at approximately two to three hours after oral ingestion. Thus, if post-operative or post-procedural anticoagulation is contemplated, these agents should not be employed too early following the operation in order to ensure that haemostasis has been secured at the operative or procedural site. This requires both a pre-procedural estimate of the anticipated risk of bleeding as well as a post-procedural determination of the adequacy of haemostasis

Clinical assessment for postoperative haemostasis should include; a subjective assessment of wound drainage, bleeding into bandages and, where appropriate, haemoglobin levels. Ideally, bridging anticoagulation should be resumed when the wound bed is considered to be dry, that is when there is no ongoing wound bleeding. This determination will vary depending on the surgery type and individual patient considerations, and may be difficult for surgery (e.g., cardiac, intracranial) where ongoing bleeding is not readily apparent. Nonetheless, attention to postoperative haemostasis is clinically important since too early resumption of anticoagulation, especially within 24 hours after surgery, is associated with a two- to fourfold increased risk for major bleeding.

However, for most minor procedures associated with a low bleeding risk, therapy with new oral anticoagulants can usually be resumed at 24 hours post-procedure, whereas for those undergoing major surgery or those with a high bleeding risk procedure, such treatment should be delayed for 48 to 72 hours after haemostasis has been secured. A prophylactic STAT dose of Low Molecular Weight Heparin (e.g. dalteparin 5,00units S/C) may be considered 6-12 hours post operatively based on the patient's thromboembolic risk and bleeding risk.

- Dabigatran dose should only be restarted if eGFR is greater than 30 after haemostasis has been secure
- Rivaroxaban, edoxaban and apixaban dose can be given provided the clinical situation allows and adequate haemostasis has been established
- Consider a prophylactic dose of low molecular heparin (e.g. dalteparin 5,00units S/C) the first 24 hours if necessary.

7. Combination with antiplatelet agents

DOACs should **NOT** be used in combination with antiplatelets such as aspirin, clopidogrel, prasugrel, ticagrelor or dipyridamole as currently there is no data to support this.

There is an increased risk of bleeding if aspirin is used in combination with dabigatran or rivaroxaban. The risk has only been well evaluated with aspirin combined with dabigatran compared to aspirin combined with warfarin. Aspirin should only be used in combination with dabigatran only where you would normally use aspirin with warfarin, and consider dose reduction to 110mg bd. Aspirin and Rivaroxaban combination is not recommended.

Dabigatran is not recommended in patients with unstable ischemic heart disease as it increases the rate of myocardial infarction relative to warfarin (RE-LY). In ROCKET-AF, rivaroxaban was associated with reduced risk of MI compared to warfarin.

A significant increase in bleeding risk was reported with the triple combination of apixaban, aspirin and clopidogrel in a clinical study in patients with acute coronary syndrome.

8. Switching from Parenteral or VKA oral anticoagulants to DOACs and vice versa

Check the product SPC for guidance on switching between DOACs and other anticoagulants. The general principles are as follows:

Switching from parenteral anticoagulants to DOACs and vice versa

- Do not administer parenteral anticoagulant and DOACs simultaneously
- For Low Molecular Weight Heparin (LMWH) this can be done at the next scheduled dose
- Unfractionated Heparin start DOAC at the time of discontinuation of infusion or 4 hour after for edoxaban.

Switching from VKA oral anticoagulants to DOACs

- Stop warfarin/sinthrome and start DOAC based on INR

Switching from DOACs to VKA oral anticoagulants

- Usually, DOACs can continue alongside warfarin/sinthrome until desired INR reached
- DOACs can affect INR values. Seek Haematology advice to interpret INR and timing of blood sample taking

9. Training and Implementation

This guideline will be available on the trust intranet “Adagio”.
All foundation year junior doctors, non-medical prescribers and all consultants working in Emergency Medicine, Surgery and Nurses working in Surgical Pre-Assessment Unit, must familiarise themselves with this guideline.
All pharmacists should be familiar with this guideline.
Any training needed by these clinical staff can be provided during induction or within their respective departments.

10. Monitoring Compliance with this document

What will be monitored	How/Method	Frequency	Lead	Reporting to	Deficiencies / gaps recommendations and actions	Implementation of any required change
Bleeding Incidents	Monitor incident forms	ongoing	Haematologists	Clinical Governance	Any adverse patient outcomes arising from incident reports will be addressed as and when they occur.	Changes to these guidelines will be made following any adverse patient outcomes or changes to the SPC for the product, or new published evidence.

11. Associated Documents/Further Reading

- Treatment pathway- prevention of stroke and systemic symbolism in adults with non-valvular atrial fibrillation.
- NICE Guideline TA256: Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation http://guidance.nice.org.uk/TA256
- NICE Guideline TA249: Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. http://guidance.nice.org.uk/TA249
- NICE Guideline TA245: Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults http://guidance.nice.org.uk/TA245
- NICE Guideline TA275: Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation http://guidance.nice.org.uk/TA275
- NICE Guideline TA170: Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults http://guidance.nice.org.uk/TA170
- NICE Guideline TA261: Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism http://guidance.nice.org.uk/TA261
- NICE Guideline TA287: Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism http://guidance.nice.org.uk/TA287
- NICE Guideline TA355: Edoxaban for the prevention of stroke in adults with non-valvular AF
- NICE Guideline TA341 Apixaban for treatment and prophylaxis for recurrent DVT and PE
- NICE Guideline TA327 Dabigatran for treatment and prophylaxis for recurrent DVT and PE
- TA354 (Edoxaban) for treatment and prophylaxis for recurrent DVT and PE

- NICE Guideline TA335 Rivaroxaban for prevention of adverse outcomes after acute management of acute coronary syndrome

12. Acknowledgments

With acknowledgement to East Kent Hospitals University NHS Foundation Trust. Dabigatran etexilate Hospital use guidelines. Authors Dr K Elliott, Dr G Evans, Dr M L Jenkinson April 2012.

13. References

1 Eerenberg ES et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011; 124: 1573-9.

2. Summary of Product Characteristic rivaroxaban, Bayer Plc Accessed August 2012 http://www.medicines.org.uk/EMC/medicine/25592/SPC/Xarelto+15mg+film-coated+tablets/

3. Summary of Product Characteristic dabigatran, Boehringer Ingelheim Limited. Accessed August 2012 http://www.medicines.org.uk/EMC/medicine/20760/SPC/Pradaxa+110+mg+hard+capsules/

4. Raza Alikhan; Managing major bleeding with new agents presented at The UK Thromboprophylaxis Forum 4th Annual meeting London 21st March 2012

5. Stangier J, Rathgen K, Stähle H, Dago M. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral Dabigatran etexilate: an open-label, parallel group, single-centre study. ClinPharmacokinet 2010; 49:259-68.

6. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010;103:1116-27.

7. http://www.icsi.org/dabigatran__consensus-based_statement_on_emergency_care_of_bleeding_protocol/dabigatran__consensus-based_statement_on_emergency_care_of_bleeding__protocol_.html

9. Jerrold H. Levy, M.D., FAHA, Nigel S. Key, M.D. Marc S. Azran, M.D. Novel Oral Anticoagulants Implications in the Perioperative Setting. Anaesthesiology 2010; 113:726 – 45

10. Makris M, Van Veen J.J., Tait C.R., Mumford A.D. and Laffan M. on behalf of the British Committee for Standards in Haematology. Guideline on the management of bleeding in patients on antithrombotic agents; British Journal of Haematology, 2012, 160, 35–46

11. Summary of Product Characteristic edoxaban tosilate, Daiichi Sankyo UK Limited Accessed December 2016 https://www.medicines.org.uk/emc/medicine/30512

12. Summary of Product Characteristic apixaban, Bristol-Myers Squibb-Pfizer. Accessed December 2016 https://www.medicines.org.uk/emc/medicine/27220

13. Daniels Paul R., Peri-procedural management of patients taking oral anticoagulants BMJ 2015;351:h2391 http://www.bmj.com/content/351/bmj.h2391 Accessed December 2016

14. Douketis JD1, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R; American College of Chest Physicians. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e326S-50S. doi: 10.1378/chest.11-2298. https://www.ncbi.nlm.nih.gov/pubmed/22315266 Accessed December 2016