MANAGEMENT OF BLEEDING IN PATIENT RECEIVING DIRECT ORAL ANTICOAGULANTS (DOAC)

Background

- Bleeding is a known complication of DOAC therapy (apixaban, dabigatran, edoxaban and rivaroxaban)
- The mainstay of bleeding management is supportive but specific anticoagulant reversal agents are available;
    - For dabigatran (idarucizumab [Praxbind®])
    - For apixaban and rivaroxaban (andexanet alpha [Ondexxya®])

Initial Assessment – ALL patients (excluding minor bleeding)

- Confirm anticoagulant drug
    - Dose
    - Time since last dose
    - Concurrent antiplatelet medication
- Check patient body weight, **calculate creatinine clearance (CrCl)** and estimate degree of anticoagulant exposure (see table 1)
- **Apply local haemostatic measures** (e.g. compression, packing, splinting) if possible
- If major bleeding establish venous access and initiate resuscitation in a monitored setting
- **Request urgent FBC, U&E, LFT, INR*, APTT*, Thrombin time*, Fibrinogen*, group & screen/cross-match** (as clinically appropriate) – send single blue, pink, purple & gold bottle via POD system & **alert haematology laboratory** informing of urgency of samples
- Arrange further investigation and **definitive management** (e.g. endoscopy, interventional radiology, neurosurgery, etc)
- **Determine the likely presence of the DOAC** and the expected elimination rate using time of last dose, drug half-life and CrCl (Table 1)
- Establish the indication for anticoagulation (where possible) - including date of previous VTE(s)/site/provoking factors; CHA_2DS_2Vasc score in AF; metallic heart valve site/brand; date/type of cardiac stent if on concomitant antiplatelet agents
- If available with timely results, consider measuring plasma concentration of DOAC using a specific assay (Table 1)
- Consult haematologist on call for advice- via switchboard

*Normal values do not exclude anticoagulant effect/nor reflect level of anticoagulation (excluding dabigatran, where normal thrombin time demonstrates no significant anticoagulant effect)

Management

MAJOR BLEEDING

- *Major Bleeding = Severe/Life threatening bleeding; bleeding in critical area eg intracranial, severe GI bleeding, impending haemodynamic instability, retroperitoneal bleed, intramuscular bleed with compartment syndrome, intra-spinal or pericardial bleeding (WHO grade 3-4; refer to Table 2)*
- **Withhold further anticoagulant** therapy
- Establish venous access, initiate resuscitation in monitored setting
- Except urinary tract bleeding, give **tranexamic acid 1 gm IV slow IV injection and then 1gm 8 hourly**
- Consider **blood component transfusion** as per clinical situation
    - Refer to major haemorrhage protocol (MHP) if appropriate
    - Consider red cell transfusion as per clinical situation; adopting restrictive transfusion thresholds where appropriate
    - Transfuse 1 ATD platelets if platelet count <50 x 10^9/L (<100 x 10^9/L with multiple trauma)
- Give **reversal agent** (see table 1) if anticoagulation administration within 3-5 half-lives
- See section on ‘Management when bleeding resolved’

SIGNIFICANT NON-MAJOR BLEEDING

- *Significant Non-major Bleeding e.g. haemodynamically stable gastrointestinal bleed, epistaxis, haematuria, or menstrual bleeding; requiring medical attention and/or intervention (WHO grade 2; refer to Table 2)*
- Withhold further anticoagulant therapy
- Arrange further investigation and definitive management (e.g. endoscopy, interventional radiology, neurosurgery, etc)
- Consider single-unit RBC transfusion for symptomatic anaemia (excludes mild symptoms)
- Consider platelet transfusion if platelet count <50 x 10^9/L
- Consult haematologist on call for advice on reversal agent if anticoagulation administration within 3-5 half-lives
- If available with timely results, consider measuring plasma concentration of DOAC using a specific assay (Table 1)
- See section on 'Management when bleeding resolved'

MINOR BLEEDING

- *Minor Bleeding e.g. extremity bruising, haemorrhoid bleeding, sub-conjunctival bleed, self-limited epistaxis (WHO grade 1, refer to Table 2)*
- Confirm anticoagulant drug, dose, intensity, duration is appropriate for indication, age, weight, renal and liver functions
- Check FBC, UE, LFT to ensure they are stable
- Review concomitant medications which may contribute to bleeding (e.g. ASA, NSAIDs)
- If bleeding stops patient can restart anticoagulation with closer follow-up
- Advise patient to report to GP or Anticoagulation service if recurrent bleeding
- If recurrent minor bleeding consider local intervention (eg haemorrhoid banding, nasal packing etc). Consider temporary anticoagulation interruption provided low thrombosis risk

Table 1 DOAC pharmacokinetics, effect on coagulation tests & 'reversal' agent

		Apixaban	**Edoxaban**	**Rivaroxaban**	**Dabigatran**
1. Mechanism of action: *Direct inhibitor of*		Factor-Xa	Factor-Xa	Factor-Xa	Thrombin
2. Half life					
	Creat clearance >50ml/min	8-12 hrs	10-14hrs	7-11hrs	7-17hrs
	Creat clearance 30-49ml/min	8-12 hrs	-	7-11hrs	17-20hrs
NB. Anticoagulant effect likely to be insignificant after 3-5 half lives					
3. Effect on coagulation tests					
	INR	Normal value does not exclude anticoagulant effect			
	APTT	Normal value does not exclude anticoagulant effect			
	TT	Not relevant			**Normal value excludes anticoagulant effect**
4. Specific DOAC Assay					
	Calibrated Anti-Xa (<30ng/ml)	Likely no significant anticoagulant effect			Not relevant
	Dilute Thrombin Time (<30ng/ml)	Not relevant			Likely no significant anticoagulant effect
5. Reversal agent		Prothrombin Complex Concentrate (Octaplex®) 50 units/kg (max 3000 units)*			Idarucizumab*** (Praxbind®) given as two 50ml bolus infusions each of 2.5 gm, (total 5gm) over 15 minutes
6. Reversal agent in specified indications*		Andexanet** (Onndexya®)	None	Andexanet** (Onndexya®)	

NB. Use should be guided primarily by bleeding (major or intracranial) and estimated degree of anticoagulant exposure (not laboratory testing), however, normal thrombin time excludes anticoagulant effect of Dabigatran (result available in approx. 40 mins).

*Prothrombin Complex Concentrate (Octaplex®) is not a specific reversal agent for the anti-Xa inhibitors. Request via transfusion laboratory (extn 74948, bleep 390). Ensure appropriate consent (pre/post use) as blood product (see policy C03). County Hospital (between 23:15-06:00 hours) PCC located in emergency drugs cupboard accessible via site manager.

**Andexanet is NICE approved for use only in life threatening or uncontrolled GI bleeding to reverse anticoagulant effect of apixaban or rivaroxaban. Supply of andexanet is governed by specific management protocol available on intranet. Contact transfusion laboratory (extn 74948, bleep 390) for supply of medication.

***Idarucizumab (Praxbind®) is held in the emergency department.

Management when bleeding resolved

- Complete **DATIX** report for anticoagulation related bleeding
- Inform Staffordshire Thrombosis and Anticoagulation centre (STAC) on 74252 or email anticoagulation.uhns@nhs.net with patient details and outcome
- Discuss with haematologist regarding **restarting anticoagulation**. Patient may be offered a different anticoagulant or dose, depending on risk of recurrent bleeding, renal function and patient preference.
- Ensure patient is well informed about the treatment options, risks and benefits of restarting anticoagulation. Patient to be advised to report immediately if any sign of recurrent bleeding.
- Ensure discharge letter has clear advice for GP on when to restart anticoagulation, choice of anticoagulant treatment, dose and instructions for monitoring for further bleeding.

Table 2: Modified World Health Organisation bleeding score (Stanworth et al 2013)

Bleeding grade	Description of bleeding
Grade 1	• Petechiae/purpura localised to 1 or 2 dependent sites, or sparse/non-confluent • Oropharyngeal bleeding, epistaxis <30 min duration
Grade 2	• Melaena, haematemesis, haemoptysis, fresh blood in stool, musculoskeletal bleeding, or soft tissue bleeding not requiring red cell transfusion within 24 hr of onset and without haemodynamic instability • Symptomatic oral blood blisters, i.e. bleeding/causing major discomfort. Multiple bruises, each >2 cm or any one >10 cm • Petechiae/purpura that is diffuse • Visible blood in urine • Abnormal bleeding from invasive or procedure sites • Unexpected vaginal bleeding saturating >2 pads in a 24 hr period • Bleeding in cavity – fluids evident macroscopically • Retinal haemorrhage without visual impairment
Grade 3	• Bleeding requiring red cell transfusion specifically for support of bleeding within 24 hr of onset and without haemodynamic instability • Bleeding in body cavity – fluids grossly visible • Cerebral bleeding noted on computed tomography (CT) without neurological signs and symptoms
Grade 4	• Debilitating bleeding including retinal bleeding and visual impairment* • Non-fatal cerebral bleeding with neurological signs and symptoms • Bleeding associated with haemodynamic instability (hypotension, >30 mmHg change in systolic or diastolic blood pressure) • Fatal bleeding from any source