PROTHROMBIN COMPLEX CONCENTRATE (OCTAPLEX®) TRANSFUSION • 1/3

BACKGROUND

- 4-factor PCC is a manufactured plasma product containing clotting Factors II, VII, IX and X, plus the natural anticoagulant proteins C and S
- Available as Octaplex® 500 IU or 1000 IU coagulation factor IX
- Store in controlled temperature <25°C for <2 yr
- Once requested keep in controlled storage at 2–8°C until required
- **Only use PCC where clinically indicated as administration may exacerbate underlying pro-thrombotic states**
- There is small risk of disseminated intravascular coagulation (DIC), particularly with repeated dosing
- **Clinician direct access** from the transfusion laboratory is available for agreed indications to ensure prompt treatment provision in recognised indications – [(RSUH: 0900–1700 hr call 74948 or out-of-hours bleep 390) (County: 0900–1700 hr call 4758 or <midnight bleep 4751)]
- for further details and relevant SOPs see Trust policy C03 or Blood and blood products intranet page

INDICATIONS

- Treatment of patients receiving warfarin or alternative vitamin K antagonists (VKA) experiencing major bleeding i.e. life, limb or eye-threatening bleeding. Includes high clinical suspicion of major haemorrhage pre-imaging
- Patients receiving warfarin or VKA requiring surgery or invasive procedure within the next 6–8 hr, due to clinical urgency only
- May be indicated for patients with major bleeding/pre-operatively receiving direct oral anticoagulants (DOACs) apixaban, rivaroxaban, edoxaban – see guidelines and seek advice from consultant haematologist (see STAC guideline '**Management of Bleeding in Patients on Antithrombotic Therapy**')
- May be indicated for patients with other acquired coagulopathies (e.g. liver disease, cardiac surgery) where there is high risk of transfusion associated circulatory overload (TACO) – seek advice from consultant haematologist

CONTRAINDICATIONS

- Hypersensitivity to the active substance or any of the excipients (see SPC)
- Known allergy to heparin or history of heparin induced thrombocytopenia (HIT)

DOSE

- Dosed in 'international units' (IU) as multiples of 500 IU
- Maximum single dose 3000 IU (120 mL)

For anticoagulant reversal

- Dosed at 25–50 IU/kg according to patient weight and INR (where known) as advised by transfusion laboratory SOP (see **Table 1** and **2**, plus flowchart below)
- **Do not await INR** or imaging if high clinical suspicion of major haemorrhage – especially if suspected intracranial bleeding
- For warfarin reversal always **ensure vitamin K (phytomenadione) 5 mg IV has been prescribed and administered** – as PCC immediately (but only temporarily) reverses the anticoagulant effects of warfarin
- Ensure anticoagulant has been omitted
- Repeat INR 10–20 min post administration (see below re assessing response)

Table 1: PCC dose if major bleeding or urgent surgery/procedure but valid INR not yet available

Weight (kg)	PCC dose (25 units/kg)
≤60	1500 units
61–80	2000 units
81–100	2500 units
>100	3000 units

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Table 2: PCC dose if major bleeding or urgent surgery/procedure plus INR available and valid (i.e. taken within 8 hr and assess possible impact of previous vitamin K use)

INR	Weight (kg)	PCC issue	PCC dose
1.6–1.9	n/a	500 iu	
2.0–3.5	≤60	1500 units	25 units/kg
	61–80	2000 units	
	81–100	2500 units	
	>100	3000 units	
3.6–5.0	≤60	2000 units	33 units/kg
	61–75	2500 units	
	>75	3000 units	
>5.0	≤60	2500 units	40 units/kg
	>60	3000 units	

As low volume FFP alternative

- Treat each 500 IU PCC as a treatment decision and evaluate clinically ± NPT post dose
- 1 IU PCC has equivalent clotting factor activity to 1 mL plasma (500 IU approximately equivalent to 2 units FFP)

ADMINISTRATION

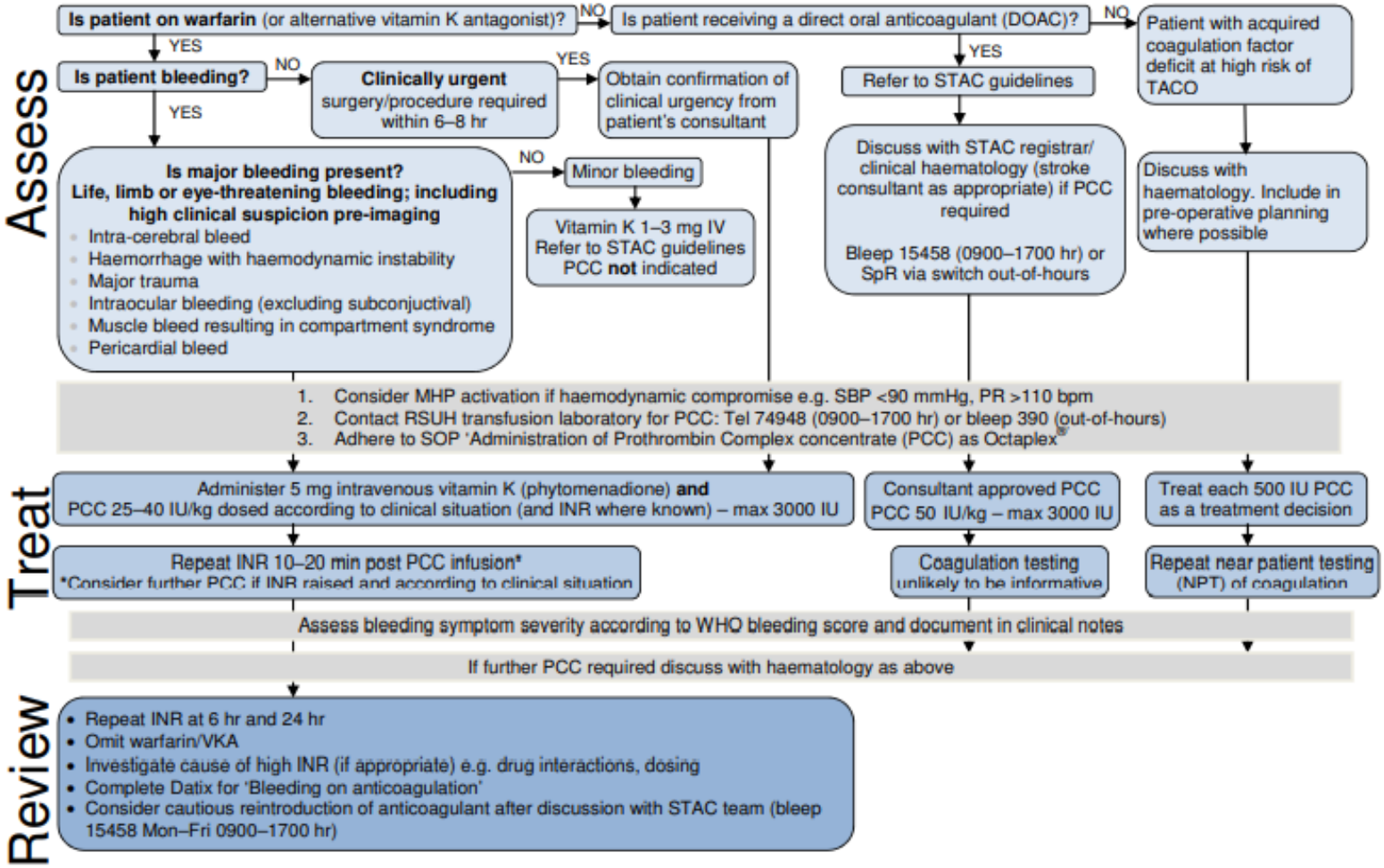
- Commence infusion at 1 mL/min and observe closely for allergic reactions/anaphylaxis
- In major bleeding increase rate to 8–10 mL/min under direct clinical instruction
- Pre-surgery/procedure increase rate to 2–3 mL/min
- Return unused PCC to transfusion laboratory as soon as possible to avoid wastage

ASSESSING RESPONSE TO TRANSFUSION

- Post PCC administration, assess and document bleeding symptom severity according to WHO bleeding severity score (see **Guiding principles of transfusion** guideline **Table 2**)
- For warfarin reversal – repeat INR 10–20 min post PCC administration
- If adequate correction, recheck clotting after 4-6 hours then daily
- If INR ≥1.5 or suboptimal correction and further PCC may be required – seek advice from a consultant haematologist
- Monitor for adverse events of PCC usage – especially thrombosis
- Complete Datix where indication is 'major bleeding on anticoagulation' and discuss with STAC registrar on 15458

PROTHROMBIN COMPLEX CONCENTRATE (OCTAPLEX®) TRANSFUSION • 3/3

Flowchart: Direct clinician access to prothrombin complex concentrate (PCC)



MANAGEMENT OF BLEEDING AND OVER-ANTICOAGULATION WITH WARFARIN • 1/2

CAUSES

- Concurrent disease process affecting clotting factor synthesis, vitamin K availability or warfarin metabolism:
  - cardiac failure
  - gastrocolic fistula
  - liver disease
  - malnutrition
  - cholestasis
  - abrupt weight reduction
  - diarrhoea
  - renal impairment
  - thyrotoxicosis
  - fever
  - malignancy
  - aged >75 yr
- Many commonly prescribed medications including most antimicrobials interfere with warfarin metabolism. Check any such interactions in the BNF and use an alternative agent if possible
- Over dosage (accidental or deliberate)
- Concurrent anti-platelet, NSAID, SSRI or SNRI use

Such patients are at high risk of over-anticoagulation and/or bleeding while on warfarin. These patients require close INR monitoring if continuing on warfarin. Refer patients to the Staffordshire Thrombosis and Anticoagulation (STAC) team for regular monitoring and dosing during inpatient stay and post-discharge

MANAGEMENT

- Management of over-anticoagulation depends on the INR, severity of bleeding and underlying thrombotic risk (**Table 1**)

In patients with prosthetic heart valves, reversal of anticoagulation may increase the risk of valve thrombosis. Discuss management with cardiothoracic unit and haematologist in non-life, limb or sight threatening situations

Table 1: Management of over-anticoagulation with warfarin

Clinical situation	INR (and special instructions)	Management
Major haemorrhage **(life, limb or sight threatening bleeding – including high suspicion pre-imaging)**	INR unknown or any raised INR ***Includes patients with a metallic heart valve*** • Intra-cerebral bleed • Bleed with haemodynamic instability • Major trauma • Intraocular bleed (excluding subconjunctival) • Muscle bleed resulting in compartment syndrome • Pericardial bleed	• Obtain venous access • Take blood for FBC, INR, APTT, Fibrinogen, U&E, LFT, G&S/crossmatching • **STOP** warfarin and reverse anticoagulation with: 1. Immediate vitamin K (phytomenadione) 5 mg slow IV **and** 2. Octaplex® (prothrombin complex concentrate PCC) – contact blood bank with patient's weight for direct PCC access request • **Do not wait** for INR result or imaging if high clinical suspicion • Activate massive haemorrhage pathway (MHP) if required
Minor haemorrhage	INR raised	• Dose reduce or temporarily discontinue warfarin • Administer IV vitamin K (phytomenadione) 1–3 mg slow IV • Oral bleeding – consider tranexamic acid mouthwash • Epistaxis – consider cautery or nasal packing
High INR without bleeding without bleeding	INR >8.0 INR 5.0–8.0 **and** high risk of bleeding* (*aged >70 yr, hypertension, diabetes, renal failure, previous CVA, previous GI bleed, liver disease)	**Unless a patient has a prosthetic heart valve (see warning box above):** • Stop warfarin • Give 2 mg oral vitamin K (phytomenadione) • Repeat INR in 24 hr • Restart warfarin at lower dose once INR <5.0 and monitor INR until stable
	INR >5.0 but ≤8.0	• Withhold 1–2 doses of warfarin • Reduce maintenance dose • Investigate cause for elevated INR

MANAGEMENT OF BLEEDING AND OVER-ANTICOAGULATION WITH WARFARIN • 2/2

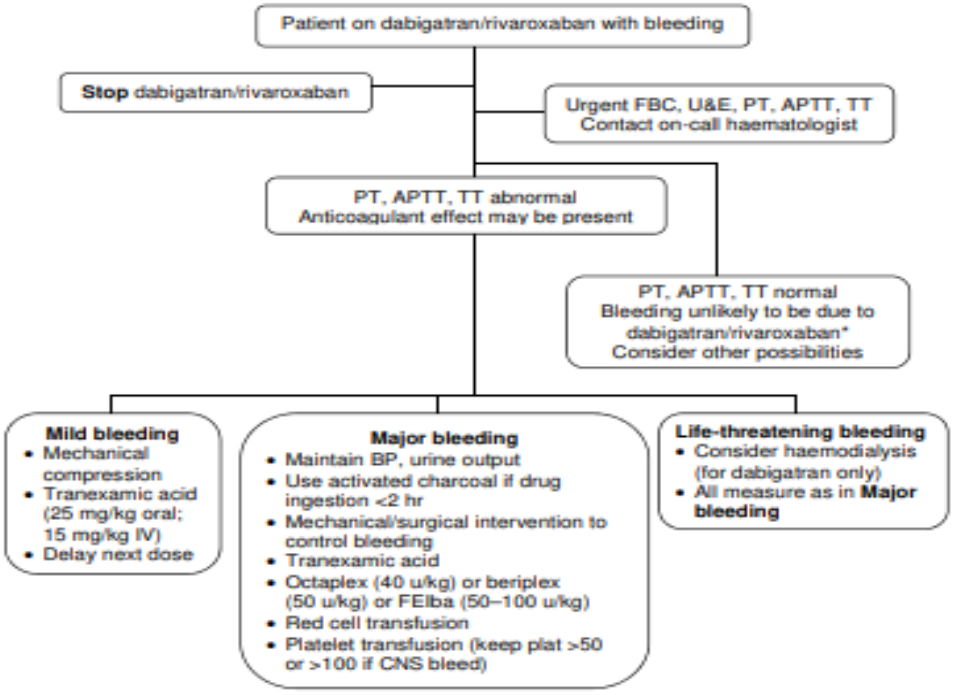
NB

- Intracranial bleeding in association with warfarin therapy is a medical emergency and requires urgent assessment, imaging and treatment (as above)
- **Do not wait for INR result or imaging if there is a high clinical suspicion of ICH**
- Delays in management may result in major morbidity and mortality. If ICH confirmed – seek neurosurgery advice
- In addition to warfarin reversal, consider local, endoscopic, interventional radiological and surgical measures early for all bleeds

RESTARTING WARFARIN AFTER A MAJOR BLEED

- Any patient with anticoagulation associated bleeding should be reported via DATIX as an adverse event
- Review the need for anticoagulation; confirm duration, intensity and concurrent medication
- Assess bleeding risk factors and address any potential cause for re-bleeding
- Seek specialist input from relevant team e.g. neurosurgery, gastroenterology
- Discussion with the haemostasis team (SpR bleep 15458) before re-starting anticoagulation is strongly advised
- Assess suitability of alternative anticoagulants
- All cases will be reviewed by the STAC governance team

MANAGEMENT OF BLEEDING IN PATIENT ON DABIGATRAN OR RIVAROXABAN • 1/1



*Normal PT, APTT, TT and fibrinogen is indicative of either no anticoagulant activity or activity equivalent to prophylactic LMWH

Summary of direct oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban
Site of action	Direct thrombin inhibitor	Xa inhibitor	Xa inhibitor
Impact on standard coagulation tests*	APTT, TT	PT, anti Xa	PT, anti Xa
Half-life (normal renal function)	12–14 hr	9–13 hr	8–15 hr
Renal excretion	80%	66%	25%
Current indication	VTE prevention, AF	VTE prevention and treatment, AF	VTE prevention
Reversal in case of bleeding	Discuss with consultant haematologist	PCC, FEIBA, rVIIa	Discuss with consultant haematologist

*Non-linear correlation, can only be used to detect absence of activity