34FM.5 DABIGATRAN: GUIDANCE FOR MANAGEMENT OF OVERDOSE, BLEEDING AND EMERGENCY/ELECTIVE SURGERY

Introduction

Dabigatran (Pradaxa®) is a direct thrombin inhibitor with a half-life of 12 - 14 hours.

Dabigatran is primarily excreted renally (80% renal excretion) and the half-life is prolonged in renal impairment.

The major adverse effect of all anticoagulant medications is bleeding.

For quick reference please see flowcharts:
Appendix 1: Dabigatran: Overdose Protocol
Appendix 2: Dabigatran: Haemorrhage Protocol
Appendix 3: Dabigatran: Emergency Surgery Protocol
Appendix 4: Dabigatran: Elective Surgery Protocol
Appendix 5: Administration of Idarucizumab for the Emergency Reversal of Dabigatran

All patients

Check coagulation screen indicating time of last dabigatran dose when requesting test.

APTT	Moderately sensitive to dabigatran, but non-linear at high levels.
Thrombin Time (TT)	Very sensitive to the presence of dabigatran. A normal result excludes the presence of significant levels of the drug.
Prothrombin Time (PT/INR)	Not sensitive to dabigatran - a high result suggests overdose of a different anticoagulant such as warfarin.
Fibrinogen	May be low - very variable!

Check full blood count, renal function and electrolytes (including calcium).

No bleeding or minor bleeding

1. *Omit dabigatran* until the bleeding stops, unless the risk of thrombosis is very high.
2. *Local measures* may be helpful.
3. *Consider cause* of bleeding.
4. *For oral cavity* bleeding also consider tranexamic acid 250 mg/5 ml mouthwash (unlicensed) – 10 ml 8 hourly.

Major/life-threatening haemorrhage (e.g. central nervous system (CNS)/major gastro-intestinal (GI), or imminent, urgent surgery

A major bleed is defined as: Symptomatic bleeding in a critical organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome. (Schulman et al. J Thromb Haemost 2010; 3:692-694)

1. *Reduction of absorption:* The administration of activated charcoal may be helpful in the event of an acute (<1 - 2 hours) overdose.
2. *Fluid replacement:* Maintain good urine output as dabigatran is excreted renally.
3. *Blood product transfusion:* Aim for platelet count >50 x 10^9/L or if CNS bleed >100 x 10^9/L. Consider platelet transfusion if patient on antiplatelet agents.
4. *Consider antifibrinolytics:* Tranexamic acid 500 mg – 1000 mg IV 8 hourly.
5. *Reversal: Discuss with consultant haematologist* for authorisation and further advice.
   - *Idarucizumab (Praxbind®)* has been shown to reverse dabigatran.
   - See Appendix 5 for advice regarding dose and reconstitution of Praxbind®.

Elective surgery

Pre-operative

1. Check creatinine clearance to guide when to stop dabigatran pre-operatively.

Timing of interruption of dabigatran prior to procedures or surgery

Calculated creatinine clearance (ml/min)	Half-life (hours)	Timing of last dose before surgery	
		Standard bleeding risk surgery* (2 or 3 drug half-lives between last dose and surgery)	**High bleeding risk surgery‡ (4 or 5 drug half-lives between last dose and surgery)**
>50	14 - 17	24 hours	2 days
>30 ≤50	16 - 18	2 days	4 days

*Standard risk procedures, e.g. cardiac catheterisation, ablation therapy, colonoscopy without removal of large polyps and uncomplicated laparoscopic procedures such as cholecystectomy.

‡High risk procedures, e.g. insertion of pacemakers or defibrillators (resulting from the risk of pocket haematoma), large hernia surgery and major cancer/abdominal/spinal/urological/ vascular surgery and neuroaxial anaesthesia.

2. Bridging therapy
   - Generally, the rapid offset and onset of dabigatran obviates the need for perioperative bridging therapy in many patients.

Post-operative

Recommencement of dabigatran after surgery

General principles: The appropriate time to re-start dabigatran after surgery will be determined by the bleeding risk of the surgery, the urgency for restarting thromboprophylaxis and the haemostatic state of the patient.

The anticoagulant onset of effect of dabigatran is within 2 hours, provided that intestinal absorption is normal.

Caution in resuming dabigatran especially in those patients who have had surgery with a high bleeding risk. Re-start once complete haemostasis is achieved and renal function is stable. In patients having high bleeding risk surgery or procedures, it is sensible to delay resumption of dabigatran for two to three days after such procedures.

Short term use of low molecular weight heparin (LMWH)/heparin may be appropriate where thromboprophylaxis is required but the risks from wound bleeding are increased or if a patient has a prolonged delay in resuming oral intake. The risk for thrombosis should be assessed. If a patient is on heparin after surgery and there is an intent to recommence dabigatran, this should be done ≤2 hours prior to the time of the next scheduled dose of LMWH or at the time IV heparin is discontinued.

Post-operative resumption of dabigatran

Low bleeding risk	High bleeding risk
Resume on day after surgery (24 hours)	Resume 2 - 3 days after surgery (48 - 72 hours post-operative)*

*For those at high risk of thromboembolism, consider administering a reduced dose of dabigatran (e.g. 110 mg – 150 mg od) on the evening after surgery and on the first post-operative day after surgery or bridging therapy with LMWH/heparin.

References

Makris M el al. Guideline for the management of bleeding of patients on antithrombotic agents. British Journal of Haematology 2012; 160: 35-46

Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood 2012:120(15): 2954-2962

Praxbind® Summary of Product Characteristics 2015. Boehringer Ingelheim.

Pollack CV Jr et al. *N Engl J Med* 2015;**373(6)**: 511–520.

Schiele F et al. *Blood* 2013;**121**: 3554-3562.

Glund S et al. *ASH* 2014: abst 334.

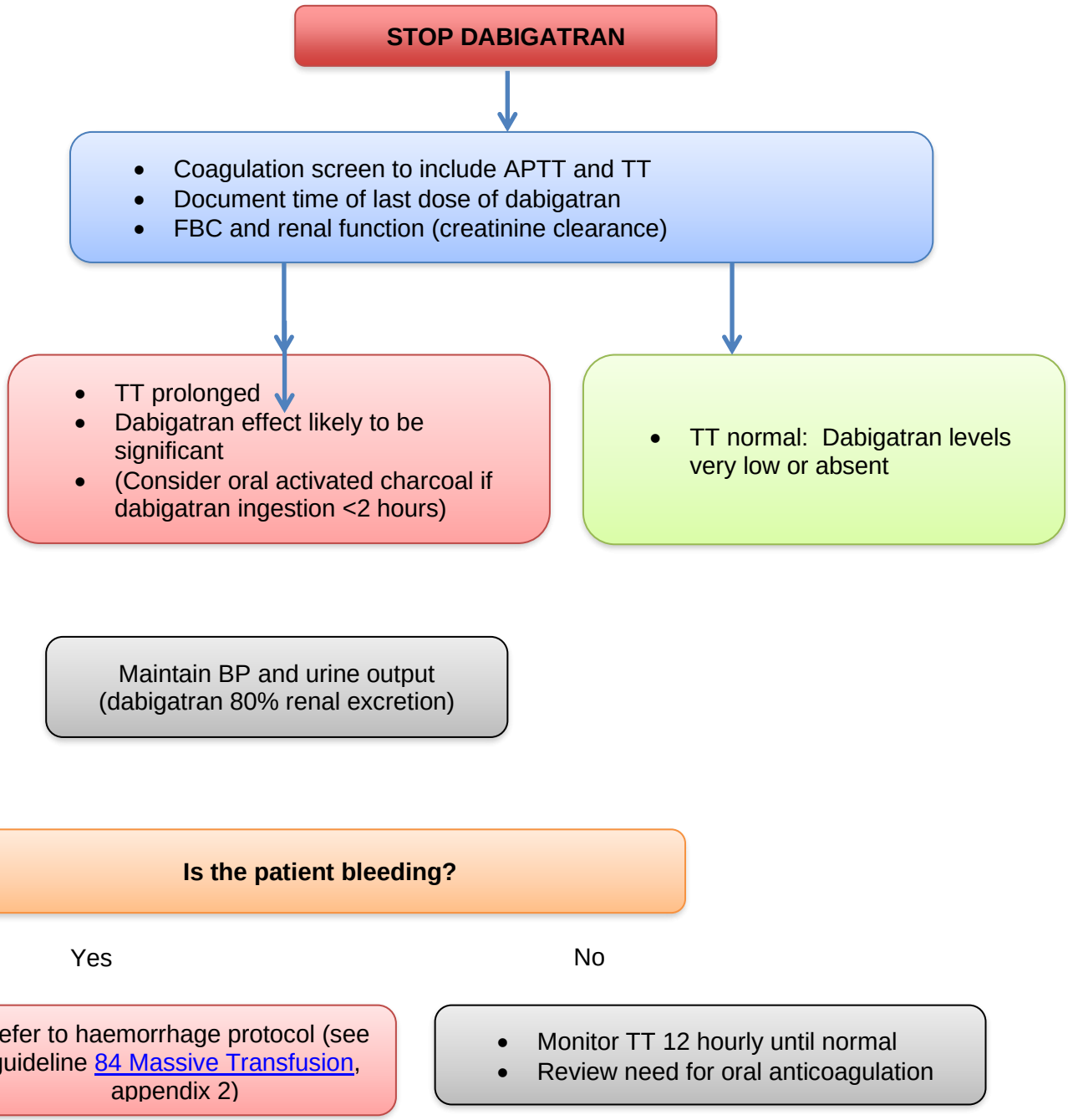
Pollack Jr CV et al. *Thromb Haemost* 2015;**114(1)**: 198-205.

See also:

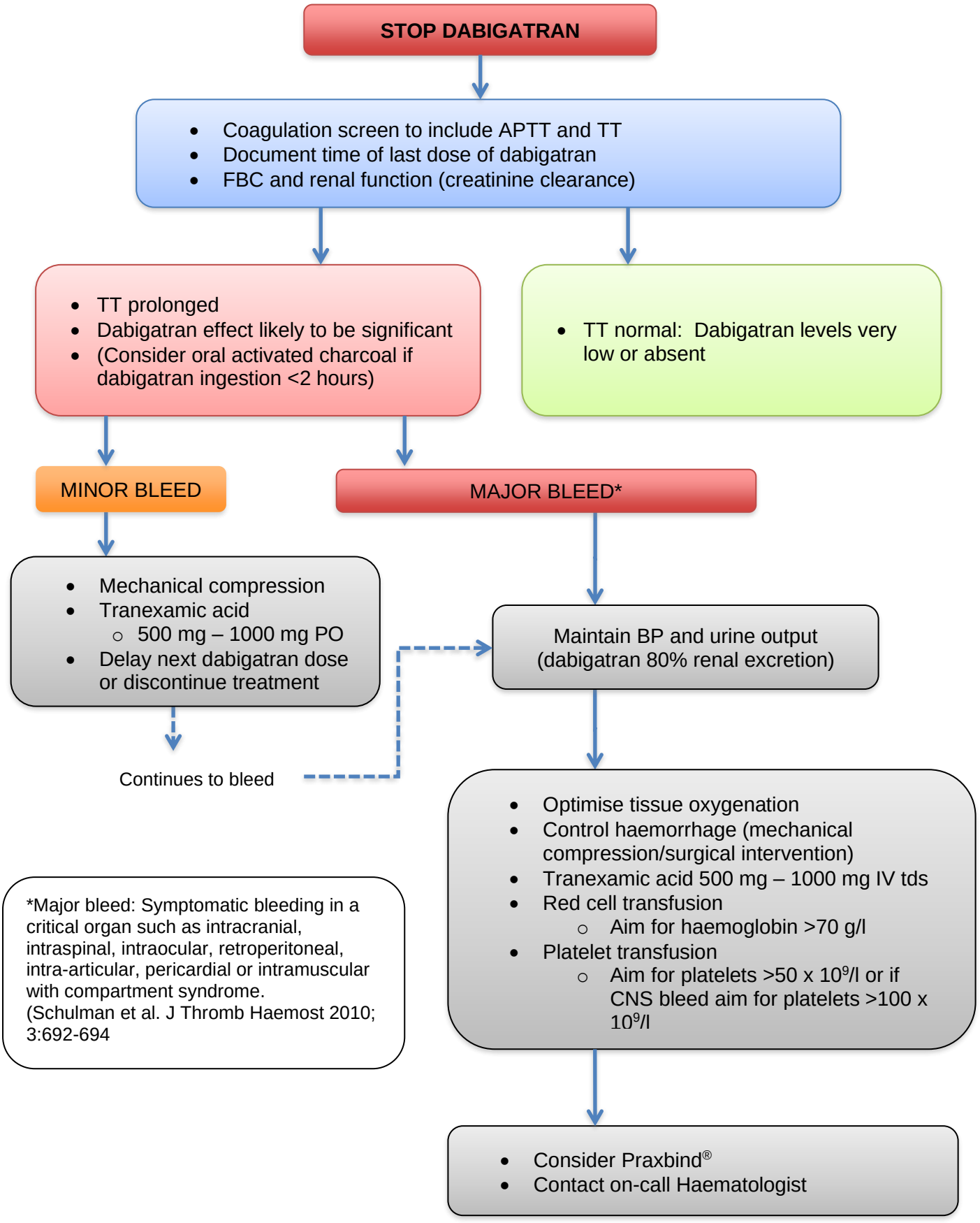
Guideline 83FM Peri-operative Bridging of Warfarin Therapy in Adult Patients undergoing Elective Surgery or Invasive Procedures
Guideline 84 Massive Transfusion (BHT users only)
Guideline 191FM Protocol for Over-Anticoagulation with Warfarin
Guideline 222 Injectables Policy and Guide (Adults) (BHT users only)
Guideline 224 Unlicensed Medicines Policy (BHT users only)
Guideline 240FM Rivaroxaban and Apixaban: Guidance for Management of Overdose, Bleeding and Emergency/Elective Surgery
Guideline 313FM Dabigatran for Atrial Fibrillation
Guideline 733FM Thromboprophylaxis in Adults

Title of Guideline	Dabigatran: Guidance for Management of Overdose and Bleeding
Guideline Number	34FM
Version	5
Effective Date	September 2016
Review Date	February 2022 (Review date extended – approved by Clinical Guidelines Group 16th February 2021)
First published on the Intranet	May 2012
Approvals:	
Clinical Guidelines Subgroup	8th September 2016
Author/s	Dr Jonathan Pattinson, Consultant Haematologist
SDU(s)/Department(s) responsible for updating the guideline	Haematology
Uploaded to Intranet	19th September 2016 and 16th February 2021
Buckinghamshire Healthcare NHS Trust	

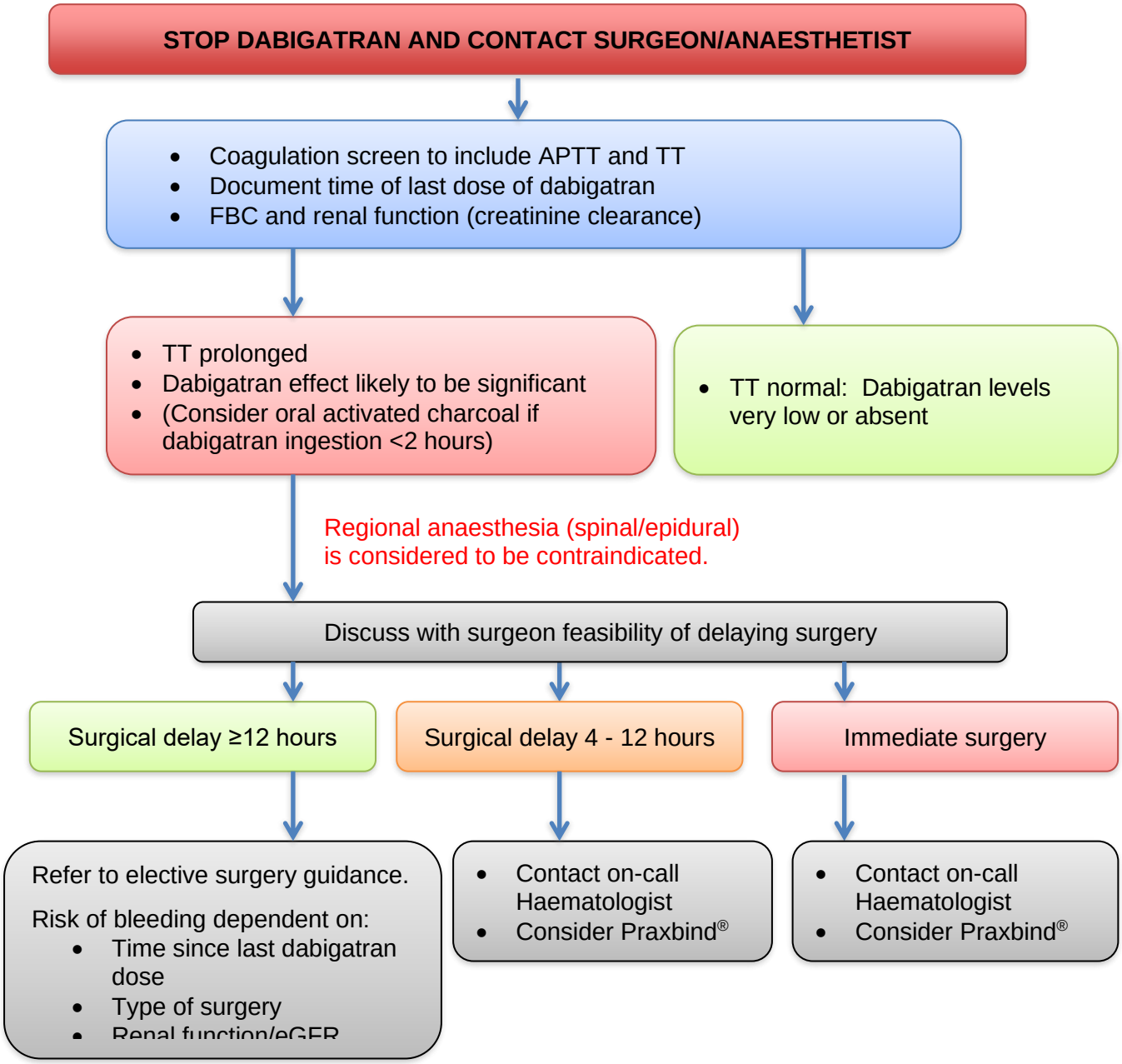
Appendix 1: Dabigatran: Overdose Protocol



Appendix 2: Dabigatran: Haemorrhage Protocol



Appendix 3: Dabigatran: Emergency Surgery Protocol



Appendix 4: Dabigatran: Elective Surgery Protocol

Pre-operative

- Check creatinine clearance
- Assess bleeding risk of surgery

Timing of interruption of dabigatran prior to procedures or surgery

Calculated creatinine clearance (ml/min)	Half-life of dabigatran (hours)	Timing of last dose before surgery	
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‡High risk procedures, e.g. insertion of pacemakers or defibrillators (resulting from the risk of pocket haematoma), large hernia surgery and major cancer/abdominal/spinal/urological/vascular surgery and neuroaxial anaesthesia.

Post-operative

- Assess bleeding risk of surgery
- Assess haemostatic state of patient and renal function
- Is the patient tolerating oral diet?

Haemostasis achieved

Patient is tolerating oral diet

Patient unable to tolerate oral diet

Post-operative resumption of dabigatran

Standard LMWH prophylaxis until able to take dabigatran

Low bleeding risk	High bleeding risk
Resume on day after surgery (24 hours)	Resume 2 - 3 days after surgery (48 - 72 hours post-operative)*

* For those at high risk of thromboembolism, consider administering a reduced dose of dabigatran (e.g. 110 mg – 150 mg od) on the evening after surgery and on the first post-operative day after surgery or bridging therapy with LMWH/heparin.

Appendix 5: Administration of Idarucizumab for the Emergency Reversal of Dabigatran

Praxbind®
idarucizumab

Praxbind - The specific reversal agent of Pradaxa

When rapid reversal of the anticoagulant effects of Pradaxa is required, Praxbind offers immediate reversal. Pradaxa is the first non vitamin K antagonist oral anticoagulant (NOAC) with a specific reversal agent. Together, Pradaxa and Praxbind set a new standard in anticoagulation care.

Praxbind indications

For the rapid reversal of the anticoagulation effects of Pradaxa in:

- Emergency surgery/urgent procedures[1,2]
- Life-threatening or uncontrolled bleeding[1,2]

Contra indications and adverse reactions

- There are no contra indications
- No adverse reactions have been identified in clinical studies

Pradaxa with Praxbind provides added confidence and keeps you more in control.

How do I administer Praxbind?

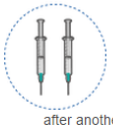
2 x 2.5g

Praxbind is given as 2 separate vials each containing 2.5 g/50 mL in a ready-to-use solution[1]

The full 5 g dose is administered intravenously as:[1]

- Two consecutive intravenous infusions over 5-10 minutes each

OR



- A bolus injection, by 2 injecting both vials consecutively one after another

A pre-existing intravenous line may be used[1]

- No other infusion should be administered in parallel via the same intravenous access