240FM.2 RIVAROXABAN AND APIXABAN: GUIDANCE FOR MANAGEMENT OF OVERDOSE, BLEEDING AND EMERGENCY/ELECTIVE SURGERY

Introduction

Rivaroxaban (Xarelto®) and apixaban (Eliquis®) are direct factor Xa inhibitors with a half-life of 12 - 14 hours.

Rivaroxaban and apixaban are eliminated by hepatic metabolism (about ⅔) and by renal excretion (about ⅓) and the AUC (area under the curve) is increased in renal impairment.

The major adverse effect of all anticoagulant medications is bleeding.

For quick reference please see flowcharts:
Appendix 1: Rivaroxaban and Apixaban: Overdose Protocol
Appendix 2: Rivaroxaban and Apixaban: Haemorrhage Protocol
Appendix 3: Rivaroxaban and Apixaban: Emergency Surgery Protocol
Appendix 4: Rivaroxaban and Apixaban: Elective Surgery Protocol

All patients

Check coagulation screen indicating time of last rivaroxaban and apixaban dose when requesting test. Always remember that there are many causes of abnormal clotting results unrelated to anticoagulant drugs.

APTT	Sensitive to rivaroxaban and apixaban.
Thrombin Time (TT)	Not sensitive to rivaroxaban and apixaban - a high result may suggest the presence of *dabigatran.*
Prothrombin Time (PT/INR)	Sensitive to rivaroxaban and variable sensitivity to apixaban - a normal result suggests that rivaroxaban levels are very low. Remember that *warfarin* also increases the PT.
Fibrinogen	Not affected by rivaroxaban and apixaban.

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

No bleeding or minor bleeding

1. *Omit rivaroxaban or apixaban* 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 (5%) mouthwash (unlicensed) – 10 ml 8 hourly.

Major/life-threatening haemorrhage (e.g. CNS/major GI)

1. *Reduction of absorption:* The administration of activated charcoal may be helpful in the event of an acute (<6 hours) overdose.
2. *Fluid replacement:* Maintain good urine output as rivaroxaban and apixaban are partly 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 particularly if patient on antiplatelet agents.
3. *Consider antifibrinolytics:* Tranexamic acid 500 mg – 1000 mg IV 8 hourly.
4. *Reversal:* There is currently no reversal agent or antidote for rivaroxaban or apixaban. The administration of clotting factors or vitamin K is NOT anticipated to be effective in reversing the effects of rivaroxaban or apixaban.
   Haemodiafiltration is NOT likely to be effective in removing rivaroxaban or apixaban as both drugs are highly protein-bound.
5. *Discuss with consultant haematologist* for further advice.
   - *Prothrombin complex concentrate* (Beriplex®) has been shown to produce reversal of the effect of rivaroxaban in healthy volunteers but there is little data to support its use in acute bleeding. There is no clinical data for apixaban. See Guideline 191FM Protocol for Over-Anticoagulation with Warfarin (Appendix 1) for advice and reconstitution of Beriplex®.

Elective surgery

Pre-op

1. Check creatinine clearance to guide when to stop rivaroxaban and apixaban pre-operatively. Note that a creatinine clearance of less than 30 ml/min has relatively little influence on the half-life of rivaroxaban or apixaban, however the AUC is significantly increased in these patients.

Timing of interruption of rivaroxaban and apixaban 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)
>30	12 – 17	24 hours	2 days
>15 ≤30	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 rivaroxaban and apixaban obviates the need for perioperative bridging therapy in many patients, but you must consider the risk of thrombosis very carefully: See Guideline 733FM Thromboprophylaxis in Adults.

Post-op: Restarting rivaroxaban and apixaban after surgery

General principles: The appropriate time to re-start rivaroxaban and apixaban 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 rivaroxaban and apixaban is within 2 hours, provided that intestinal absorption is normal.

Caution is required when resuming rivaroxaban or apixaban, 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 rivaroxaban or apixaban 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 intent to restart rivaroxaban or apixaban, 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 rivaroxaban and apixaban

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

**For those at high risk of thromboembolism,* consider administering a reduced dose of rivaroxaban or apixaban on the evening after surgery and on the first post-operative day after surgery or bridging therapy with LMWH/heparin.

References

1. Tanaka KA, Szlam F. Treatment of massive bleeding with prothrombin complex concentrate: argument for. Journal of Thrombosis and Haemostasis 2010; 8: 2589-91.
2. Makris M el al. Guideline for the management of bleeding of patients on antithrombotic agents. British Journal of Haematology 2012; 160: 35-46.
3. Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood 2012:120 (15): 2954-2962.
4. Kubitza D et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct factor Xa inhibitor. Br J Clin Pharmacol. 2010 November; 70(5): 703–712.
5. Baglin T et al. Effects on routine coagulation screens and assessment of anticoagulant intensity in patients taking oral dabigatran or rivaroxaban and apixaban: Guidance from the British Committee for Standards in Haematology. British Journal of Haematology 2012, 159, 427–429.
6. Erenberg E et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation. 2011 Oct 4; 124(14): 1573-9.

See also:

Guideline 34FM Dabigatran: Guidance for Management of Overdose, Bleeding and Emergency/Elective Surgery
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 Adult and Paediatrics Injectables Guide (BHT users only)
Guideline 313FM Dabigatran, Rivaroxaban, Edoxaban and Apixaban for Atrial Fibrillation
Guideline 733FM Thromboprophylaxis in Adults

BHT Policy 071 – Unlicensed Medicines Policy (Annexe 4 of the Medicines Policy)

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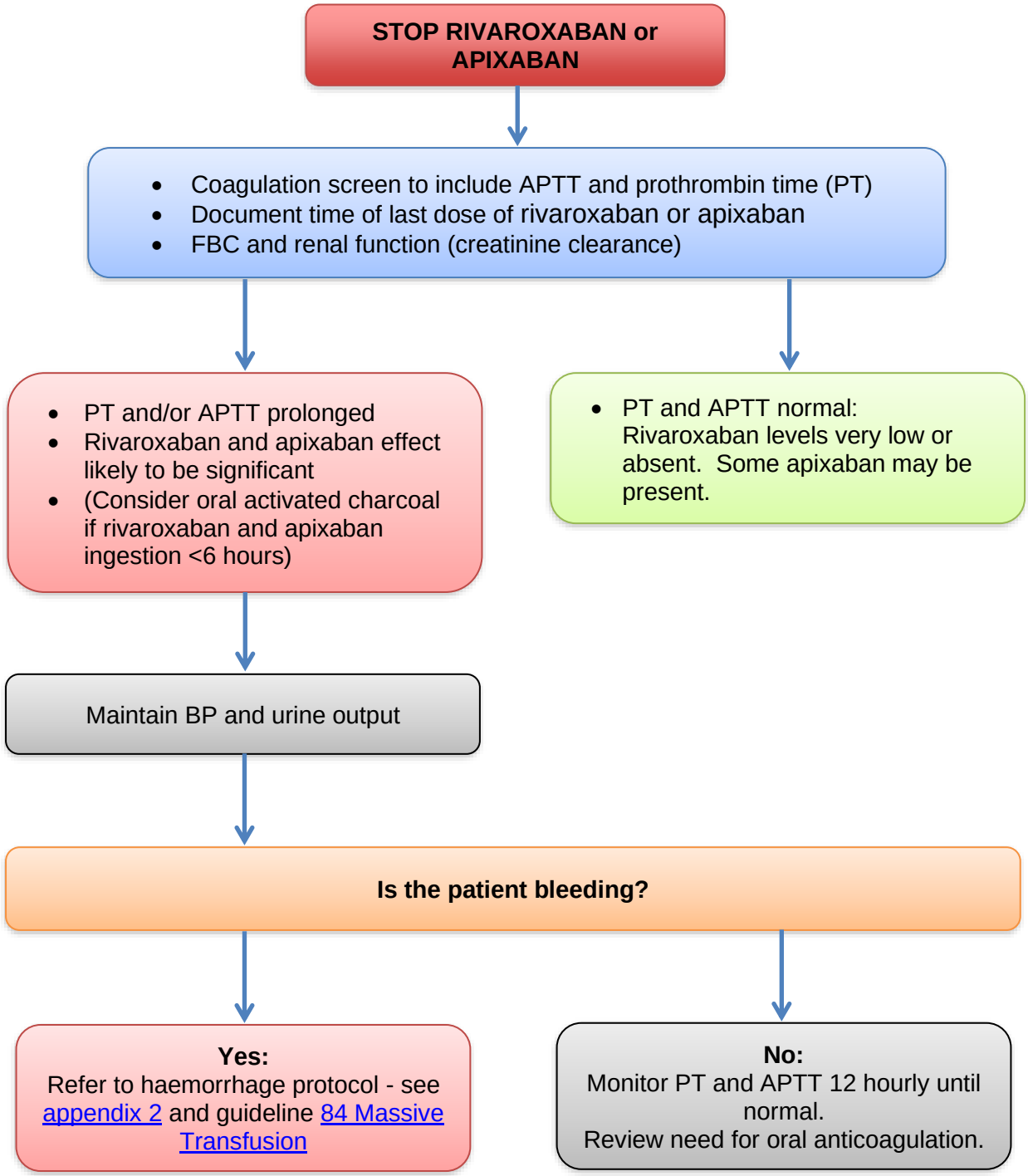
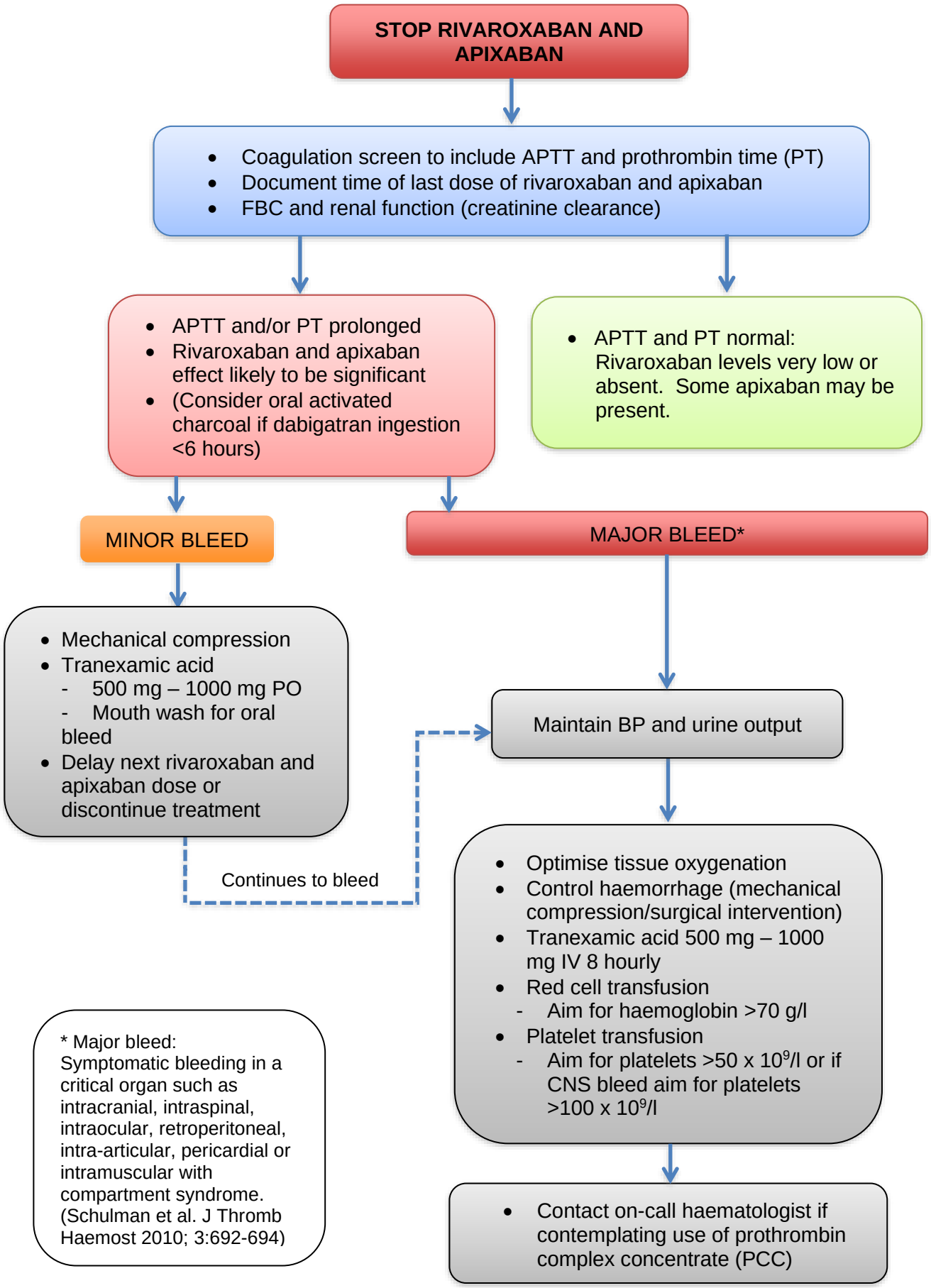
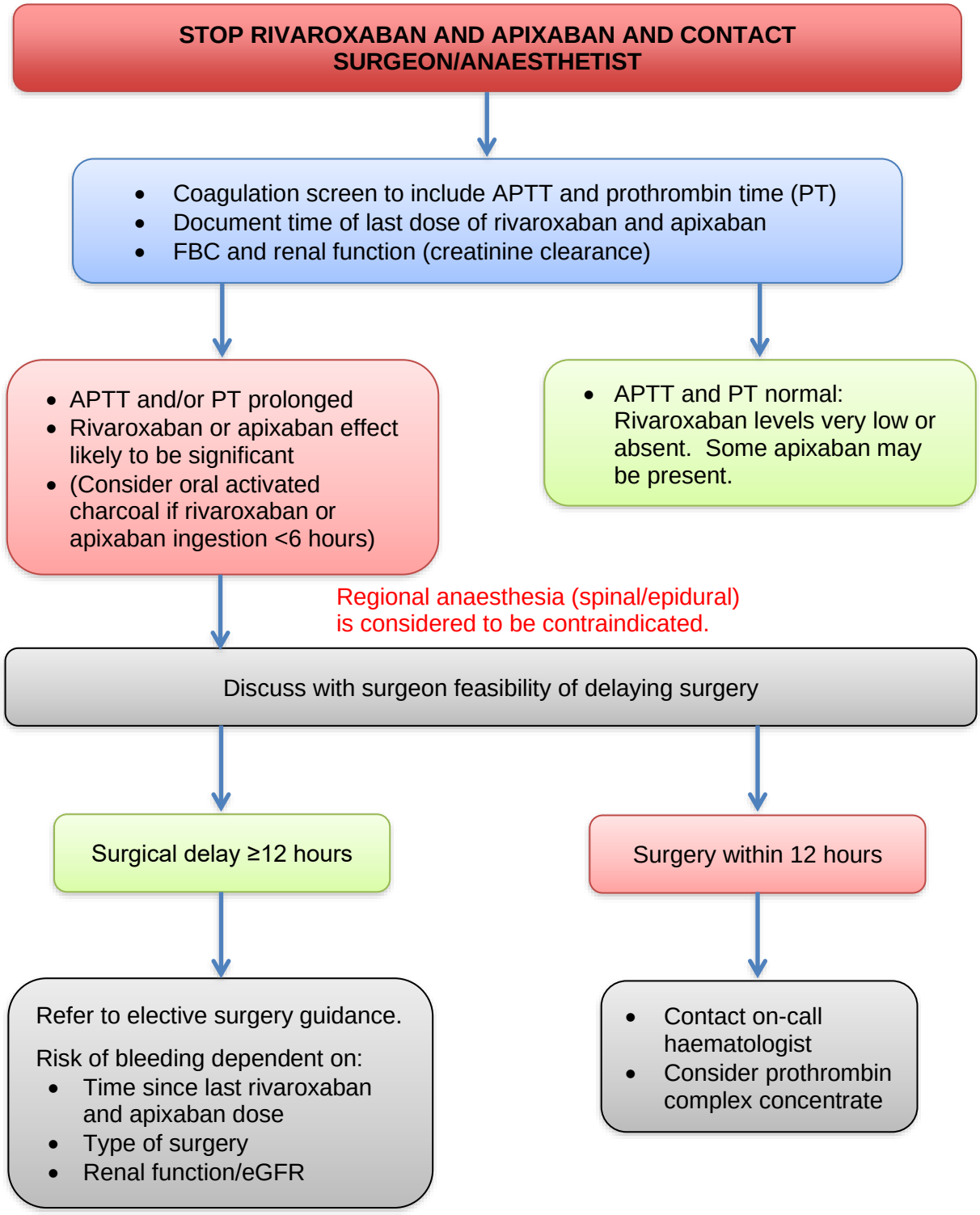
Appendix 1: Rivaroxaban and Apixaban Overdose Protocol



Appendix 2: Rivaroxaban and Apixaban Haemorrhage Protocol



Appendix 3: Rivaroxaban and Apixaban Emergency Surgery Protocol



Appendix 4: Rivaroxaban and Apixaban Elective Surgery Protocol

Pre-op

- Check creatinine clearance
- Assess bleeding risk of surgery

Timing of interruption of rivaroxaban and apixaban prior to procedures or surgery

Calculated creatinine clearance (ml/min)	Half-life of rivaroxaban and apixaban (hours)	Timing of last dose before surgery	
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*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.

Post-op

- 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

Post-operative resumption of rivaroxaban and apixaban

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

Patient unable to tolerate oral diet

Standard LMWH prophylaxis until able to take rivaroxaban and apixaban

* For those at high risk of thromboembolism, consider administering a reduced dose of rivaroxaban and apixaban on the evening after surgery and on the first post-operative day after surgery or bridging therapy with LMWH/heparin.