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<th><strong>State if the document is a Trust Policy/Procedure or a Clinical Guideline</strong></th>
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<tr>
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<td>Reversal of the anticoagulant effects of the novel oral anticoagulants for management of bleeding, emergency surgery or overdose (Dabigatran, Rivaroxaban and Apixaban)</td>
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<td>Novel oral anticoagulants (NOACS) Dabigatran, Rivaroxaban, Apixaban Bleeding Atrial fibrillation Prothrombin complex concentrate (Octaplex)</td>
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<td>Novel oral anticoagulants in Atrial fibrillation Administration of prothrombin complex concentrate- see warfarin guideline- CG247</td>
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Reversal of the anticoagulant effects of the novel oral anticoagulants
(Dabigatran, Rivaroxaban and Apixaban)

Introduction
Dabigatran, Rivaroxaban and Apixaban are newer oral anticoagulants which are being used increasingly, either for atrial fibrillation, thromboprophylaxis for orthopaedic surgery or for treatment and prevention of VTE. Although major haemorrhage is infrequent, management can be difficult especially with anticoagulants for which there are no specific reversal agents.

Purpose
The objective of this document is to guide healthcare professionals on the management of patients receiving these new oral anticoagulants who experience significant bleeding or who require emergency surgery or an invasive procedure along with management of an overdose. The basis of this guideline is to provide a protocol to assist in the management of such patients. Guidance on reversal of vitamin k antagonists can be found in CG228.

This document will include information on Dabigatran, Rivaroxaban and Apixaban
- Protocol for haemorrhage
- Protocol for overdose
- Reversal prior to emergency surgery

Consultation and communication with stakeholders
This guideline was reviewed and discussed at the Hospital Thrombosis committee meeting on 24th April 2013.
Staff present were Miss Brown, Sr Pamela Fox, Dr Preena Patel, Dr S McLaggan, Saleh Ahmed, Dr Yogasakaran.

Management of bleeding- general measures
There is no specific reversal agent for Dabigatran, Rivaroxaban or Apixaban.
Routine monitoring of these agents is not required, and there is no role for routine monitoring to assess efficacy of treatment.

Monitoring is reasonable in the following circumstances:
- Patients presenting as an emergency with adverse events (thrombosis or bleeding)
- Cessation of anticoagulation required e.g. for surgery.
For Dabigatran patients, presence of the drug is indicated by prolongation of the APTT and thrombin time (TT)

For Rivaroxaban patients, the Prothrombin time (PT) is prolonged with presence of the drug

For Apixaban patients, the PT and APTT will be prolonged with presence of the drug

These coagulation tests are not validated to measure the efficacy of the anticoagulant

In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Renal function must be assessed for all three drugs as this will give an indication of how prolonged the anticoagulant effect will be.

Appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescriber’s discretion. Diuresis should be encouraged by oral or IV fluid replacement to increase excretion of the drug, but diuretic drugs should be avoided as these may reduce plasma volume and increase the concentration of the drug. Protamine sulphate and vitamin K are ineffective at reducing the anticoagulant effect of Rivaroxaban, Apixaban and Dabigatran.

Bleeding in a patient receiving Dabigatran

1. Stop Dabigatran immediately and contact the oncall haematologist
2. Send urgent samples for FBC, renal and liver function, PT, APTT and TT
3. Document timing and amount of last dose of Dabigatran
4. If APTT (and TT) are prolonged Dabigatran anticoagulant effect is likely still present
5. If ingestion is within 2 hours consider activated charcoal
6. If APTT and TT are normal it is likely that no anticoagulant effect is present

Mild bleeding

1. Delay next dose of Dabigatran
2. Apply mechanical compression
3. Administer Tranexamic acid - Oral 1g (or maximum dose 25mg/kg) every 6-8hrs or IV 1g (maximum dose 15mg/kg) every 6-8hrs
4. If bleeding continues see recommendations for major bleeding

Moderate/Major Bleeding

Definition of Major Bleed: symptomatic bleeding in a critical organ e.g. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome
1. Plasma expanders/Red cells to maintain Blood Pressure and Urine Output
2. Optimise tissue oxygenation
3. Control Haemorrhage
   i. mechanical compression
   ii. surgical intervention
4. Tranexamic acid 1g IV stat and continue (maximum dose 15mg/kg) every 6-8hours
5. Transfuse red cells to maintain Hb>80g/l
   a. Transfuse Platelets to maintain Plt >75 x10^9/l
   b. or 100X10^9/L if CNS bleed
6. If bleeding continues, consider Prothrombin Complex Concentrate 25iu/kg (maximum dose 3000iu) can reverse the coagulation abnormalities but data on clinical efficacy is not available
7. Identify and treat bleeding source e.g surgery, endoscopy. Consider for interventional radiology (only available in tertiary referral centres)
8. Consider haemofiltration if rapidly available on ITU

Life threatening Bleeding

1. Plasma Expanders/Red cells to maintain Blood Pressure and Urine output
2. Optimise tissue oxygenation
3. Oncall haematologist to authorise haemostatic agent Prothrombin Complex Concentrate 50iu/kg (maximum dose 3000iu).
4. Control Haemorrhage
   -mechanical compression
   -surgical/radiological intervention
5. Tranexamic acid 1g IV stat and and continue (maximum dose 15mg/kg IV or 25mg/kg oral) every 6-8hours
6. Transfuse red cells to maintain Hb>80g/l
   Transfuse Platelets to maintain Plt >75 x10^9/l
   or 100X10^9/L if CNS bleed
7. Identify and treat bleeding source e.g surgery, endoscopy. Consider for interventional radiology (only available in tertiary referral centres)
8. Consider haemodialysis/haemofiltration if rapidly available

Protocol for Patient Receiving Dabigatran Requiring Emergency surgery

1. Stop Dabigatran
2. Contact surgeon/haematologist/anaesthetist
3. Send urgent samples for FBC, renal and liver function, PT,APTT and TT
4. Document time of last dose of Dabigatran
5. If APTT (and TT) are prolonged Dabigatran anticoagulant effect is likely to be present
6. Consider activated charcoal if ingestion is <2hrs and anaesthetist agrees
7. Maintain BP and urine output
8. Optimise tissue oxygenation
9. Control Haemorrhage
   - mechanical compression
   - surgical intervention
10. Tranexamic acid 1g IV stat and continue (maximum dose 15mg/kg) every 6-8 hours
11. Transfuse red cells to maintain Hb>80g/l
    Transfuse Platelets to maintain Plt >75x10^9/l or 100x10^9/l if CNS bleed

12. Discuss with surgeon possibility of delaying surgery
13. Risk of bleeding depends on:
    - Time since last dose
    - Type of surgery
    - Renal function

14. If immediate surgery required consider need for haemostatic agent perioperatively or postoperatively. First line is Prothrombin Complex Concentrate 25-50iu/kg (maximum dose 3000iu)- must be authorised by oncall haematologist
15. If surgical delay of 4-12 hrs consider haemodialysis/haemofiltration available on ITU or consider need for Prothrombin Complex Concentrate (Octaplex)

**Protocol for Dabigatran Overdose**

1. Stop Dabigatran
2. Contact oncall haematologist
3. Send urgent samples for FBC, renal and liver function, PT, APTT and TT
4. Document time of last dose of Dabigatran
5. If APTT (and TT) are prolonged Dabigatran anticoagulant effect is likely to be present
6. Consider activated charcoal if ingestion within 2 hrs
7. If patient is bleeding institute the above guidelines according to whether mild/major or life-threatening bleeding
8. Consider haemofiltration if rapidly available
9. If APTT and TT are normal it is likely that no anticoagulant effect is present but APTT and TT should be repeated 2 hrs later and the above guideline followed
Management of Bleeding in a Patient Receiving Rivaroxaban/Apixaban

1. Stop Rivaroxaban/Apixaban immediately
2. Contact oncall haematologist
3. Send urgent samples for FBC, renal and liver function, PT, APTT, TT and antiXa assay if available
4. Document dose and timing of last dose of Rivaroxaban/Apixaban
5. If PT is prolonged Rivaroxaban anticoagulant effect is likely to be present or in the case of Apixaban, prolonged PT and APTT would indicate presence of the drug
6. Consider activated charcoal if ingested within 2 hrs
7. If PT/APTT normal Rivaroxaban/Apixaban anticoagulant effect is unlikely

Mild Bleeding

1. Delay next dose Rivaroxaban/Apixaban or discontinue
2. Investigate aetiology of bleed
3. Mechanical compression
4. Administer Oral 1g (or maximum dose 25mg/kg) every 6-8hrs or IV 1g (maximum dose 15mg/kg) every 6-8hrs

Moderate/Major bleeding

1. Optimise tissue oxygenation
2. Control Haemorrhage
   - mechanical compression
   - surgical intervention/endoscopy
3. Tranexamic acid 1g IV stat
4. Transfuse red cells to maintain Hb>80g/l
   Transfuse Platelets to maintain Plt >75x10^9/l or 100x10^9/l if CNS bleed
5. Identify bleeding source
6. If bleeding continues, consider Prothrombin Complex Concentrate(Octaplex) 25iu/kg (maximum dose 3000iu)

Life threatening bleeding

1. Haemostatic agent Prothrombin Complex Concentrate(Octaplex) 50iu/kg bolus dose (maximum dose 3000iu) can reverse the coagulation abnormalities but data on clinical efficacy is not available.
2. Tranexamic acid 1g IV
3. Repeat 1 and 2 if necessary
Protocol for Patient receiving Rivaroxaban/Apixaban requiring emergency surgery

1. Stop Rivaroxaban/Apixaban
2. Contact surgeon/haematologist/anaesthetist
3. Send urgent samples for FBC, renal and liver function, PT, APTT and TT and antiXa assay, if available
4. Document time of last dose of Rivaroxaban/Apixaban
5. If PT is prolonged Rivaroxaban anticoagulant effect is likely to be present in the case of Apixaban, prolonged PT and APTT would indicate presence of the drug
6. Consider activated charcoal if ingestion is <2hrs and anaesthetist agrees
7. If active bleeding maintain BP and urine output
8. Optimise tissue oxygenation
9. Control Haemorrhage
   - mechanical compression
   - surgical/radiological intervention
10. Tranexamic acid 1g IV
11. Transfuse red cells to maintain Hb>80g/l
    Tranfuse Platelets to maintain Plt >75x10^9/L or 100x10^9/L if CNS bleed
12. Discuss with surgeon possibility of delaying surgery
13. Risk of bleeding depends on:
    - Time since last dose
    - Type of surgery
    - Renal function
14. If immediate surgery required consider need for haemostatic agent perioperatively or postoperatively. First line is Prothrombin Complex Concentrate (Octaplex)

Protocol for Rivaroxaban/Apixaban overdose

Limited absorption of Rivaroxaban at higher concentrations
Doses of 50mg or greater – no further increase in plasma exposure

1. Stop Rivaroxaban/Apixaban
2. Contact oncall haematologist
3. Send urgent samples for FBC, renal and liver function, PT, APTT, TT (antiXa assay, if available)
4. Document time of last dose of Rivaroxaban/Apixaban
5. If PT is prolonged Rivaroxaban anticoagulant effect is likely to be present, in the case of Apixaban prolonged PT and APTT would indicate presence of the drug
6. Consider activated charcoal if ingestion within 2 hrs
7. If patient is bleeding institute the above guidelines according to whether mild/major or life-threatening bleeding
8. If PT/APTT is normal it is likely that no anticoagulant effect is present but PT should be repeated 2 hrs later and the above protocol followed
9. Review ongoing use of Rivaroxaban/Apixaban
Long-term Considerations for all NOACS

- Consider drug interactions
- Concomitant use of NSAIDS, antiplatelets, co-existing bleeding disorder
- Consider safety for re-anticoagulation- warrants discussion with haematology

Quick Reference Guide

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<thead>
<tr>
<th>Bleeding Severity</th>
<th>Mild</th>
<th>Moderate/Major</th>
<th>Life-threatening</th>
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<tr>
<td>General action</td>
<td>Stop NOAC immediately and contact the oncall haematologist Send urgent samples for FBC, renal and liver function, PT, APTT and TT (anti-Xa level if Rivaroxban/Apixaban) Document dose and time of NOAC If clotting tests are prolonged, NOAC anticoagulant effect is likely still present If ingestion is within 2 hours consider activated charcoal</td>
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<td>Action Specific to bleeding severity</td>
<td>-Mechanical compression -Tranexamic acid -Investigate cause for bleed -If bleeding continues move to guidance for major bleeding</td>
<td>-Optimise tissue oxygenation Control Haemorrhage -mechanical compression -surgical intervention/endoscopy -Tranexamic acid 1g IV stat -Transfuse red cells to maintain Hb&gt;80g/l -Transfuse Platelets to maintain Plt &gt;75x10^9/l or 100x10^9/l if CNS bleed -Identify bleeding source -If ongoing bleeding, consider Prothrombin Complex Concentrate(Octaplex) 25iu/kg (max 3000iu)</td>
<td>-Follow steps for major bleeding -Give Prothrombin Complex Concentrate (Octaplex) 50iu/kg bolus (maximum dose 3000iu) -Tranexamic acid 1g IV stat</td>
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Acknowledgements

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References


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