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1. **Aim/Purpose of this Guideline**

1.1. This guidance is intended to provide necessary information to enable the treatment and prevention of thrombosis.

1.2. This version supersedes any previous versions of this document.

2. **Reducing the risk of venous thrombo-embolism in patients in hospital.**

2.1 Venous thrombo-embolism (VTE) is common in hospitalised adult medical patients, with a clinical incidence in high-risk groups of 5% and an associated risk of fatal pulmonary embolism of 1-10%. Thrombo-embolism prophylaxis is proven in similar risk groups in surgical cases, but audit shows this to be poorly implemented. Some 25,000 patients are estimated to die with hospital acquired thrombosis, half of which are avoidable. Therefore prophylaxis needs to be systematically considered for all patients, at the time of admission clerking, with documentation of the assessment and action.

2.2 The National Institute of Clinical Excellence has considered the evidence for hospitalised patients, including day case surgery and made recommendations for risk assessment, appropriate prophylaxis, documentation and audit in adults (NICE 92 January 2010 and Quality Standards). The Chief Medical Officer and NHS Medical Director have instructed Chief Executives of all acute providers that mandatory data collection should be undertaken from 1 June 2010 to allow performance in VTE risk assessment to be reported and monitored nationally, based on a National VTE risk assessment tool, which has been incorporated into this revised guidance and the schema for hospital thrombo-prophylaxis.

2.3 Hospitalised children generally have a low risk of venous thrombo-embolic disease (5.3 per 10,000 hospital admissions), except in relation to indwelling catheters or significant co-morbidities, who comprise 90% of cases. Many aspects of haemostasis are age-depndant. With sexual maturity there is an increase in thrombosis, though this remains relatively unusual and the evidence for general thrombo-prophylaxis is limited, such that decisions should be made on clinical basis. Guidance supports use of physical methods of thrombosis prophylaxis and for “children, particularly adolescents, with multiple risk factors for thrombosis should be considered for thromboprophylaxis with LMWH (grade 2C)”.

2.4 Hereafter, this guidance refers to evidence from, licensing for and direction for the management of adults, unless specified otherwise.

3. **Venous thrombo-embolism disease.**

3.1. Acute venous deep venous thrombosis and pulmonary embolism, requires prompt objective documentation of the thrombosis, confirmation of disease being made in 30-50% of cases. When diagnostic procedures are delayed heparin therapy should be instituted. Traditional standard heparin has a poor therapeutic index, such that low molecular weight heparin is the treatment of choice, given on a per weight basis without the requirement for monitoring. Warfarin should be introduced using a dosing nomogram. On discharge responsibility for the future monitoring of anticoagulant care should be determined and an appropriate discharge referral made, usually to the General Practitioner.
3.2. Acute therapeutic regimens are also used in arterial thrombo-embolic disease, such as unstable cardiac disease, embolic peripheral vascular disease and cerebral embolic disease in association with atrial fibrillation, mitral disease and replacement heart valves.

3.3. Major bleeding may be seen in 0.5-5% of patients being acutely anticoagulated, with a prevalence of 1-3% per annum with long term warfarinisation. A paradoxical life threatening thrombotic syndrome with thrombocytopenia may be seen in up to 5% of patients receiving heparin, early on with previous exposure, or after 5-7 days in previously unexposed patients.

3.4. Thrombophilia is a term used to describe an inherent tendency to thrombose, either due to congenital (heritable) deficiency of the natural anticoagulant pathways, or acquired immune antibodies, with either a personal or family (first degree relative) history.

3.5. The National Institute of Clinical Excellence has considered the evidence and issued guidance regarding the management of venous thromboembolic diseases, including investigation, therapy and the role of thrombophilia testing (June 2012), which has been incorporated into this update.

3.6. The following guidance has been reviewed and revised to be informed by and comply with the National Patient Safety Agency (NPSA) Safety alert 18 (March 2007): Actions that can make anticoagulant therapy safer. This was undertaken given the burden of thrombosis within current medical practice and the benefits and risks of anticoagulant care. As part of this work, it is recognised that education and proof of competency in anticoagulant care are essential. Work is being undertaken to facilitate assessment of all involved clinical staff, meanwhile medical e-learning modules (registration required) with certification are available from the British Medical Journal website via the ‘BMJ Learning’ link and also from the website ‘www.doctors.net.uk’.

4. **Purpose of this guidance**

   This guidance provides information on the risks and prevention of VTE in the setting of hospital in-patients and the management of venous thrombosis, together with reference to other areas of clinical practice and Trust guidance, such as ischaemic heart and cerebral disease and also special circumstances such as pregnancy.

5. **Scope**

   Persons who are at risk of, or suffer from, arterial or venous thrombo-embolism.

6. **Ownership and Responsibilities**

   6.1. The Royal Cornwall Hospitals Trust Thrombosis Prevention and Anticoagulation Steering Committee (TPAS).

   6.2. Chair of TPAS and Thrombosis Clinical Lead: Dr MD Creagh Consultant Haematologist.

   6.3. Dr R Parry Consultant and Trust Medical Director
### 7. Definitions / Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>anti-embolism (stockings)</td>
</tr>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>Antiphospholipid Syndrome</td>
<td>an acquired thrombophilic state associated with auto-antibodies against phospholipids, diagnosed by the in vitro finding of abnormal phospholipid dependant coagulation assays (ie lupus anticoagulant) and, or anticardiolipin antibodies on immuno-assay.</td>
</tr>
<tr>
<td>APTT</td>
<td>activated partial thromboplastin time</td>
</tr>
<tr>
<td>Bio-prosthetic valve</td>
<td>a non-human tissue heart valve implant</td>
</tr>
<tr>
<td>Bridging</td>
<td>per-operative therapy with treatment dose LMWH</td>
</tr>
<tr>
<td>DOAC</td>
<td>Direct Oral Anticoagulant (formerly Novel Oral Anticoagulants)</td>
</tr>
<tr>
<td>DVT</td>
<td>deep venous thrombosis</td>
</tr>
<tr>
<td>EMC</td>
<td>Electronic Medicines Compendium</td>
</tr>
<tr>
<td>EPMA</td>
<td>Electronic Prescribing and Medicines Administration</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalised Ratio (based on the prothrombin time)</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>UNITS</td>
<td>international units</td>
</tr>
<tr>
<td>MS</td>
<td>mitral stenosis</td>
</tr>
<tr>
<td>LMWH</td>
<td>low molecular weight heparin</td>
</tr>
<tr>
<td>LVF</td>
<td>left ventricular failure</td>
</tr>
<tr>
<td>PCC</td>
<td>prothrombin complex concentrate</td>
</tr>
<tr>
<td>PE</td>
<td>pulmonary embolus</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>ileo-femoral or popliteal vein thrombosis ie “above knee”.</td>
</tr>
<tr>
<td>PT</td>
<td>prothrombin time</td>
</tr>
<tr>
<td>Recurrence</td>
<td>three or more episodes</td>
</tr>
<tr>
<td>SC</td>
<td>sub-cutaneous</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischaemic attack</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>inherited or acquired disorders of the haemostatic system that may result in an increased risk of thrombosis</td>
</tr>
<tr>
<td>UF</td>
<td>unfractionated (sic heparin)</td>
</tr>
<tr>
<td>VKA</td>
<td>vitamin K antagonist</td>
</tr>
<tr>
<td>VTE</td>
<td>venous thrombo-embolic disease</td>
</tr>
</tbody>
</table>
8. Anticoagulants

If a systemic anticoagulant is to be commended, eg heparin, a coumarin or a direct inhibitor and a patient is currently on anti-platelet therapy, the indication for this should be reviewed and will usually stopped, or as need considered by the appropriate specialist.

8.1. Heparins:

8.2. Low Molecular Weight Heparins (LMWH) are refined versions of standard unfractionated heparin, derived from animal products, with a predictable therapeutic effect and longer subcutaneous half-life of around 4-5 hours. Their effect is more marked against activated factor X (anti-Xa) than activated thrombin (anti-IIa) compared to unfractionated heparin. These pharmacological characteristics have generally made LMWH’s the treatment of choice over unfractionated heparin, in the prophylaxis and treatment of venous thrombo-embolism and ischaemic heart disease.

8.3. Currently commonly available LMWH’s are dalteparin, enoxaparin, tinzaparin and also bemiparin and reviparin. As their molecular weight varies each specific heparin is prescribed based on a specific schedule of anti-Xa units. Their licensed indications vary from product to product.

8.4. For prophylaxis commonly a standard anti-Xa dose is prescribed for the given risk, generally monitored by clinical assessment, without the need for plasma monitoring, even in patients with severe renal failure.

8.5. In the treatment of venous thrombo-embolism and ischaemic heart disease, LMWH’s are prescribed as anti-Xa units, on a per kg weight basis, monitored by clinical assessment and without the need for plasma monitoring, unless there is severe hepatic or renal failure (GFR <30ml/min approximating to a creatinine of 150 mmol for females, and 200 mmol for males).

8.6. In severe chronic renal failure (GFR <30ml/min), or acute renal failure, unfractionated (UF) heparin should be administered (eg prophylactic SC calcium heparin, or therapeutic IV sodium heparin Pump-Hep®).

8.7 Caution is advised in the use of LMWH in patient with significant kidney disease (stable CKD stage 4 and 5, eGFR <30mls/min or AKI stage 2). Patients with significant kidney disease who are treated with repeated standard therapeutic doses of LMWH are likely to have elevated levels of anti-factor Xa and will be at an increased risk for major and minor bleeding. This may be accentuated with the co-prescription of anti-platelet agents.

Attenuated treatment dose LMWH, enoxaparin 1.0mg/kg once a day per should be used as per the licensed indication (see appendix 1), with monitoring of the peak (3-4 hours) anti-factor Xa level from the second dose (target 1.0-2.0iu/ml) and dose adjustment should be employed. Further monitoring of Anti Xa levels should be undertaken every 48-72 hours whilst patient remains on therapy. Where there is an identified risk for haemorrhage, unfractionated heparin may be a preferable option.

8.8 In patients with end stage renal failure and/or who are requiring dialysis treatment there is no routine requirement to monitor anti-Xa levels when LWMH is given at prophylactic doses or when used in dialysis extra-corporeal circuits.
8.9 Unfractionated (UF) heparin (standard strength 1000u/ml), administered intravenously, has a shorter half-life of 45-90 minutes compared to LMWH. UF heparin also requires monitoring by the activated partial thromboplastin time (APTT) ratio, which measures the extrinsic pathway (factors II, V, VIII, IX and X). As its effect is more rapidly reversed it is the treatment of choice for patients with either venous thrombo-embolism or ischaemic heart disease at risk of haemorrhage, certain patients undergoing invasive procedures previously on warfarin, or therapeutic doses of LMWH and also patients with peripheral vascular disease.

8.10 Contraindications to heparin:
8.11 Relative contraindications are untreated haemophilia and other haemorrhagic disorders, thrombocytopenia with platelets <75 x10^9/l, a history of heparin-induced thrombocytopenia, peptic ulcer, recent cerebral haemorrhage, severe hypertension, severe liver disease, oesophageal varices, major trauma and recent neurosurgery or eye surgery.

8.12 Danaparoid sodium
Danaparoid is a heparinoid consisting of a mixture of glycosaminoglycans with an anti-Xa/anti-IIa ratio. It is used therapeutically and prophylactically in patients with heparin-induced thrombocytopenia. It is administered as an initial bolus followed by an intravenous infusion. It is excreted renally and has a plasma half-life of anti-Xa activity of approximately 24 h. Danaparoid may be monitored by anti-Xa assay using a danaparoid standard. Major bleeding occurred in 8.1% of patients treated with danaparoid for heparin-induced thrombocytopenia.

8.13 Fondaparinux
Fondaparinux is a synthetic pentasaccharide anticoagulant, which acts as a catalyst for the anti-thrombin inhibition of coagulation factor Xa. It is licensed in thrombo-prophylaxis for medical patients and in major orthopaedic or abdominal surgery, 2.5 mg once daily administered post-operatively by subcutaneous injection, eg given 6 hours following surgical closure provided that haemostasis has been established.

8.14 It is offered for those patients who decline LMWH, for reasons of personal belief.

8.15 Treatment should be continued until the risk of venous thrombo-embolism has diminished, usually until the patient is ambulant, at least 5 to 9 days after surgery, or extended for example elective hip or fracture surgery for 35 days.

8.16 It is also licensed for the treatment of DVT and PE, and unstable angina or non-ST elevation MI in patients where urgent PCI is not indicated (see section 24).

8.18 Coumarin anticoagulants including warfarin:
Warfarin is the most commonly used coumarin oral anticoagulant, having a low incidence of side effects, other than for haemorrhage. Warfarin reduces the synthesis of the vitamin-K dependant clotting factors II, VII, IX and X, and also the natural anticoagulant proteins C and S. The half-life for warfarin effect is around 40 hours, its effect being monitored by the International Normalised Ratio (INR) derived from the prothrombin time (PT) measurement of the intrinsic pathway (factors II, V, VII and X). Hence, a given dose of warfarin takes some two days to have a measurable effect on the INR.

8.19 Other coumarin oral anticoagulants are acenocoumarol (Sinthrome®), which has
a half-life of 8-11 hours, and the indanedione, phenindione (Dindevan®), which has a half-life of 5-10 hours.

8.20 Laboratory Monitoring
A general haematology form is used, detailing the prescribed anticoagulant and the required test e.g. INR, APTT ratio, or anti-Xa level. Tests are performed on a CIRTRATED sample (sky blue topped bottle), which should be correctly filled to the line (adults 2.7ml) to avoid a dilutional effect of the anticoagulant.

8.21 Direct Oral Anticoagulants (DOAC – formerly Novel Oral AntiCoagulant)
8.22 Direct oral inhibitors of specific activated coagulation factors have been licensed in orthopaedic surgical prophylaxis and in local use since 2010. More recent licensing and NICE technology appraisals have resulted in their use in the prevention of stroke and systemic embolism in atrial fibrillation and in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Licensed drug indications and local use

<table>
<thead>
<tr>
<th>Indication</th>
<th>Medication</th>
<th>NICE technology appraisal approved</th>
<th>In local use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomboprophylaxis in hip and knee replacement surgery</td>
<td>Apixaban (Eliquis®)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Dabigatran (Pradaxa®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban (Xarelto®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Edoxaban (Lixiana®)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prevention of stroke and systemic embolism in atrial fibrillation</td>
<td>Apixaban (Eliquis®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Dabigatran (Pradaxa®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban (Xarelto®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Edoxaban (Lixiana®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE</td>
<td>Apixaban (Eliquis®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Dabigatran (Pradaxa®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban (Xarelto®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Edoxaban (Lixiana®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NB Off license prescriptions, for example in cardiac disease may also be considered, under specialist direction for patients who are intolerant of coumarin or heparin therapy.

8.23 Rivaroxaban (Xarelto)
This inhibits activated factor X (anti-Xa). Rivaroxaban is rapidly absorbed with
maximum concentrations appearing 2 - 4 hours after tablet intake and a mean half-life between 7-11 hours. When used in orthopedic prophylaxis it is started post-operatively.

8.24 It does not require laboratory coagulation monitoring in routine clinical use, although inhibition of Factor Xa activity results in prolongation of the prothrombin time (PT), for example 2 - 4 hours after a 10mg prophylactic tablet intake (i.e. at the time of maximum effect) reported as ranging from 13 to 25s compared to baseline values before surgery of 12 to 15s (equivalent upper limit for INR 1.4). The activated partial thromboplastin time (aPTT) is also prolonged dose-dependently; however, these are not recommended to assess the pharmacodynamic effect of rivaroxaban.

8.25 Rivaroxaban is eliminated 75% in the liver and 25% in the kidneys. It has a prolonged half-life in patients with renal impairment is not recommended in patients with creatinine clearance < 15 ml/min and is to be used with caution in patients with creatinine clearance 15-29 ml/min. It is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors (e.g. ritonavir).

8.26 Bleeding may occur in around 3% of patients. There is no specific antidote and if significant, management of the haemorrhage may include delay of therapy, local measures, haemodynamic and blood product support and if procedure or life-threatening bleeding possibly administration of prothrombin complex concentrate may be considered, although there is very limited experience with the use of these products in patients taking rivaroxaban and this recommendation is based on limited non-clinical data.

8.27 An epidural catheter is not to be removed earlier than 18 hours after the last administration of rivaroxaban. The next rivaroxaban dose is to be administered not earlier than 6 hours after the removal of the catheter.

8.28 If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

8.29 SpMC product information can be found via the EMC website.

8.30 Apixaban (Eliquis®):
This is another inhibitor of activated factor X (anti-Xa) licensed in the thromboprophylaxis of hip and knee replacement surgery, the treatment of DVT and PE and the prevention of recurrent DVT and PE in adults, and non-valvular AF. Currently is on the Formulary for non-valvular AF and VTE treatment. It is eliminated 75% in the liver and 25% in the kidneys.

8.31 SpMC product information can be found via the EMC website.

8.32 Dabigatran elixate (Pradaxa®):
This inhibits activated factor II (anti-IIa), being licensed in orthopaedic surgical prophylaxis, but is not currently used in this Trust. It is also licensed in the prevention of stroke and systemic embolism in atrial fibrillation and the treatment of DVT and PE and the prevention of recurrent DVT and PE in adults. Dabigatran is rapidly adsorbed
with the peak plasma concentration and anticoagulant effect achieved within 2-3 h of oral administration and a mean half-life between 12-17 hours.

8.33 Dabigatran does not require laboratory coagulation monitoring in routine clinical use, although inhibition of Factor IIa activity results in prolongation of the activated partial thromboplastin time (APTT) and less so the prothrombin time (PT).

8.34 Dabigatran is 80% eliminated in the kidney and has a prolonged half-life in patients with renal impairment. It is contraindicated in severe renal impairment (creatinine clearance [CrCl, or the surrogate of eGFR] <30 ml/min), and requires dose reduction in moderate renal impairment CrCL 30-50 ml/min, in patients over age 80 years with AF, and similarly so in orthopedic prophylaxis for patients over 75 years of age. It is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk

8.35 Bleeding may occur in around 3% of patients. Idarucizumab (Praxbind®) is available for the management of life-threatening bleeding and for the reversal of Dabigatran for emergency intervention or surgery (see section 33.51) Management of minor haemorrhage should include delay of therapy and local haemostatic measures.

8.36 Routine clotting tests (PT, APTT and TT) cannot be used to estimate the extent of the anticoagulant effect, though they may be helpful in the management of significant bleeding.

8.37 Edoxaban (Lixiana®): This is another inhibitor of activated factor X (anti-Xa) licensed in the treatment of DVT and PE and the prevention of recurrent DVT and PE in adults, and non-valvular AF with one or more risk factors.

8.38 When used for the treatment of VTE Edoxaban should be given following the administration of a parenteral anticoagulant (ie LMWH) for at least 5 days.

8.39 As a result of FXa inhibition, edoxaban also prolongs clotting time in tests such as prothrombin time (PT), and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests are expected at the therapeutic dose, however, these changes are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of edoxaba.

8.40 A specific antidote to Edoxaban is not currently available. Overdose may be managed by use of activated charcoal, delay of therapy and haemodynamic and blood product support

8.41 SpMC product information can be found via the EMC website.

8.42 Drug interactions, cautions and contra-indications for Direct Oral Anticoagulants (DOAC’s)

These drugs are generally contra-indicated with other anticoagulants or anti-platelet agents, except when switching therapy in which event manufacturers’ recommendations should be followed.
<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contraindicated with</strong></td>
<td>azole antifungals (but not fluconazole), protease inhibitors</td>
<td>Ketoconazole, itraconazole, posaconazole, ciclosporin, tacrolimus, protease inhibitors, tacrolimus, rifampicin, St. John’s wort, carbamazepine, phenytoin, dronedarone</td>
<td>-azole antifungals (but not fluconazole), protease inhibitors, dronedarone</td>
<td>P-gp inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole</td>
</tr>
<tr>
<td><strong>Dose reduction advised</strong></td>
<td>AF patients if &gt;2 of: &gt;80y, &lt;60kg, creat &gt;133micromol/L</td>
<td>Verapamil, quinidine, amiodarone</td>
<td>Low body weight &lt;60kg.</td>
<td>-</td>
</tr>
<tr>
<td><strong>Caution with</strong></td>
<td>Antiplatelets, NSAIDs, rifampicin, phenytoin, carbamazepine, St. John’s wort</td>
<td>Clarithromycin, Anticoagulants/ antiplatelets NSAIDs</td>
<td>Anticoagulants/ antiplatelets NSAIDs, rifampicin, St. John’s wort, carbamazepine, phenytoin, phenobarbital</td>
<td>Anti-platelets, NSAIDs phenytoin, carbamazepine, phenobarbital or St. John's Wort</td>
</tr>
<tr>
<td><strong>Renal CrCL &gt;50mL/Min</strong></td>
<td>Normal Dose</td>
<td>Normal Dose</td>
<td>Normal dose</td>
<td>Normal Dose</td>
</tr>
<tr>
<td><strong>Renal: CrCL 30-50mL/min</strong></td>
<td>Normal dose</td>
<td>Reduce dose for higher risk bleeding</td>
<td>Reduce dose (AF patients)</td>
<td>Reduce dose</td>
</tr>
<tr>
<td><strong>Renal: CrCL 15-29 mL/min</strong></td>
<td>Caution (VTE) Reduce dose (AF patients)</td>
<td>Contraindicated</td>
<td>Caution</td>
<td>Reduce dose</td>
</tr>
<tr>
<td><strong>Renal: CrCL &lt;15</strong></td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

SPC product information can be found via the EMC website.

**8.43 Electronic Prescribing and Medicines administration**

8.44 An Electronic Prescribing and Medicines Administration system (JAC) has been introduced to RCHT. This system allows for the electronic prescribing of all anticoagulation agents and enables, through reporting, a real-time overview of oral and parenteral anticoagulation prescribed for inpatients as well as being able to collate data on levels of prescribing, correct thromb-prophylaxis, and missed doses.

8.45. This system incorporates an electronic VTE risk assessment (excluding VTE risk assessment in pregnancy) as part of a ‘gate-keeping’ system thus promoting the completion of assessments for all applicable patients.

**8.46 Patient education for Direct Oral AntiCoagulants**

- Patients need to understand the benefits and risks of the new anticoagulants through fully informed decision making – a copy of this guidance may be appropriate for some patients
• Patients and carers must have a copy of the patient information leaflet

• **Patients should be advised to carry an appropriate anticoagulant alert card.** The current yellow NPSA Oral Anticoagulant Therapy card may be useful, whilst pharmaceutical company provided patient cards are available for Dabigatran (Pradaxa®), Rivaroxaban (Xarelto®), and Apixan (Eliquis®). Patients should be advised that in the event of haemorrhage or significant acute illness to OMIT their anticoagulant medication and seek urgent medical advice

### 8.47 Monitoring Direct Oral AntiCoagulants

Whilst the prothrombin time (PT) and activated partial thromboplastin time (aPTT) may be prolonged dose-dependently; they are not recommended to assess the pharmacodynamic effect DOACs, but may be useful in the assessment of haemorrhage.

In situations of possible or established malabsorption, or questions of compliance specific assessment of drug level can be arranged with the Coagulation Section of the Haematology Laboratory (ext 3864).

### 8.48 Anti-platelet agents: aspirin, clopidogrel, prasugrel, ticagrelor in cardiac and peripheral vascular prophylaxis. Abciximab in coronary artery disease

#### 8.49 Aspirin

8.50 This inhibits platelet activation by inactivating platelet cyclo-oxygenase, with a rapid onset of action after oral administration (<1 hour but 3-4 hours with enteric coated preparations) and has a plasma half-life of ~20 min. Laboratory evidence of platelet inhibition may persist for 4 days because the effects of aspirin on individual platelets is irreversible.

8.51 Aspirin increases the risk of surgical bleeding 1.5-fold, but does not increase the severity of bleeding for most procedures. As 10% of acute cardiovascular events are preceded by aspirin withdrawal and the average time interval from withdrawal to acute stroke and acute coronary syndrome are 14.3 and 8.5 days respectively, aspirin should not usually be withdrawn before surgery.

#### 8.52 P2Y<sub>12</sub> antagonists clopidogrel, prasugrel and ticagrelor

8.53 The P2Y<sub>12</sub> antagonists include the pro-drugs clopidogrel and prasugrel and the active drug ticagrelor. Clopidogrel may show a delayed onset of platelet inhibition of 4-8 hours because it requires activation by two-stage hepatic metabolism. Prasugrel, which requires one-stage activation, and ticagrelor exert an anti-platelet effect within 2-4 hours. The active metabolites of clopidogrel and prasugrel have short plasma half-lives (~0.5 hours and ~7 hours respectively) but as irreversible P2Y<sub>12</sub> antagonists, the duration of platelet inhibition may be 5-7 days. Ticagrelor is a potent P2Y<sub>12</sub> antagonist that has a plasma half-life of 8-12 hours is more reversible than clopidogrel and prasugrel. However, the anti-platelet effect of ticagrelor may persist for 3-5 days

#### 8.54 GPIIa/IIIb inhibitors (abciximab, eptifibatide and tirofiban)

8.55 Abciximab is a monoclonal antibody and (the more currently used) eptifibatide and tirofiban are small molecule antiplatelet agents. They are given intravenously in combination with aspirin and heparin in percutaneous coronary intervention and
unstable angina on the advice of an interventional cardiologist.

8.56 Graduated Elastic Compression Stockings for the prevention of VTE

8.57 Anti-embolism stockings (15-18 mm Hg at the ankle):
8.58 These promote venous blood flow and when correctly applied, with reference to standard guidance, are a safe, non-invasive method of “mechanical prophylaxis” against venous thrombo-embolic disease. Below knee stockings are the treatment of choice.

8.59 Patients must be assessed for pre-disposing conditions, for which the use of anti-embolism stockings are contra-indicated or require close monitoring. Contra-indications are acute ischaemic stroke, peripheral vascular disease, pulmonary oedema/CCF, diabetic peripheral neuropathy or leg ulcers and dermatitis.

8.60 Anti-embolism stockings must be prescribed on the patient’s electronic prescription chart, following medical assessment of the risk of thrombosis.

8.61 Discharge with stockings must be done following assessment by the medical staff.

9. Venous Thrombo-embolism Assessment and Prophylaxis
9.1. The incidence of VTE in different groups of hospital in-patients varies greatly in the literature. The risk of symptomatic PE in the absence of prophylaxis has been estimated at 5% following surgery in the highest risk groups, and around 1% in acutely ill medical patients.

9.2. Regard medical patients as being at increased risk of VTE if they:

▪ have had or are expected to have significantly reduced mobility for 3 days or more or;
▪ Are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in the table below.
▪ Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
  o Surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb.
  o Acute surgical admission with inflammatory or intra-abdominal condition.
  o Expected significant reduction in mobility.
9.3. **General risk factors for venous thrombo-embolism:**

<table>
<thead>
<tr>
<th><strong>Background Factors</strong></th>
<th><strong>Disease or Surgical Procedure</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 years</td>
<td>Trauma or surgery, especially of pelvis, hip, lower limb</td>
</tr>
<tr>
<td>Obesity (body mass index ≥ 30 kg/m²)</td>
<td>Malignancy, especially pelvic, abdominal, metastatic, or cancer treatment</td>
</tr>
<tr>
<td>Immobility (paralysis, limb in plaster or bed rest over 3 days)</td>
<td></td>
</tr>
<tr>
<td>Continuous travel of more than 3 hours approximately 4 weeks before or after surgery</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Puerperium (6 weeks post-partum)</td>
<td>Recent myocardial infarction</td>
</tr>
<tr>
<td>Contraceptive and HRT hormonal therapy</td>
<td>Paralysis of lower limb(s)</td>
</tr>
<tr>
<td>Artifical reproductive technology (hormonal)</td>
<td>Ovarian hyperstimulation syndrome (OHSS)</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>Severe infection</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>- deficiency of antithrombin</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>- protein C or protein S</td>
<td>Myeloproliferative disease eg</td>
</tr>
<tr>
<td>- activated protein C resistance</td>
<td>Polycythaemia</td>
</tr>
<tr>
<td>- antiphospholipid antibody or lupus anticoagulant</td>
<td>Paraproteinaemia</td>
</tr>
<tr>
<td>Homocystinaemia</td>
<td>Paroxysmal nocturnal haemoglobinuria</td>
</tr>
<tr>
<td>Central venous catheter in situ</td>
<td>Bechet’s disease</td>
</tr>
<tr>
<td></td>
<td>Varicose veins with associated phlebitis</td>
</tr>
</tbody>
</table>

9.4. **Acknowledged factors for risk of bleeding for consideration as possible preclusions to pharmacological intervention:**

- Haemophilia or other known bleeding disorder
- Known platelet count <75
- Acute stroke in previous month (haemorrhagic or ischaemic)
- Blood pressure >200 systolic or 120 diastolic
- Active bleeding with severe liver disease (prothrombin time above normal or known varices)
- Severe renal disease
- Active bleeding
- Major bleeding risk, existing anticoagulant therapy or anti platelet therapy
- Neurosurgery, spinal surgery or eye surgery
- Other procedure with high bleeding risk Lumbar puncture/spinal/epidural in previous 4 hours
10. Procedure for Risk Assessment, Appropriate Prophylaxis, and Documentation on Admission to Hospital:

10.1. Risk assessment is recommended for all adult patients on admission to hospital.

10.2. VTE risk assessment should be undertaken using the schema derived from the above tables for thrombosis and haemorrhagic risk assessment and the Department of Health's venous thrombo-embolism (VTE) risk assessment tool (2010).

10.3. The schema is reproduced within the Electronic Prescribing and Medicines Administration system (JAC).

10.4. Recommendations for specific thrombo-prophylaxis and its duration (are derived from NICE guidance 92 (2010) and are summarised below

10.5. Day case patients who as a “cohort” are determined to be at low risk for thrombosis, may be exempt from further risk assessment and prophylaxis as per page 23. This recommendation was not exhaustive and allows local Trust Medical Director’s to designate other “low risk” cohorts using the Department of Health/National Institute for Health and Clinical Excellence risk assessment categories and detailed National Institute for Health and Clinical Excellence guidance.

10.6. Patients at risk of venous thrombo-embolism should be informed of the risks, signs of VTE and what to do if symptomatic post-discharge from hospital. Printed information booklets are available for routine issue to patients.

10.7. Assessment is done and recorded by (tick) completion in five steps:

**STEP ONE** – Action for initial assessment on admission of general patient groups

<table>
<thead>
<tr>
<th>Tick</th>
<th>categorise patient as</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>surgical</td>
<td>medical expected to have ongoing immobility</td>
<td>assess</td>
</tr>
<tr>
<td>medical NOT expected to have ongoing immobility</td>
<td>assessment not required</td>
<td></td>
</tr>
</tbody>
</table>

[Image: Risk Assessment for Venous Thromboembolism (VTE)]
STEP TWO – Thrombosis risk

Review the patient and procedure-related risk factors and

*Tick* any such risk for thrombosis risk, which should prompt consideration for thrombo-prophylaxis.

**STEP THREE – Haemorrhagic risk**

Review the patient and procedure-related risk factors

*Tick* any bleeding risk, which should prompt consideration of whether the bleeding risk is sufficient to preclude pharmacological intervention.

<table>
<thead>
<tr>
<th>Bleeding risk</th>
<th>Patient related</th>
<th>Admission related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active bleeding</td>
<td>Neurosurgery, spinal surgery, or eye surgery</td>
<td></td>
</tr>
<tr>
<td>Acquired bleeding disorders (such as acute liver failure)</td>
<td>Other procedure with high bleeding risk</td>
<td></td>
</tr>
<tr>
<td>Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR &gt;2)</td>
<td>Lumbar puncture, epidural/spinal anaesthesia expected within the next 12 hours</td>
<td></td>
</tr>
<tr>
<td>Acute stroke</td>
<td>Lumbar puncture, epidural/spinal anaesthesia within the previous 4 hours</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia (platelets &lt; 75x10^9/L)</td>
<td>Emergency Department patient not expected to be admitted - VTE assessment not indicated</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled systolic hypertension (230/120 mmHg or higher)</td>
<td>Paediatric patient (&lt;18 years) - VTE assessment not indicated</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled haemorrhagic disorders (such as haemophilia and von Willebrand’s disease)</td>
<td>Antithrombotic stockings are contraindicated in this patient</td>
<td></td>
</tr>
</tbody>
</table>

**Please note.** An extra box has been added here specifically for patients who are within the ED and who are not expected to be admitted. If this box is ticked then the RA can be considered complete. The RA will need to be reviewed and the patient re-assessed if their status changes to medical or surgically admitted patient.

Additional boxes are included for paediatric patients who do not require routine VTE RA and for the recording of contra-indications to AES.
**STEP FOUR** – Document appropriateness of thrombo-prophylaxis
Assess and decide on the appropriateness of thrombo-prophylaxis

The electronic VTE risk assessment can be accessed for its completion on the nurses drug round:

**STEP FIVE** – Prescription of thrombo-prophylaxis
Prescribe medical and/or anti-embolism stocking thrombo-prophylactic measures in the ‘EPMA patient record as per the clinical indication and recommendations in the following tables

Re-assessment at 24 hours from admission

As risk may change all patients should be reassessed during an inpatient stay within 24 hours of admission and then further re-assessed whenever the clinical situation changes
10.8. **Recommendations for prophylaxis in medical and non-interventional surgical in-patients, usually to be given until discharge.**

Regard medical patients as being at increased risk of VTE if they:

- have had or are expected to have significantly reduced mobility for 3 days or more or;
- Are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown previously table

<table>
<thead>
<tr>
<th>Prophylaxis based on risk category:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at increased risk</td>
</tr>
<tr>
<td>At increased risk</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Myocardial infarction:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Duration:** Generally until discharge,

**Contraindications and relative contra-indications:**

**Heparin:**
- cerebral bleeding, or acute gastro-intestinal other than ulcerative colitis*,
- previous heparin induced thrombocytopenia.

**Graduated elastic compression stockings:**
- stroke patients
- peripheral vascular disease, pulmonary oedema/CCF,
- diabetic peripheral neuropathy or leg ulcers and dermatitis.

**Patients who are contra-indicated to both LMWH and AES should be considered for prophylaxis with intermittent pneumatic compression (IPC)**

**Stroke patients – Patients with stroke are contraindicated to both graduated elastic stockings and LMWH and should only receive thrombo-prophylaxis in the form of intermittent pneumatic compression (IPC).** See IPC protocol at:

http://intra.cornwall.nhs.uk/DocumentsLibrary/RoyalCornwallHospitalsTrust/Clinical/DementiaAndEldercare/PreventionOfDVTAndPEInStrokePatients.pdf

*Ulcerative colitis and other inflammatory colitides may be associated with risk for VTE, such that prophylaxis may be indicate even in active bleeding and so should be considered.

Patients with decompensated liver disease are at high risk of VTE and should receive prophylaxis with LMWH even if their INR is at therapeutic levels.
10.9. **Prophylaxis recommendations for surgery by specialty and identifiable risk factors usually given until discharge.**

Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- Surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb.
- Acute surgical admission with inflammatory or intra-abdominal condition.
- Expected significant reduction in mobility and/or one or more of the VTE risk factors shown previously.

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Prophylaxis Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgery, orthopaedic, Urological and Gynaecological surgery (excluding peri-natal care and caesarean section) from admission</td>
<td>Graduated anti-embolism elastic compression stockings until discharge</td>
</tr>
<tr>
<td>Patients with one or more risk factors for VTE should also receive:</td>
<td>LMWH: Dalteparin 5,000 (anti-Xa) units SC daily (2200hrs)</td>
</tr>
<tr>
<td>Specifically for orthopaedic cases</td>
<td>Lower limb surgery and trauma:</td>
</tr>
<tr>
<td>Hip fracture surgery:</td>
<td>LMWH: Dalteparin 5,000 (anti-Xa) units SC daily (2200hrs) usually to be continued for 5 weeks.</td>
</tr>
<tr>
<td>Elective hip surgery including replacement:</td>
<td>Rivaroxaban 10mg daily started 6-10 hours post-surgery usually continued for 5 weeks after surgery.</td>
</tr>
<tr>
<td>Elective Knee replacement surgery:</td>
<td>Rivaroxaban 10mg daily started 6-10 hours post-surgery and continued for 2 weeks after surgery.</td>
</tr>
</tbody>
</table>

**Contraindications:**

**Heparin:**
- acute gastro-intestinal, or cerebral bleeding, Stroke
- previous heparin induced thrombocytopenia.

**Rivaroxaban:**
- cerebral bleeding, or acute gastro-intestinal other than ulcerative colitis*,
- Severe renal failure, severe hepatic impairment, pregnancy,
- chronic warfarin usage, continuing on Aspirin and Clopidogrel (eg cardiac intervention within 12 months) eg stenting (use LMWH)
- iv Rifampacin ( reduces the effectiveness by 50%)
- Patients under 18 years

**Graduated elastic compression stockings:**
- Ischaemic stroke patients, peripheral vascular disease, pulmonary oedema/CCF,
- diabetic peripheral neuropathy or leg ulcers and dermatitis.

*Ulcerative colitis and other inflammatory colitides may be associated with risk for VTE, such that prophylaxis may be indicate even in active bleeding and so should considered.

**Surgical patients who are contra-indicated to both LMWH and AES should be considered for prophylaxis with intermittent pneumatic compression (IPC)**
10.10. **Doses of thromboprophylaxis appropriate for adult patients at extremes of body weight: Obesity and low weight (less than 50kg).**

10.11. The following extracts are based on commentary and suggested guidance from the Haemostasis, Anticoagulation & Thrombosis (HAT) Committee, UK Clinical Pharmacy Association (2010).

10.12. Obesity is a risk factor for the development of venous thrombo-embolism (VTE). NICE uses a definition of obesity as patients with a body mass index greater than or equal to 30 kg/m².

10.13. **Low molecular weight heparin (LMWH)**

10.14. There is a lack of good evidence-based data to inform the prescribing of low molecular weight heparin for thrombo-prophylaxis in obese patients. Manufacturers’ information for enoxaparin, dalteparin and tinzaparin does not recommend dosage adjustments for extremes of body weight. However, the summary of product characteristics for dalteparin does recommend monitoring anti-Xa levels in extremes of body weight.

10.15. Local consideration has been given to published schedules for dose adjustment, particularly with reference to bariatric surgery, with a decision for on-going audit of outcomes to include venous thrombosis, which episodes occurring within three months of hospital admission will be identified by recently commenced systematic RCA.

10.16. **Apixaban**
The manufacturer’s information advises that no dosage adjustment is necessary for body weight.

10.17. **Rivaroxaban**
The manufacturer’s information advises that no dosage adjustment is necessary for body weight.

10.18. **Dabigatran**
Dabigatran is less protein bound and has a higher volume of distribution than rivaroxaban; therefore it is possible that extremes of body weight could have a greater effect on its pharmacodynamics. However, given the lack of clinical data in patients at extremes of body weight the manufacturer’s information should be followed and no dosage adjustment is required.

10.19. **Lower limb plaster casts**
Consider offering pharmacological VTE prophylaxis to patients with lower limb plaster casts after evaluating the VTE risks and benefits based on clinical discussion with the patient. Offer LMWH (or enoxaparin or UFH for patients with renal failure) until lower limb plaster cast removal. A patient self-assessment form is available for patients who are non-weight bearing in POP or airboot to identify those patients who may be targeted as being at highest risk of developing VTE whilst immobilized. Appendix 7

10.20. **Day case procedures, which may be exempted from further formal assessment.**
10.21. Following detailed consideration and consultation by Strategic Health Authority Medical Directors within the NHS, a consensus has built around day case procedure groups, where patients admitted for the same procedure (cohorts):

- have a similar low risk profile;
- have been assessed, as a group as being at low risk of Venous Thromboembolism using the Department of Health/NICE risk assessment categories and consistent with detailed NICE.

The identified day case procedure groups are:

- Haemodialysis.
- Endoscopy.
- Chemotherapy.
- Ophthalmological procedures with local anaesthetic/regional/sedation and not full general anaesthetic.
- Non-cancer ENT surgery lasting less than 90 minutes with local anaesthetic/regional/sedation and not full general anaesthetic.
- Non-cancer plastic surgery lasting less than 90 minutes with local anaesthetic/regional/sedation and not full general anaesthetic.
- Non-cancer dental and maxillo-facial surgery lasting less than 90 minutes with local anaesthetic/regional/sedation and not full general anaesthetic.
- Other similar minor procedures lasting less than 90 minutes to be signed off to be considered as “cohort risk assessed” by the Medical Director with local anaesthetic/regional/sedation and not full general anaesthetic.

10.22 Monitoring for heparin induced thromobcytopaenia (HIT).

- All LMWH recipient patients must have a platelet count before starting treatment.
- Medical patients and obstetric patients receiving heparin do not need routine platelet monitoring.
- Post-operative patients (other than cardiopulmonary bypass patients) receiving LMWH do not need routine platelet monitoring.
- All post-operative recipients of unfractionated (UF) heparin should have a repeat count every 2-3 days from days 4 to 14, to screen against HIT.
- Post-operative patients and cardiopulmonary bypass patients who have been exposed to heparin in the last 100 days and are receiving any type of heparin should have a platelet count 24 hours after starting heparin.
- All cardiopulmonary bypass patients receiving LMWH should have platelet count monitoring performed every 2-3 days from days 4 to 14 or until heparin is stopped.

10.23 If a measured platelet count falls by 50% or more and/or if a patient develops new thrombosis or skin allergy or any of the other rarer manifestations of HIT between days 4 to 14 of heparin administration HIT should be considered and a clinical assessment made in accordance with Appendix 4.
11. Thrombotic Risk of Hormonal Therapy

11.1. The combined oral contraceptive pill (COC):
Evidence in surgical patients has determined a risk for users of the low dose (30-35mcg ethinyloestradiol) contraceptive pill for post-operative thrombo-embolism of 0.96% in users against 0.5% in non-users. Stopping the combined pill may result in an unwanted pregnancy with its risks, including those of surgery and anaesthesia in pregnancy and possible termination. Twenty-five percent of young women will be users of such contraception. Risk factors for venous thrombo-embolism should be assessed for each individual, at the time a patient is listed for surgery.

- Advise patients to consider stopping oestrogen-containing oral contraceptives or hormone replacement therapy 4 weeks before elective surgery.
- Whenever patients are advised to discontinue the COC it is mandatory to inform them of the need for alternative contraceptive measures (e.g. progesterone-only pill, or barrier methods) to avoid those risks associated with unwanted pregnancy and issue them with an information sheet.

11.2. If a patient chooses to continue with the COC due to contraceptive difficulties, (in which case their decision should be documented), or if a patient undergoes emergency admission, then the COC should not be stopped, while prophylactic measures should be determined according to their additional risk factors (table 1).

11.3. Hormone replacement therapy (HRT):
There is no data on whether HRT increases the risk for venous thrombo-embolism (VTE) following surgery. Recent evidence suggest a “background” risk for VTE in current users of HRT is 0.2-0.3 per 1,000 women per year, against a risk of 0.1 per 1,000 women per year for women who have never used HRT. By the nature of their surgical procedure, it is likely that many women using HRT would be due to receive thrombo-prophylaxis. The Royal College of Obstetricians and Gynaecologists advise against stopping HRT provided appropriate thrombo-prophylaxis such as heparin with or without TED stockings is used.

11.4. If women are advised to discontinue HRT they should be warned of the possible menopausal like side effects of withdrawal, which may be considerable.

11.5. Hence if women are to continue HRT through surgery, then unless contra-indicated it is reasonable to use thromboprophylaxis.

11.6. Information for women on the COC or HRT:
Royal Cornwall Hospitals Trust (Infolink) Information leaflets on the OCP and HRT and surgery will be available for giving to patients, generally at the time their surgery is booked.

11.7. Artificial reproductive technology (hormonal) - Ovarian hyperstimulation syndrome (OHSS):
The risk of thrombosis in the presence of OHSS has been estimated at 1 per 128 and therefore equates to a risk of a thrombotic event of three in 8000 ART cycles. With OHSS prophylaxis with graduated elastic compression stockings and LMW heparin should be considered and may be necessary for at least for 1 month after confirmation of a pregnancy.
12. Analgesia and Thrombo-embolism Prophylaxis

12.1. Epidural analgesia
Evidence suggests a haemorrhagic risk if an epidural or spinal is sited, or removed, in patients who have recently received heparin prophylaxis. Therefore:

- LMWH prophylaxis is commenced 12 hours prior to surgery/siting of an epidural.
- If blood is present during needle or catheter placement initiation of LMWH therapy should be delayed for 24 hours.
- Post-operatively LMWH is given at least 6-8 hrs later the following late evening.
- Epidural Catheters should be removed 10-12 hours after the last dose of LMWH.

12.2. This is scheduled by a standard practice of prescribing once daily thrombo-embolism prophylaxis at 2200 hours.

These drugs inhibit platelet function, the duration varying amongst the individual preparations, and may increase inter-operative and post-operative bleeding. Preferably they should therefore be discontinued one week prior to surgery (with appropriate alternative analgesia), although this may not always be possible. If required post-operatively then an NSAID preparation with a short half-life such as diclofenac is best, with close attention given to any undue haemorrhage, in which event advice can be obtained from a Consultant Haematologist.

12.3 Aspirin:
This drug inhibits platelet function and should be avoided in the week prior to surgery, except in patients with coronary artery disease.

13. Therapeutic Anticoagulation

13.1. In the absence of a significant risk of bleeding, initial anticoagulation with low molecular weight heparin, prescribed on a per Kg weight basis is recommended, dalteparin (Fragmin®) being licensed for deep venous thrombosis, pulmonary embolism and ischaemic heart disease.

13.2. Generally monitoring is by clinical assessment, without the need for plasma monitoring.

13.3. In severe chronic renal failure (GFR <30ml/min, plasma creatinine) unfractionated (UF) heparin (Pump-Hep®) should be administered, by intra-venous infusion, with monitoring by the APTT ratio (cf section 2.5). Alternatively in chronic renal failure, attenuated dose enoxaparin (Clexane) LMWH can be used, as per the licensed indication, (see appendix 1). If attenuated enoxaparin LMWH is used, clinical monitoring is the best predictor for the risk of potential bleeding, but also with “peak” anti-Xa levels measured 4-6 hours post injection, from the second treatment dose.

13.4. In acute renal failure unfractionated (UF) heparin (Pump-Hep®) should be administered, by intra-venous infusion,
13.5. Caution is advised in severe hepatic failure, when unfractionated (UF) heparin (Pump-Hep®), as above, may be preferable, or otherwise monitoring by use of the anti-Xa ratio.

13.6. **LMWH monitoring by anti-Xa levels:**

13.7. When indicated a standard dose should be commenced and on the following dose the patient sampled by a 4-6 hour post injection “peak” anti-Xa level, taken into citrate the request naming the specific product, with a target level of 0.5-1.0 anti-Xa units/ml.

13.8. Possible bleeding complications should be investigated and managed as per section 33.3

13.9. Patients who already have a significant risk of bleeding, e.g. post recent surgery or intercurrent cerebral or gastrointestinal bleed, acute renal failure should receive unfractionated heparin by intravenous infusion (Pump-Hep®), as this has a shorter half-life then LMWH and if necessary the anticoagulant effect can be rapidly neutralised.

### 14. Venous Thrombo-embolic Disease

14.1. **Investigation for the diagnosis of DVT and or PE:**

Objective diagnosis is mandatory, clinical evaluation being supported by confirmatory imaging:

- NICE recommends use of a “2 level” Wells type pre-test clinical probability score (likely or unlikely) in DVT and PE and as appropriate D-dimer when screening patients to determine those who require definitive radiological imaging.
- D-Dimer should not be used to exclude VTE in pregnant patients or those who have been admitted to hospital for >24 hours.
- Doppler Compression ultrasound (CUS) is the current diagnostic investigation of choice, being sensitive to ileo-femoral thrombosis. for the diagnosis of DVT
- Venography may be necessary and is more sensitive to calf thrombosis, alternately CUS may be repeated at a weeks interval to exclude popliteal extension in cases of negative above knee ultrasound scans.
- Around 10-15% of cases are positive for DVT.
- Multi detector row CT pulmonary angiography is the current investigation of choice for pulmonary embolus though isotopic perfusion scintigraphy can be used to reduce radiation dose in patients with low pre-test probability and a normal chest X-ray.

14.2. For out-patients with first presentation DVT screening by pre-test probability (PTP) and D-dimer assay may be used, as per RCHT DVT Clinic protocol.

14.3. A FBC, coagulation screen (APTT/INR) U+E’s, bone and LFT’s should be taken as baseline tests.
14.4. **Investigations for cancer in unprovoked** DVT or PE.

14.5. VTE is a common complication of diagnosed cancer. In addition unprovoked VTE appears to be a significant increase in the risk for the diagnosis of cancer within the subsequent first 1-2 years, with a standardised incidence ratio of 4.4 in a Swedish population-based study for patients over 18 years, equivalent to approximately 11% of all patients. This risk appears to be in those patients over 40 years of age. Investigation may inform the patient, affect survival rates and reduce morbidity in patients. Therefore offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:

- a physical examination (guided by the patient's full history) and
- a chest X-ray and
- blood tests (full blood count, serum calcium and liver function tests) and
- urinalysis.

14.6. Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation.

14.7. **Heparinisation for Venous thrombo-embolic disease (DVT and PE):**

14.8. **Pending confirmation of the diagnosis LMW heparin should be commenced as:**

- Dalteparin (Fragmin) prescribed in anti-Xa international units, at 200 anti-Xa units per kg **once** daily, ie **once every 24 hours** subcutaneously (S.C.).
- The **preferred site for subcutaneous administration** is the abdomen and the anterior or lateral thigh.
- The maximum dose is 18,000 units when given once daily, larger doses should be given as 100 units/kg twice daily S.C.
- In patients at risk of bleeding, e.g. post-surgery, 100 units/kg twice daily S.C. dalteparin is recommended, using appropriately dosed pre-filled syringes (see appendix). With this treatment schedule the maximum dose is 10,000 units bd.
- Heparin should normally be continued for at least 5-6 days and until 2 consecutive therapeutic INR’s are recorded.

14.9. **Note:**

If patients are currently on anti-platelet therapy, the indication for this should be reviewed and will usually stopped, or as need considered by the appropriate specialist.

14.10. **Heparin induced thrombocytopenia.**

14.11. Medical patients on heparin do not need routine platelet monitoring. If, however, a patient develops new thrombosis or skin allergy or any of the other rarer manifestations of HIT, or a measured platelet count falls by 50% or more, between days 4 to 14 of heparin administration HIT should be considered and a clinical assessment made in accordance with Appendix 3.
14.12. **Venous thrombosis despite chemical (drug) prophylaxis or therapy**

14.13. When a patient has been on prophylactic LMW heparin or rivaroxaban, given the short half-life of these drugs and the likely time that will have elapsed since the last dose, patients should receive a full dose of therapeutic LMW heparin.

14.14. When a patient has been on therapeutic LMW heparin or Dabigatran wait 12 hours after the last dose and for rivaroxaban wait 24 hours before switching to a parenteral anticoagulant.

14.15. If screening proves negative then 24 hours after the last therapeutic heparin, prophylactic LMW heparin rivaroxaban should be re-introduced.

14.16. **Superficial venous thrombosis and phlebitis**

14.17. Superficial vein thrombosis or thrombophlebitis (STP) in the lower limb is a relatively common, painful, and in many cases self-limiting condition. Around 10-21% of patients with STP will already have DVT at presentation and a further 3-4% will progress to it if untreated. Patients with at least 5 cm of thrombus in a superficial vein are more likely to have underlying DVT if the STP is in the proximal long saphenous vein (within 10 cm of the saphenofemoral junction). STP within a varicose vein is less likely to be associated with underlying DVT.

- Patients with clinical signs of superficial thrombophlebitis affecting the proximal long saphenous vein should have an ultrasound scan to exclude concurrent DVT.
- Patients with confirmed SVT within 3 cm of the sapheno-femoral junction should be considered for therapeutic anticoagulation (2B)
- Patients with superficial thrombophlebitis, without DVT, should have antiembolism stockings and be considered for treatment with prophylactic doses of LMWH for up to 30 days or fondaparinux for 45 days.
- If LMWH is contraindicated, 8-12 days of oral NSAIDs should be offered.

14.18. Patients with upper extremity DVT without underlying risk factors (such as anti-phospholipid antibodies) do not require prolonged (more than 3-6 months) anticoagulant treatment
15. Dalteparin schedule for DVT and PE treatment:

<table>
<thead>
<tr>
<th>Bodyweight to nearest kg</th>
<th>Anti – Xa units daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 46 kg</td>
<td>7500 units</td>
</tr>
<tr>
<td>46 – 56 kg</td>
<td>10,000 units</td>
</tr>
<tr>
<td>57 – 68 kg</td>
<td>12,500 units</td>
</tr>
<tr>
<td>69 – 82 kg</td>
<td>15,000 units</td>
</tr>
<tr>
<td>83 – 100 kg</td>
<td>18,000 units</td>
</tr>
</tbody>
</table>

NB The single daily dose should not exceed 18,000 UNITS.

Currently (non-pregnant) obese patients above 100kg weight are treated as per the licensed maximum dose, which is in the process of a Trust wide audit.

15.1. **Before prescribing LMWH the patient should be weighed.** This weight should be recorded in kg on the inpatient treatment sheet and in the patient’s clinical notes. If it is not possible to weigh the patient for clinical reasons the patient should be asked to report their weight. If the patient is unable to report their weight the person prescribing the LMWH should estimate their weight. In both of these circumstances it should be recorded that the weight is either ‘reported by patient’ or ‘estimated’ and the patient should be weighed as soon as possible.

16. Massive pulmonary embolus (with haemodynamic instability)

16.1. Massive PE is highly likely if:
- collapse/hypotension, and
- unexplained hypoxia, and
- engorged neck veins, and right ventricular gallop (often)

16.2. Emergency echocardiography may support the diagnosis by the demonstration of right ventricular strain.
- Thrombolysis is the first line treatment for massive PE.
- This may be instituted on clinical grounds alone; a 100 mg infusion of alteplase is recommended (see section 18)
- This should be followed with heparin, either as LMWH or unfractionated bolus and infusion.

17. Venous thrombolytic therapy:

17.1. No randomised trial exists to determine the value of this therapy, nevertheless alteplase and streptokinase are both licensed for use in life threatening PE (with
haemodynamic instability), streptokinase is additionally licensed in proximal deep venous thrombosis causing critical limb ischaemia.

17.2. NICE 144 recommends consideration of catheter-directed thrombolytic therapy for patients with symptomatic ilio-femoral DVT who have:

- symptoms of less than 14 days' duration and good functional status and
- a life expectancy of 1 year or more and
- a low risk of bleeding.

17.3. Contra-indications are:

- Major surgery, trauma or invasive procedures within previous 10 days,
- GI or GU bleeding within 6 months,
- CVA within 6 months, recent TIA, previous intra-cranial bleed, head trauma, within 1 month, previous neurosurgery, intra-cranial tumour,
- acute severe hypertension,
- bleeding disorders,
- pregnancy in first 18 weeks, or within 10 days of delivery,
- known/suspected aortic dissection or pericarditis.

18. Alteplase for PE:

18.1. A total dose of 100 mg of alteplase should be administered in 2 hours. Most experience is available with the following dose regimen:

<table>
<thead>
<tr>
<th>Concentration of alteplase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1mg/ml</td>
</tr>
<tr>
<td>2mg/ml</td>
</tr>
</tbody>
</table>

10 mg as an intravenous bolus over 1 - 2 minutes

<table>
<thead>
<tr>
<th>Concentration of alteplase</th>
</tr>
</thead>
<tbody>
<tr>
<td>10ml</td>
</tr>
<tr>
<td>5ml</td>
</tr>
</tbody>
</table>

followed by an intravenous infusion of 90 mg over 2 hours

<table>
<thead>
<tr>
<th>Concentration of alteplase</th>
</tr>
</thead>
<tbody>
<tr>
<td>90ml</td>
</tr>
<tr>
<td>45ml</td>
</tr>
</tbody>
</table>

18.2. The total dose should not exceed 1.5 mg/kg in patients with a body weight below 65 kg.

18.3. Streptokinase may be administered as 250,000 units by IV infusion, over 20-30 minutes, followed by an infusion at a rate of 100,000 per hour for 24-72 hours, without laboratory monitoring (BNF section 2.10.2). It is then followed by anticoagulation with heparin/warfarin.

18.4. NB Streptokinase should never be used again beyond 4 days from the initial use.

18.5. Direct oral anticoagulants (DOACS) and new episodes of VTE
Rivaroxaban, Apixaban, Dabigatran and Edoxaban have received NICE approval for limited courses of treatment in new episodes of non-cancer DVT and also PE and are currently available within RCHT for these indications. Appropriate patients with
confirmed VTE should be offered the option of treatment with these new medications which should include some counselling with regards to their current non-reversibility. Preference should be given to either Rivaroxaban or Apixaban for first line treatment of VTE. If patients elect for treatment with a DOAC treatment regimens are as follows.

**Rivaroxaban (Xarelto ®)**

<table>
<thead>
<tr>
<th>Dosing schedule</th>
<th>Maximum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>15mg twice daily for the first 21 days</td>
<td>30mg</td>
</tr>
<tr>
<td>followed by 20mg once daily</td>
<td>20mg</td>
</tr>
</tbody>
</table>

**Apixaban (Eliquis ®)**

<table>
<thead>
<tr>
<th>Dosing schedule</th>
<th>Maximum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>10mg twice daily for the first 7 days</td>
<td>20mg</td>
</tr>
<tr>
<td>followed by 5mg twice daily for up to 6 months</td>
<td>10mg</td>
</tr>
</tbody>
</table>

For prevention of recurrent DVT and/or PE following completion of 6 months of treatment dose is 2.5mg twice daily

If patients have received treatment with LMWH following diagnosis of VTE this should be taken into account when calculating the remaining dosing schedule to be prescribed for the appropriate drug

NOTE: Unlike with Warfarin there is no requirement for concurrent use of LMWH when patients with confirmed VTE are treated with either of the above medications

**Dabigatran (Pradaxa®)**

*Following treatment with a parenteral anticoagulant for at least 5 days* dosing is as follows

<table>
<thead>
<tr>
<th>Dosing schedule (standard patient)</th>
<th>Maximum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>150mg twice daily</td>
<td>300mg</td>
</tr>
<tr>
<td>Patients age &gt;80 and/or taking verapamil</td>
<td>220mg</td>
</tr>
</tbody>
</table>

For the following groups the total daily dose of Pradaxa of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding:

- Patients between 75-80 years
- Patients with moderate renal impairment
- Patients with gastritis, esophagitis or gastro-oesophageal reflux
- Other patients at increased risk of bleeding

**Edoxaban (Lixiana®)**

*Following treatment with a parenteral anticoagulant for at least 5 days* dosing is as follows
<table>
<thead>
<tr>
<th>Dosing schedule (standard patient)</th>
<th>Maximum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>60mg once daily</td>
<td>60mg</td>
</tr>
<tr>
<td>Patients with moderate to severe renal failure (CrCl 15-50ml/min) or low body weight (&lt;60kg)</td>
<td>30mg once daily</td>
</tr>
</tbody>
</table>

19. **Graduated Elastic Compression Stockings (Post deep venous thrombosis compression support hosiery >23 mm Hg at the ankle)**

19.1. Post-thrombotic syndrome (PTS) is a long-term complication of deep vein thrombosis (DVT) characterised by chronic pain, swelling and skin changes in the affected limb. One in every three patients with DVT may develop post-thrombotic complications within five years.

19.2. A Multi Centre randomized placebo-controlled trial of compression hosiery versus placebo (Sox trial, 2014) concluded that wearing of compression support hosiery did not prevent PTS after a first event proximal DVT. Compression hosiery therefore should not be offered to patients to prevent post-thrombotic syndrome or VTE recurrence after a proximal DVT. This recommendation does not cover the use of elastic stockings for the management of leg symptoms after DVT. (NICE.2015).

19.3. If stockings are provided for management of leg symptoms then:

- advise patients to ideally continue wearing the stockings for at least 2 years
- ensure that the stockings are replaced two or three times per year or according to the manufacturers' instructions.
- advise patients that the stockings need to be worn only on the affected leg or legs.

19.4. Compression hosiery for the management of leg symptoms after DVT requires exclusion of arterial disease (risk of precipitating ischaemia). This can usually be performed clinically by general practitioners, but in cases where doubt exists ankle brachial pressure indices and/or arterial duplex may be required.

20. **Inferior vena caval (IVC) filters**

20.1. IVC filters are indicated where anticoagulation is contraindicated or unsuccessful in preventing recurrence of PE from continuing DVT.

- IVC filters are not indicated in unselected patients with VTE who will receive conventional anticoagulant therapy
- Free floating thrombus it is not an absolute indication for insertion of an IVC
- Thrombolysis is not an absolute indication for filter insertion. If a filter is used a removable filter should be used if available
- They may be sited temporarily for 12-14 days, for example for per-operative cover
- If a filter remains in-situ and the risk of VTE persists generally systemic anticoagulation is required to prevent DVT and venous obstruction.
20.2. **Complications:**
20.3. Fatal complications are seen in less than 0.5% per annum of cases.

- Immediate complications are misplacement 1.3%, and less than 1% for each of pneumothorax, haematoma, air embolism, carotid artery puncture, and arterio-venous fistula.
- Early complications are insertion site thrombosis (8.5%) and infection.
- Late complications are recurrent DVT (21%), IVC thrombosis (2 to 10%), and less than 1% for each of IVC penetration, filter migration, filter tilting and fracture and entrapment of guide wires.

21. **Cancer and VTE disease, complications and choice of anticoagulant.**
21.1. Patients with active cancer have a greater risk for thrombosis, though this may be occult and on occasions found incidentally during routine (CT) scanning. Standard therapy has been with initial LMH heparin and then warfarin till a therapeutic INR target 2.5 (range 2.0-3.0) but:

- Studies and guidance (ASCO 2007) support the efficacy of therapeutic dose eg 200u/kg daily dalteparin LMW heparin, compared to warfarin at a standard INR of 2.5, with less recurrent thrombosis (see page 21).
- After the first month therapy can be reduced to 150u/kg daily if no recurrence.
- After initial monitoring by platelet count, no specific heparin monitoring is required
- Therapeutic dose LMW heparin would be given for 3-6 months then reviewed for ongoing anticoagulation with the option for warfarin (INR target 2.5).
- For chemotherapy-induced thrombocytopenia, consideration should be given to dose attenuation or as needs interruption as per license
- If anticoagulation is contra-indicated by significant haemorrhage then an IVC filter should be considered and when possible anticoagulation be re-instituted
- Therapy should be agreed with the patient’s primary cancer doctor. eg an oncologist
- Review within 6 months of a confirmed proximal deep vein thrombosis or pulmonary embolism to discuss the risks and benefits of continuing anticoagulation therapy.

21.2. This option may also be helpful as some patients may prove difficult to warfarinise or have volatile INR’s.

22. **Recurrent thrombosis despite anticoagulation**
22.1. In studies this has been reported for around 20% of warfarinised patients and 10% of those on LMW heparin

- If a patient is on LMW heparin then consider increasing the dose by 20-25% informing their oncologist or as needs discussion with a haematologist.
Specific monitoring (anti-Xa levels) is not required unless there is haemorrhage or renal impairment.

If a patient does receive warfarin and develops progressive or recurrent thrombosis despite a therapeutic INR (target 2.5), then therapeutic dose LMW heparin should be considered or intensification of the Warfarinisation to an INR target of 3.5.

23. Anti-platelet therapy for acute coronary syndrome (cf RCHT chest pain and Acute coronary syndrome pathway):

23.1 Aspirin and Clopidogrel (but not Ticagrelor) may be used in combination with an Oral Anticoagulant on the recommendation from a cardiologist. The intended duration of this combination therapy should be made clear in the notes, and communicated to the GP on discharge.

23.2 In all ACS (STEMI/NSTEMI/Unstable Angina) anti-platelet therapy should be commenced as:

- Aspirin 300mg loading dose, (75mg OD for indefinite period, **AND**)
- Ticagrelor 180mg loading dose (90mg BD for 12 months)
- If ticagrelor is contra-indicated patients should receive:
  - STEMI – Prasugrel 60mg loading dose (10mg OD for 12 months)
  - NSTEMI/UA – Clopidogrel 300mg loading dose (75mg OD for 12 months)
- Ticagrelor should be avoided if the patient is on Warfarin or other oral anticoagulants

24. Anti-thrombotic schedule for acute coronary syndrome (cf RCHT chest pain and Acute coronary syndrome pathway)

24.1. In NSTEMI/UA anti-thrombotic therapy should be commenced as:

- Fondaparinux 2.5mg sub-cutaneous ONCE daily at night for 2-8 days or until interventional or discharge whichever is sooner. Fondaparinux should be omitted on the day of coronary angiography +/- PCI
- If eGFR <20ml/min – Enoxaparin (Clexane®) 1mg/kg sub-cutaneous ONCE daily
- LMWH (based on Dalteparin 120units/kg twice daily) should be used instead of Fondaparinux if there is another indication for full anticoagulation e.g AF, Mechanical Heart Valve, DVT, PE

25. Cardiac thrombolysis and the use of tenecteplase and enoxaparin LMWH for the clinical diagnosis of myocardial infarction.

- This is uncommonly required, given standard practice of primary angioplasty, however it may be indicated if angioplasty is not possible.
Give IV bolus of 30mg of enoxaparin first;
followed by IV bolus of tenecteplase over 10 seconds as per appendix.
then give S/C enoxaparin at a dose of 1mg/Kg every 12 hours for 48 hours- with
the first two S/C doses not to exceed 100mg each.
Acute STEMI in patients ≥75 years of age 0.75mg/kg SC twice daily without
initial bolus
The first s/c dose must be given immediately after the tenecteplase.
After 48 hours, change to prophylactic s/c dalteparin 5000 units at 2200hrs if the
patient is stable, or full dose s/c dalteparin bd (120units/Kg to a maximum dose
of 10 000 units) if the patient has ongoing symptoms, as for acute coronary
syndromes


26.1. Further guidance on this subject is available via the Trust’s document library
Thrombolysis is undertaken, in CT confirmed ischaemic stroke, within 4.5 hours of
onset of symptoms according to protocol.

Following assessment for clinical status, exclusion criteria and blood tests, at
the direction of the stroke doctor and acute stroke nurse on call, IV recombinant
tissue plasminogen activator (rt-PA, alteplase) is administered 0.9 mg/kg or 90
mg, whichever is the lesser, as per protocol (10% as bolus and remainder over
1h).
Suspected cerebral haemorrhage is managed, as per protocol, by
discontinuation of the rt-PA infusion and consideration of tranexamic acid 10
mg/kg IV and/or cryoprecipitate (rich in fibrinogen).

26.2. Haemorrhage with thrombolysis is also considered in section 34.8

27. Unfractionated heparin (Pump-Hep®) indications and
schedule:

27.1. The indications for unfractionated heparin (Pump-Hep®) are:
- patients with either ischaemic heart disease or VTE, at risk of haemorrhage
- Patients undergoing invasive procedures previously on warfarin, or LMWH.
- Patients with peripheral vascular disease.
- Patients in acute or chronic severe renal failure

27.2. Unfractionated heparin may be commenced with a 5,000 units bolus, followed by
30,000 units by pump per 24 hours, prescribed as 1000units/ml sodium heparin
(Pump-Hep®) with the dose given as a rate in ml/hr. Set up pump and adjust dose as
per nomogram, checking the APTT ratio between 4-6 hours. On average 32,000 units
per 24 hours is required to attain a therapeutic dose giving an APTT ratio of 1.5-2.5.
NB – Due to specific monitoring requirements and the potential for adverse events
unfractionated heparin should only be used in clinical areas which have staff who are
suitably experienced in its’ administration
27.3. **Schedule for the use of unfractionated heparin:**

1. **Check baseline APTT/INR**
   
   Give bolus loading dose 5,000 units IV over 3 minutes.
   
   10,000 units IV in severe PE.

2. Establish an infusion of unfractionated heparin 1000 u/ml (one 20 ml vial of Pump-Hep® containing 20,000 units), to a 50 ml syringe in a syringe driver. Do not dilute.

3. Set infusion rate of 1.3 ml per hour (approximately 30,000 u/24 hrs).

4. **Check APTT 4-6 hours after starting infusion.**

5. Repeat APTT ratio 6-8 hours after each alteration (more frequently if ratio > 7). Adjust infusion rate to achieve therapeutic APTT ratio of 1.5-2.5 within 24 hours.

6. Thereafter continue monitoring APTT ratio at an at least daily interval.

**NOMOGRAM FOR THE DOSAGE OF UNFRACTIONATED HEPARIN 1000 u/ml**

<table>
<thead>
<tr>
<th>APTT RATIO</th>
<th>RATE CHANGE</th>
<th>adjustment to Pump-Hep® rate ml/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 7</td>
<td>Stop for 1 hour, then reduce by 500 units/hr</td>
<td>reduce by 0.5 ml/hr</td>
</tr>
<tr>
<td>5.1-7.0</td>
<td>Reduce by 500 units/hr</td>
<td>reduce by 0.5 ml/hr</td>
</tr>
<tr>
<td>4.1-5.0</td>
<td>Reduce by 300 units/hr</td>
<td>reduce by 0.3 ml/hr</td>
</tr>
<tr>
<td>2.6-4.0</td>
<td>Reduce by 100 units/hr</td>
<td>reduce by 0.1 ml/hr</td>
</tr>
<tr>
<td>1.5-2.5</td>
<td>NO CHANGE</td>
<td>NO CHANGE</td>
</tr>
<tr>
<td>1.2-1.4</td>
<td>Increase by 200 units/hr</td>
<td>Increase by 0.2 ml/hr</td>
</tr>
<tr>
<td>&lt; 1.2</td>
<td>consider IV bolus Increase by 400 units/hr</td>
<td>Increase by 0.4 ml/hr</td>
</tr>
</tbody>
</table>


**Management of bleeding when on IV Heparin refer to section 3.1 page 22.**

28. **Warfarin, loading schedule, target INR and duration of therapy**

28.1. All patients on warfarin must have a written record of their results and dose changes.

28.2. If patients are currently on anti-platelet therapy, the indication for this should be reviewed and will usually stopped, or as need considered by the appropriate specialist.

28.3. With therapeutic doses there is no significant synergistic action between heparin and warfarin, hence these drugs are used concurrently, the heparin having immediate effect, while warfarin due to its 40 hour half-life usually takes 4-7 days to attain a therapeutic INR.
28.4. In venous thrombo-embolic disease provided the diagnostic procedure is to be performed within 24 hours warfarin may be commenced on admission.  
- A single dosage preparation of the 3 mg (blue) tablet, given as multiples and, or split tablets is often simplest, practiced to avoid confusion over different doses of the drug, common particularly among the elderly.  
- Nevertheless, particularly when approaching stable dosing at discharge, patients should be offered an option of constant daily dosing, avoiding alternate day dosing and the breaking of tablets, both of which may be difficult.  
- To facilitate constant daily dosing, warfarin tablets can also be supplied as 0.5mg (white), 1mg (brown) and 5mg (pink).

28.5. The standard loading dose of 9mg should be modified for patients aged over 70, of low body weight (i.e. less than 50kg), or with CCF for example to 6mg. Also significant liver dysfunction will prolong a baseline INR and indicate the requirement for a modified dosing schedule.

29. Therapeutic loading schedule for acute thrombosis:
- Commencing on day 1, in conjunction with heparin
- Check baseline INR.
- If INR > than 1.4 reduce loading dose pro rata and check daily.
- Otherwise, initially using 3mg tablets, follow loading dose schedule for acute therapy:

<table>
<thead>
<tr>
<th>Day</th>
<th>INR</th>
<th>Dose mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;1.4</td>
<td>9.0</td>
</tr>
<tr>
<td>2</td>
<td>&lt;2</td>
<td>9.0</td>
</tr>
<tr>
<td>3</td>
<td>2.0-2.5</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>2.6-3.0</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>3.1-4.0</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>&gt;4.1</td>
<td>Nil</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day</th>
<th>INR</th>
<th>Dose mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;1.4</td>
<td>6.0</td>
</tr>
<tr>
<td>2</td>
<td>&lt;2</td>
<td>6.0</td>
</tr>
<tr>
<td>3</td>
<td>2.0-2.5</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>2.6-3.0</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>3.1-4.0</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>&gt;4.1</td>
<td>Nil</td>
</tr>
</tbody>
</table>

- Day 4 continue on day 3 dose rechecking on day 5, or discharge on this dose for early review. (Modified from Fennerty et al 1988)

30. Prophylactic warfarin initiation schedule (e.g. as with AF):
“Loading” is unnecessary and a standard dose may be commenced e.g. 6 mg, or for patients with weight <50kg, liver dysfunction, CCF or over 70 years of age 3 mg with the INR being checked 5-7 days later.

31. Warfarin target INR and duration of therapy (cf BNF 2.8.2):
31.1. Clinical and computerised dosing support systems use a defined target INR, with an acceptable deviation of 0.5 units before a dose is altered. The following recommendations include both a single target INR, to be entered on the anticoagulant prescription chart and DOH Anticoagulant Therapy Record and an acceptable target INR range.
31.2. For provoked (secondary) cases of venous thrombosis a defined duration of anticoagulation is recommended.

31.3. For unprovoked (idiopathic) cases other than calf DVT, or for individuals with persistent risk factors such as cancer, immobility, or thrombophilia, continued treatment should be considered.

Proximal DVT = DVT above the calf               Recurrence = three or more episodes

<table>
<thead>
<tr>
<th>Target INR</th>
<th>Acceptable INR range</th>
<th>Clinical indication</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>2.0-3.0</td>
<td>Calf DVT 1st event provoked proximal DVT or PE, 2nd provoked DVT and, or PE Unprovoked 1st event PE</td>
<td>6 weeks at least 3 months at least 3 months at least 3 months, then offer long-term with consideration of risk/benefit at least 3 months, then consider long-term with respect to risk/benefit at least 3 months, then offer long-term with consideration of risk/benefit d/w Haematologist long-term consider long-term long-term Cardiologist's decision* Cardiologist's decision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unprovoked 1st event proximal DVT (ileo-femoral or popliteal vein) Recurrent unprovoked DVT and, or PE while not on warfarin DVT/PE with inherited thrombophilia Atrial fibrillation Antiphospholipid syndrome Rheumatic mitral valve disease mural thrombus,cardiomyopathy bio-prosthetic valves</td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>2.5-3.5</td>
<td>Cardioversion</td>
<td>3 weeks before and 4 weeks after cardioversion</td>
</tr>
<tr>
<td>3.5</td>
<td>3.0-4.0</td>
<td>Recurrent unprovoked DVT and PE, whilst on therapeutic warfarin mechanical prosthetic valves**</td>
<td>long-term long-term</td>
</tr>
</tbody>
</table>

31.4. Consider the risk benefits and offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient’s risk of VTE recurrence and whether they are at increased risk of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.

31.5. **Management of sub-therapeutic anticoagulation in the first month after acute VTE**

31.6. **Recommendation:**
31.7. Bridging therapeutic heparin should be considered if the INR becomes significantly sub-therapeutic within the first month of an acute VTE.

31.8. **Cardiologist’s or Cardiothoracic surgeon’s decision***:
31.9. For these indications the required duration of anticoagulation is not determined, hence decisions are made on the basis of the patient’s history and investigations, at their Consultant’s discretion.

31.10. **the risk of embolism may be stratified by the site and type of valve such that surgeons may make specific target range recommendations on the discharge of patients from Cardio- thoracic centres, whilst published general recommendations are:

### Table: Recommended target INRs for mechanical heart valves adapted from Vahanian et al (2007)

<table>
<thead>
<tr>
<th>Prosthesis Thrombogenicity*</th>
<th>INR target No patient risk factors</th>
<th>INR target Patient-related risk factors**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Medium</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>High</td>
<td>3.5</td>
<td>3.5***</td>
</tr>
</tbody>
</table>

*Prosthesis thrombogenicity:
Low: Carbomedics (aortic position), Medtronic Hall, St Jude Medical (without silzone);
Medium: Bjork- Shiley, other bileaflet valves;
High: Starr-Edwards, Omniscience, Lillehei-Kaster.

32. Warfarin anticoagulation continued:

#### 32.1. Peripheral vascular disease

- Patients with intermittent claudication should not routinely be treated with anticoagulants (1A).
- Patients who suffer acute arterial embolism and proceed to embolectomy should be considered for long-term anticoagulation with warfarin with an INR target of 2.5.

#### 32.2. Conditions for which anticoagulation is not generally indicated:

32.3. In general, (randomised controlled) studies have determined that for the following uncomplicated diagnoses anticoagulation is not indicated:

- Ischaemic stroke without atrial fibrillation.
- Peripheral arterial thrombosis and grafts.
- Coronary artery thrombosis.
- Coronary artery graft thrombosis.
- Coronary angioplasty and stents

32.4. In specific circumstances a clinician may decide that anticoagulation is required for a determined period, with generally a target INR of 2.5 (acceptable range 2.0-3.0)
for stroke and the other indications 3.5 (range 3.0-4.5).

32.5 Conditions for which anticoagulation is unproven:

- Retinal vein occlusion

32.6 Cessation of therapy

Once the therapeutic period is completed warfarin may simply be stopped, as the half-life is around 40 hours and the effect on the INR slowly wanes off.

32.5 Combination warfarin and antiplatelet therapy

- Patients receiving an anti-platelet agent as primary prophylaxis for cardiovascular disease on developing an indication for warfarin should stop their antiplatelet agent
- Patients with peripheral artery disease or previous ischaemic stroke on antiplatelet therapy should stop this agent if warfarin is commenced.
- Patients on aspirin or clopidogrel as secondary prophylaxis with stable ischaemic heart disease (often defined as >12 months following acute myocardial infarction) should stop their antiplatelet agent while being treated with warfarin.
- Patients on a single antiplatelet agent <12 months following an ACS, who require to start warfarin therapy should continue aspirin therapy until 12 months post ACS, unless they are regarded as having a high bleeding risk.
- Patients on aspirin and clopidogrel, following an ACS or stent placement, who develop an indication for warfarin should be carefully assessed for bleeding risk and discussed with their cardiologist, with a view to introducing warfarin and minimizing the duration of triple therapy.
- When combined warfarin and single antiplatelet agent are indicated, consideration should be given to use of aspirin given the higher bleeding risk associated with clopidogrel.

32.7 Patients on warfarin who develop an indication for antiplatelet agents

- Patients requiring a coronary artery stent should be considered for bare metal stent (rather than drug eluting stent) which would only necessitate triple therapy for 4 weeks, followed by aspirin and warfarin to 12 months.
- Patients who do not undergo PCI should be considered for 4 weeks triple therapy, after which clopidogrel should be stopped, and aspirin continued for a further 11 months.

33. Complications of therapeutic anticoagulation including bleeding

33.1 Head injury in patients on vitamin K antagonists eg warfarin

- Patients on vitamin K antagonists eg warfarin with a strong suspicion of intracerebral haematoma after a clear head injury should have their INR reversed with PCC dose eg 25u/kg. Unless CT scanning is immediately available reversal
with PCC should take place before CT head and any laboratory INR result is available

- Delayed intracranial bleeding can occur in patients on warfarin even when the initial CT scan is normal (Cohen et al, 2006). In view of this, patients with a supra-therapeutic INR should have this corrected into the therapeutic range with oral vitamin K.
- It is suggested that the INR is maintained as close to 2.0 as possible for the 4 weeks after a significant head injury and a normal CT scan.

33.2. **Bleeding**

33.3. Bleeding may be seen with all anticoagulants, particularly during the introduction of therapy with the risk increased by drug interactions, co-morbidity or recent surgery.

33.4. In many cases, simple non-pharmacological measures and stabilisation of the patient whilst the antithrombotic is eliminated are sufficient to treat or prevent bleeding.

33.5. **General non-pharmacological measures.**

- Stop the antithrombotic drug
- Document the timing and amount of the last drug dose and presence of pre-existing renal or hepatic impairment
- Estimate the half-life and length of functional defect induced by the drug
- Assess the source of bleeding
- Request full blood count, prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen concentration, creatinine concentration
- If available, request a specific laboratory test to measure the antithrombotic effect of the drug
- Correct haemodynamic compromise with intravenous fluids and red cell transfusion
- Apply mechanical pressure, if possible use endoscopic, radiological or surgical measures

33.6. Additional specific pharmaceutical measures are as detailed in the following sections.

33.7. Where bleeding is unexpected, or due to iatrogenic error, then an incident report should be submitted through the Trust’s Datix incident reporting system for future analysis and risk management.

33.8. **Unfractionated Heparin**

Significant bleeding is generally only seen with therapeutic doses of heparin.

33.9. At therapeutic doses unfractionated heparin is rapidly excreted with a half-life of around 45–90 minutes. However, at higher doses, this mechanism becomes saturated and renal clearance results in a longer half-life.

33.10. Spontaneous bleeding is unusual with APTT ratio <2.5. Protamine sulphate reverses the anti-IIa inhibitory effect of heparins, the dose dependent on the amount of heparin to be neutralised, with 1mg neutralising at least 100 UNITS of mucous heparin or 80 UNITS of lung heparin if given within 15 minutes of heparin.
administration.

33.11. **Bleeding with standard IV therapeutic unfractionated heparin (UFH), ie Pump-Hep®, (cf BNF Section 2.8.3):**
- Stop heparin pump
- Check APTT ratio and a FBC (with APTT ratio >3.0 INR may be unreliable)
- UFH can be rapidly reversed with protamine sulphate, derived from fish sperm and forms a stable, inactive salt with heparin. Consider reversal by administration of protamine sulphate injection by slow intravenous injection (max rate 5 mg/min) over a period of >5 minutes, dosing as follows:

33.12. The dose may be calculated from the quantity of UFH administered in the 2 h prior to reversal using the assumption that 1 mg protamine sulphate neutralizes 80–100 units of UFH.

- For example, bleeding during an IV infusion of UFH 1250 units/h requires 25 mg protamine sulphate.
- Bleeding soon after a bolus dose of 5000 units requires 50 mg.
- The half-life of protamine is 7 min, which is shorter than UFH, thus, prolonged Protamine sulphate administration may be necessary if UFH has been administered subcutaneously, causing entry into the circulation to be delayed et al, 2008).

33.13. The reversal effect of protamine can be monitored by the APTT.

- Protamine sulphate can cause severe allergic reactions including anaphylaxis, hypotension, bronchospasm and skin reactions in up to 10% of patients. Risk factors are previous exposure to protamine sulphate (including protamine-containing insulin preparations), rate of administration, vasectomy and fish allergy.
- Protamine sulphate should be given slowly over >5 min.
- Patients at risk may be pre-treated with corticosteroids and antihistamines.
- At higher doses, protamine sulphate may have significant anticoagulant and antiplatelet effects

33.14. **To antagonise an unfractionated heparin during extracorporeal circulation:**
- Administer protamine sulphate 1.5 mg per 100 UNITS heparin (slow intravenous injection (max rate 5 mg/min) over a period of 10 minutes).

33.15. The requirement for further protamine sulphate may be monitored by APTT.

33.16. **Bleeding on Low molecular weight heparin, eg dalteparin or enoxaparin:**
33.17. Discontinue, consider reversal by administration of protamine.

33.18. Low molecular weight heparin has a half-life of approximately 4 hours. Bleeding is rare even with high anti-Xa levels. Due to the relatively greater anti-Xa
activity bleeding may occur even with a normal APTT ratio. Protamine sulphate does not fully reverse the anti-Xa inhibition.

33.19. Therapeutic heparin has usually decayed to prophylactic doses by 12hrs post injection so:
- Check FBC, coagulation screen and request freeze “plasma”.
- LMWH administration within 8 h of the time of requirement for correction of anticoagulation: give protamine sulphate (1 mg per 100 anti-Xa units of LMWH).
- If ineffective, consider further protamine sulphate 0_5 mg per 100 anti-Xa units (2C). Protamine sulphate should be given slower than 5 mg/min to minimise the risk of adverse reactions.
- LMWH administration greater than 8 h from the time of requirement for correction of anticoagulation: consider smaller doses of protamine (2C).
- Consider rFVIIa if there is continued life-threatening bleeding despite protamine sulphate and the time frame suggests there is residual effect from the LMWH contributing to bleeding. (2C).

33.20. If in doubt seek advice from the Consultant Haematologist on-call.

33.21. **Bleeding on Fondaparinux sodium**
33.22. Fondaparinux is a synthetic and selective inhibitor of activated Factor X (Xa). Doses above the recommended regimen may lead to an increased risk of bleeding.
- There is no known antidote to Fondaparinux. Management of bleeding should be through cessation of treatment and general haemostatic measures
- Recombinant FVIIa should be considered for critical bleeding.

33.23. **Bleeding on Danaparoid sodium**
33.24. Danaparoid has a plasma half-life of anti-Xa activity of approximately 24 hours. Danaparoid may be monitored by anti-Xa assay using a danaparoid standard.
- There is no specific antidote for danaparoid. Management of bleeding should be through cessation of treatment and general haemostatic measures
- Plasmapheresis may be considered for critical bleeding.

33.25. **Bleeding on vitamin K antagonist anticoagulants eg warfarin (cf BNF 2.8.2)**
33.26. Present commonly with bruising, mucocutaneous bleeding, or haematuria. This is uncommon with INR’s <5.0. Per annum the general risk is of haemorrhage is of the order of 0.25% death, 2% for hospitalisation and 5-7% for minor bleeding.

33.27. Active intervention may be appropriate for those patients with major bleeding or those with minor bleeding and classified as being at high risk for haemorrhage. Asymptomatic standard risk patients do not require INR reversal at INR <7.0 but correction should be considered in “high risk” patients whose risk of bleeding is approximately 15 fold higher.

33.28. In haemorrhagic cases, withholding warfarin and normalisation of the INR for brief periods is associated with a low risk (0.7-1%) of thrombo-embolism.

33.29. **Bleeding classification:**
33.30. Examples of "major" bleeding:

1. Intracranial (CT or MRI documented)
2. Retroperitoneal (CT or MRI documented)
3. Intra-ocular (excludes conjunctival)
4. Spontaneous muscle haematoma associated with compartment syndrome
5. Pericardial
6. Non-traumatic intra-articular
7. Any invasive procedure to stop bleeding
8. Active bleeding plus either BP ≤ 90 mmHg systolic, oliguria, or ≥ 2 g/dl fall in haemoglobin

33.31. Examples of "minor" bleeding:
Any other bleeding that would not influence your decision to anticoagulate a patient

33.32. **High risk for bleeding is determined** by:

1. Age over 70 years, Anaemia, renal failure, diabetes mellitus, previous MI
2. Previous GI bleed, previous CVE
3. Anticoagulation in the first 100 days

33.33. Fresh frozen plasma (FFP) only increases factor levels to at best 20-30% and will not normalise the INR, whereas this may be achieved with the more potent prothrombin complex concentrates, containing factors II, V, VII and IX. Intra-venous vitamin K may reduce the INR within four hours, whereas the oral preparation is less predictable and should be re-assessed with repeat INR.

33.34. **Actions to be taken for high INR**

- INR > 8.0, no bleeding or minor bleeding
  - stop vitamin K antagonist (eg warfarin), restart when INR < 5.0;
  - if there are other risk factors for bleeding give phytomenadione (vitamin K1) 1-3 mg by slow intravenous injection or up to 5 mg by mouth (for partial reversal of anticoagulation give smaller oral doses of phytomenadione e.g. 1–2.5 mg using the intravenous preparation orally); Intra-venous vitamin K may reduce the INR within four hours, whereas the oral preparation is less predictable. If there are concerns the INR should be repeated at 4-6hours.

- INR 5.0–8.0, no bleeding or minor bleeding
  - stop vitamin K antagonist (eg warfarin) for 1–2 doses
  - restart when INR < 5.0 with the maintenance dose should be reduced
  - The INR should decline to <5.0 in 24-72 hours
  - The cause of the elevated INR should be investigated

33.35. **Unexpected bleeding at therapeutic levels**—always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal tract pathology
33.36. Management of bleeding with warfarin or other vitamin K antagonist oral anticoagulants:

ASSESS BLEEDING:

Major eg
- gastro-intestinal
- CNS haemorrhage
- Intra-ocular
- any bleed requiring invasive procedure

*Vitamin K 5 mg slow iv over 5 minutes
Hospitalise urgent FBC, INR, Group and antibody screen
Administer **Prothrombin complex concentrate IV

25-50 units per Kg, dependant on INR
(from Haematology Laboratory)

Immediate check
PT and APTT

Adequate correction INR <1.5
Inadequate correction

Repeat PT and APTT in 4-6 hours

Consider other factors contributing to prolonged coagulation tests
eg
- DIC
- Congenital coagulation factor deficiency
- Liver disease
- Inadequate replacement
- Lupus inhibitor

As needs seek haematological advice
33.37. The use and dosage of **Beriplex® P/N prothrombin complex concentrate (factors II, VII, IX and X) in major bleeding in coumarin anticoagulated patients

33.38. Standard Operating Procedure

- Request from Haematology Laboratory
- Dose as 25-50 units of FIX per Kg, titrated against INR
- Each bottle of Beriplex® P/N 500 contains 500 units FIX in 20mls.
- Reconstitute as per manufacturers instruction eg 500 units in 20ml water for injection warmed to maximum 37oC.
- **Maximum single dose 5000 UNITS FIX (200mls).**
- Administer infusion: first 1ml over 1 minute in case of reaction, then 8ml/min (max equivalent to approx 210 units/min)
- Patients may have reactions, commonly chills, as with other blood products.
- Administer vitamin K 5mg IV, as the PCC only has a half-life of some 6 hours, compared to 30-40 hours for warfarin.
- See nomograms for guide for given Kg body weight range and INR

<table>
<thead>
<tr>
<th>Initial INR</th>
<th>2.0 – 3.9</th>
<th>4.0 – 6.0</th>
<th>&gt;6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate dose units (Factor IX)/kg body weight</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Approximate dose ml/kg body weight</td>
<td>1</td>
<td>1.4</td>
<td>2</td>
</tr>
<tr>
<td>Maximum Single Dose for patients weighing 100kg or over</td>
<td>2500 units</td>
<td>3500 units</td>
<td>5000 units</td>
</tr>
</tbody>
</table>

33.39. **NB Check INR immediately after infusion to demonstrate correction, as per protocol**

33.40. Repeated dosing with prothrombin complex concentrate (Beriplex® P/N) for patients requiring urgent reversal of Vitamin K antagonist treatment is not supported by clinical data and therefore not recommended
33.41. **Approximate dose of Beriplex® P/N Prothrombin complex concentrate per Kg weight at different initial INR levels:**

<table>
<thead>
<tr>
<th>Initial INR</th>
<th>2.0 – 3.9</th>
<th>4.0 – 6.0</th>
<th>&gt;6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate dose units (Factor IX)/kg body weight</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Approximate dose ml/kg body weight</td>
<td>1</td>
<td>1.4</td>
<td>2</td>
</tr>
<tr>
<td>Kg body weight range and estimated dose units rounded to nearest 500 for INR reading</td>
<td>2.0 – 3.9</td>
<td>4.0 – 6.0</td>
<td>&gt;6.0</td>
</tr>
<tr>
<td>41-50 kg</td>
<td>1000 units</td>
<td>1500 units</td>
<td>2000 units</td>
</tr>
<tr>
<td>51-60 kg</td>
<td>1500 units</td>
<td>2000 units</td>
<td>2500 units</td>
</tr>
<tr>
<td>61-70 kg</td>
<td>1500 units</td>
<td>2500 units</td>
<td>3000 units</td>
</tr>
<tr>
<td>71-80 kg</td>
<td>2000 units</td>
<td>2500 units</td>
<td>3500 units</td>
</tr>
<tr>
<td>81-90 kg</td>
<td>2000 units</td>
<td>3000 units</td>
<td>4000 units</td>
</tr>
<tr>
<td>91-100 kg or above 100 kg</td>
<td>2500 units</td>
<td>3500 units</td>
<td>5000 units</td>
</tr>
</tbody>
</table>

33.42. **NB Check INR immediately after infusion to demonstrate correction, as per protocol**

33.43. Repeated dosing with prothrombin complex concentrate (Beriplex® P/N) for patients requiring urgent reversal of Vitamin K antagonist treatment is not supported by clinical data and therefore not recommended.

33.44. **Vitamin K administration**

Colloidal Vitamin K (10 mg/ml, Konakion MM, Roche).

*IV may rarely cause anaphylaxis*

Withhold in patients with history of previous severe allergic reaction

Otherwise administration should be:

- draw up vitamin K dose in a 1ml insulin syringe
- inject dose into a 10ml graded syringe
- then make ~10% dilution with water for injection
- ie 0.1ml vitamin K (1mg) to 1ml water for injection
- administer as slow iv bolus 1mg/min

33.45. For oral administration of vitamin K
33.46. Use the colloidal Vitamin K preparation preparation for injection (10 mg/ml) ie Konakion MM (Roche).

- draw up vitamin K dose in a 1ml insulin syringe
- inject dose into a 10ml gradated syringe
- then make ~10% dilution with water for injection
- ie 0.1ml vitamin K (1mg) to 1ml water for injection
- “squirt” diluted solution into mouth and instruct patient to swallow

For the urgent reversal of warfarin to enable surgery see section 37.4.

33.47. Example of warfarin oral anticoagulant dose reduction schema
(Modified Cambridge Addenbrook’s)

**INR target 2.5 (2.0-3.0)**

<table>
<thead>
<tr>
<th>INR</th>
<th>% reduction</th>
<th>omit</th>
<th>x days</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1-5.0</td>
<td>25</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>5.1-6.0</td>
<td>25</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6.1-7.9</td>
<td>33</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>&gt;8.0</td>
<td>50</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

**INR target 3.5 (3.0-4.0)**

<table>
<thead>
<tr>
<th>INR</th>
<th>% reduction</th>
<th>omit</th>
<th>x days</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1-5.0</td>
<td>15</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>5.1-6.0</td>
<td>25</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6.1-7.9</td>
<td>33</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>&gt;8.0</td>
<td>50</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
33.48. **Management of Variable INRs**
Due to hepatic enzyme polymorphisms, some patients may have “unstable” INR’s, not attributable to any of the usual known causes for instability. This results in frequent testing with dose adjustments and in some cases, bleeding or thrombotic episodes. Control may possibly be improved by a broader therapeutic target range (eg 2.0-4.0), or a trial may be considered of supplemental daily low-dose oral vitamin K (100 to 200 mcg, Solgar Vitamins Ltd), with close monitoring of the INR and warfarin dose adjustment to counter an initial lowering of the INR in response to vitamin K.

33.49. **Warfarin drug interactions (cf BNF appendix 1)**
Almost any drug can interact with oral anticoagulants, in particular:

- Alcohol, steroids and hormones, analgesics, antibiotics, antidepressants, antiepileptics, antifungals, antiplatelet drugs, barbiturates, hormone antagonists, lipid lowering drugs, thyroxine, ulcer drugs, vitamins e.g. Vitamin K.
- When prescribing, a non-interacting drug is preferable, otherwise:
  - **If a new warfarin potentiating drug lasts <7 days either:**
    - Make no change, minor dose reduction, or miss one complete warfarin dose
  - **If a new warfarin potentiating drug lasts >7 days then:**
    - Check INR 3-7 days after start of drug. Adjust dose on basis of result.

33.50. **Bleeding with thrombolytic therapy:**
Bleeding, by process of de-fibrination, is more common than with heparin (around 3%).

- Check a full coagulation screen (and FBC)
- Consider tranexamic acid 10 mg/kg IV and/or cryoprecipitate (rich in fibrinogen).
- Advice is as needs available from the on-call Consultant Haematologist, or specifically for stroke thrombolysis, the on-call Consultant Physician for Care of the Elderly.

33.51. **Bleeding with Anti Xa inhibitors (Rivaroxaban, Apixaban, Edoxaban):**
33.52. Bleeding may be seen in around 3% of patients and given the short half-life of these drugs, minor bleeding can be managed by:

- Delay next drug administration or discontinue treatment as appropriate.
- **There is currently no specific antidote for the oral Anti-Xa Inhibitors**

33.53. **Bleeding with Dabigatran Exetilate (Pradaxa®):**
33.54. Bleeding may be seen in around 3% of patients. In cases of life-threatening bleeding associated with Dabigatran patients should be administered Idarucizumab (Praxbind®).
- Praxbind is only licensed for the reversal of Dabigatran in cases of life-threatening bleeding and where Dabigatran reversal is required for emergency surgery or intervention
- Praxbind has no reversal effect on the oral Anti-Xa inhibitors and should not be used to reverse the effects of Rivaroxaban, Apixaban or Edoxaban
- Praxbind is available in 2x2.5g vial packs. Standard adult dose is 5g given by IV infusion or bolus (total volume 100mls)
- Praxbind is stored in the Emergency Department drug fridge at RCHT
- In non life-threatening Dabigatran-related bleeding, if a patient has taken a dose within the last 2 hours consider oral activated charcoal to prevent further absorption of the drug

33.55. The assessment and hospital management of major bleeding (cerebral or gastro-intestinal)
- There is currently no specific antidote for the oral Anti-Xa inhibitors
- Determine time since last dose
- Initiate resuscitation with IV fluids, blood transfusion and other general haemostatic supportive measures as necessary
- Check FBC, U&E’s and a coagulation screen (PT, Thrombin Time and APTT); If within the normal reference ranges, then there is likely to be only a low level of the anticoagulant present.
- If platelets <60 consider transfusion
- In situations with ongoing Rivaroxaban-related life-threatening bleeding, not controlled by the above measures, administration of prothrombin complex concentrate (PCC) 25 units per kg may be considered
- In situations with ongoing dabigatran related life-threatening bleeding Idarucizumab (Praxbind®) should be administered (as per section 33.54)
- In Dabigatran related minor bleeding, if a patient has taken a dose within the last 2 hours consider oral activated charcoal to prevent further absorption.

**NB The estimated time for restoration of haemostasis after cessation of therapeutic doses, with adequate renal function is usually within 12 hours for dabigatran or 24 hours for rivaroxaban

33.56. Overdose:
- For Dabigatran or rivaroxaban give oral activated charcoal if within 2 hours of ingestion.
- Rivaroxaban (and apixaban) are highly protein bound and are not dialysable
33.55 Management of bleeding with Apixaban, Edoxaban and Rivaroxaban oral anticoagulants:

Determine interval since therapy

**ASSESS BLEEDING:**

- **Major eg**
  - gastro-intestinal
  - CNS haemorrhage
  - Intra-ocular
  - any bleed requiring invasive procedure

- **Minor eg**
  - bruising, brief epistaxis
  - transient haematuria

Hospitalise

- if within 2 hrs of therapy consider oral charcoal

Resuscitate and urgent blood tests

- FBC
- coagulation screen (PT, Thrombin Time & APTT)
- Group and screen biochemistry

- If platelets <60 consider transfuse 1 adult dose platelets

- Abnormal Drug present
  - If < normal reference ranges = likely low level anticoagulant

Review progress

- ongoing life-threatening bleeding, not controlled by the above measures

Consider Tranexamic Acid (1g i.v.)

Administer

- Prothrombin complex concentrate IV
- 25 units per Kg, (from Haematology Laboratory)
33.56 Non-steroidal analgesics or anti-platelet therapy (aspirin and the P2Y12 inhibitors [clopidogrel and prasugrel] and GPIIa/IIIb inhibitors (eg abciximab):

33.57 Check an FBC and as indicated a coagulation screen.
- Decisions to withhold anti-platelet drugs or to administer pro-haemostatic agents should be made after a careful multi-disciplinary assessment of the risks and benefits of intervention.
- Bleeding in patients during treatment with aspirin, P2Y12 antagonists or GPIIa/IIIb inhibitors should be managed in the first instance with general haemostatic measures. If necessary, drug cessation and reversal of the effect of coprescribed anticoagulants should also be considered.
- Platelet transfusion (2–3 adult doses) should be considered as an additional measure for critical bleeding or prevention of bleeding before emergency surgery.
- Platelet transfusion should be considered to prevent bleeding in severe thrombocytopenia (<10 x 10⁹/l) caused by abciximab

33.58 Platelets are of uncertain limited use in the immediate phase of bleeding with clopidogrel, as this is a pro-drug, the metabolite circulating for approximately 18 hours.
- There are no specific reversal agents for the P2Y12 antagonists.

33.59 Fibrinolytic drugs
33.60 The fibrinolytic drugs currently licensed in the UK are: alteplase, tenecteplase, reteplase, urokinase and streptokinase. All five agents function indirectly by promoting generation of plasmin, which then mediates clot lysis. Specific information is available from relevant Trust guidance. General recommendations for the management of bleeding are:

33.61 For major bleeding (e.g. intracerebral) within 48 h of administration of a fibrinolytic drug:
- Stop infusion of fibrinolytic drugs and other antithrombotic drugs.
- Administer FFP 12 ml/kg.
- Administer intravenous tranexamic acid 1 g tds.
- If there is depletion of fibrinogen, administer cryoprecipitate or fibrinogen concentrate.
- Further therapy should be guided by results of coagulation

34 Heparin induced thrombocytopenia (HIT)
34.57 A paradoxical life threatening immune mediated thrombotic syndrome with thrombocytopenia may be seen in about 1% of medical and up to 5% of surgical patients receiving unfractionated heparin or after coronary artery surgery. This occurs with both unfractionated and less so with LMW heparins or low-dose prophylactic therapy. It occurs after 5-7 days in previously unexposed patients, or earlier with previous drug exposure within 100 days.

34.58 If a measured platelet count falls by 50% or more and/or if a patient develops new thrombosis or skin allergy or any of the other rarer manifestations of HIT between days 4 to 14 of heparin administration HIT should be considered, as once thrombosis occurs there is at least a 50% mortality.
A clinical assessment should be made and a clinical pre-test probability score calculated (see Appendix 4)

- If the score is low, HIT can be excluded without the need for laboratory investigation
- Otherwise heparin must be stopped, an alternative anticoagulant eg danaparoid started in full dosage and laboratory tests for heparin associated antibodies undertaken.
- Low molecular weight heparin should not be used in the treatment of HIT (1A).
- Warfarin should not be used, or as needs reversed until the platelet count has recovered to the normal range. When introduced, an alternative anticoagulant must be continued until the INR is therapeutic
- Patients should be therapeutically anticoagulated for 3 months after HIT with a thrombotic complication and for 4 weeks following HIT without a thrombotic complication
- Women with HIT in pregnancy should be treated with a non-cross reacting anticoagulant. Danaparoid should be used where available and Argatroban also considered, most usefully in renal impairment (GFR less than 30 ml/min)
- As necessary advice can be sought from the on-call Consultant Haematologist or SpR.

34.59 The heparinoid danaparoid (Orgaran®) is licensed for HIT, which has an anti-Xa half-life of approximately 24 hours, with less effect on thrombin (IIa).

- Administered intravenously as a bolus of 2500 anti-Xa units (for patients less than 55kg 1250 units, if over 90kg, 3750 units)
- followed by an intravenous infusion of 400units/h for 2 hours,
- then 300 units/h for 2 hours,
- then a maintenance infusion of 200 units/h for 5 days.

34.60 In general monitoring of plasma anti-Xa activity is not necessary. However, in patients suffering from renal insufficiency (GFR less than 30 ml/min) and/or patients weighing over 90kg, monitoring (using an amidolytic assay) is recommended.

34.61 The expected plasma anti-Xa levels are 0.5-0.7 units/ml 5-10 minutes after the bolus, not higher than 1.0 units/ml during the adjustment phase of maintenance infusion and 0.5-0.8 units/ml during the maintenance infusion.
- It is not reversible by protamine.

34.62 Argatroban (Exembol®)

34.63 This is a direct thrombin inhibitor which is administered intravenously, license in the therapy of HIT
- The key feature that makes it attractive in the management of HIT is its hepatic metabolism in a condition which is often complicated by established or developing renal impairment.
- An argatroban infusion adjusted to an APTT ratio of 1.5-3.0 (but not exceeding 100 seconds) is a suitable alternative anticoagulant for the treatment of patients with HIT
• Patients on argatroban being transitioned to warfarin should have an INR ≥4 for two days prior to discontinuing argatroban

### Administration table for Argatroban

**Standard dosing schedule**  
*Initial Infusion Rate 2 mcg/kg/min.*

<table>
<thead>
<tr>
<th>aPTT (s)</th>
<th>Infusion Rate change</th>
<th>Next aPTT</th>
<th>Infusion Rate change</th>
<th>Next aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5 times baseline</td>
<td>Increase by 0.5 mcg/kg/min.</td>
<td>2 hours</td>
<td>Increase by 0.1 mcg/kg/min.</td>
<td>4 hours</td>
</tr>
<tr>
<td>1.5-3.0 times baseline (not exceeding 100 s)</td>
<td>No change</td>
<td>2 hours; after 2 consecutive aPTT’s within target range, Check at least once per day</td>
<td>No change</td>
<td>4 hours; after 2 consecutive aPTT’s within target range Check at least once per day</td>
</tr>
<tr>
<td>&gt; 3.0 times baseline or &gt; 100 s</td>
<td>Stop infusion until the aPTT is 1.5-3.0 times baseline; Resume at half of the previous infusion rate</td>
<td>2 hours</td>
<td>Stop infusion until the aPTT is 1.5-3.0 times baseline; Resume at half of the previous infusion rate</td>
<td>4</td>
</tr>
</tbody>
</table>

The maximum recommended dose is 10 microgram/kg/min. The maximum recommended duration of treatment with argatroban is 14 days, although there is limited clinical experience of administration for longer duration

### Method of administration

Exembol is supplied as a concentrate (250 mg/2.5 ml) which must be diluted 100-fold prior to infusion to a final concentration of 1 mg/ml. Standard infusion rates for the 2 microgram/kg/min recommended initial dosage (1 mg/ml final concentration) are detailed in the table below. The standard infusion rates for patients with moderate hepatic impairment (Child-Pugh Class B), after cardiac surgery and critically ill patients with a starting infusion rate of 0.5 microgram/kg/min are also detailed in the table below:

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Infusion Rate (ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 microgram/kg/min</td>
</tr>
<tr>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>70</td>
<td>8</td>
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<tr>
<td>80</td>
<td>10</td>
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<td>90</td>
<td>11</td>
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<td>100</td>
<td>12</td>
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<tr>
<td>110</td>
<td>13</td>
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<tr>
<td>120</td>
<td>14</td>
</tr>
<tr>
<td>130</td>
<td>16</td>
</tr>
<tr>
<td>140</td>
<td>17</td>
</tr>
</tbody>
</table>
34.64 Future management

- All confirmed (HIT antibody) cases must be recorded as an alert for HIT to the front and inside cover of the hospital notes.
- Although recurrence is rare, where a patient with previous HIT requires a period of anticoagulation or anticoagulant prophylaxis an alternative to UFH or LMWH should be prescribed.
- Danaparoid may be used as may new anticoagulants such as dabigatran, rivaroxaban and apixaban depending on the clinical circumstances e.g. dabigatran, rivaroxaban and apixaban may be used as per licensed indications such as orthopaedic surgery. This is best co-ordinated through follow up in the haematology clinic.

35 Discharge of patients on anticoagulants, education, the DOH Anticoagulant Therapy Record and liaison with primary care.

35.57 Commonly patient understanding of anticoagulant therapy is limited, (even in patients on long-term therapy) and may be problematic. A further area of concern is liaison, particularly with primary care, where the majority of discharged patients are subsequently dosed by their General Practitioners, when adequate information is essential for safe practice.

35.58 To ensure that patients are adequately informed as to their therapy and improve liaison with the doctor undertaking follow-up the (yellow) Department of Health “Anticoagulant Therapy Record” booklet has been introduced as standard practice for patients receiving anticoagulation with Warfarin.

35.59 All patients given Warfarin anticoagulation must receive a DOH Anticoagulant Therapy Record booklet prior to discharge. Use of the booklet is best done by commencing to enter details in parallel with the EPMA electronic prescription and INR results. Guidance for the target dose and duration of therapy are available on reference charts displayed on the Ward.

35.4 Patients commenced on DOAC’s should be provided with specific approved information booklets regarding their medication. Bespoke information booklets produced by pharmaceutical companies for the individual DOACs and anticoagulation indications are available.

35.5 The attending doctor or anticoagulant nurse is responsible for the education and instruction of the patient, completion of the patient information booklet and follow-up arrangements. They should undertake:

35.6 Patient information:
- Using the DOAC/DOH information booklet, explain to patient:
  - Why they are anticoagulated and how anticoagulation works,
  - the haemorrhagic signs of overdose,
  - to avoid excessive alcohol and diets,
  - to beware new medications,
whom to contact in the event of problems/haemorrhage.

- **Women of a fertile age must be instructed not to become pregnant because of warfarin embryopathy, the greatest risk being in the first trimester.**

35.60 **Liaison for follow up (Warfarin/VKA patients only):**
- Request the ward clerk to make an appointment with the clinician managing follow-up (usually the GP) for the next INR test/attendance. Then record in the DOH booklet:
  - the anticoagulant drug
  - the indication for anticoagulation, target dose and duration,
  - the clinician managing follow-up,
  - the INR result’s and warfarin doses during the in-patient stay,
  - the designated date for next INR test/attendance for follow-up, no longer than 7 days from discharge.
  - Instruct the patient to attend the appointment, taking their DOH booklet.

35.61 **Pro-forma to accompany discharge script** (see Appendix 5)
- To be completed by the doctor/anticoagulant nurse discharging a patient who is prescribed an oral anticoagulant.
- Send to Pharmacy with the TTO, in-patient drug chart, anticoagulant chart and yellow book –
  - The form will then be faxed to the GP surgery by the Pharmacy Department.

36 **Special Circumstances**

36.57 **Thrombophilia**
36.58 This describes either a familial (heritable) or acquired tendency to thrombosis. Whilst it is unusual for these anomalies to alter management, recommended criteria for subjects who can be considered for screening are:

36.59 **Antiphospholipid antibody screening (lupus anticoagulant and anticardiolipin)**

36.60 Vascular thrombosis:
- One or more clinical episodes of premature arterial thrombosis (<55 in men, and <65 in women),
- One or more clinical episodes of unprovoked venous thrombosis (before 40 years or recurrent), if it is planned to stop anticoagulation treatment.
- Small vessel thrombosis in any tissue or organ (vasculitis).
- Thrombosis must be confirmed by objective validated criteria.
- Do not offer thrombophilia testing to patients who have had provoked DVT or PE.
36.61 Unexplained Pregnancy morbidity, including recurrent miscarriage:

- a) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; or
- b) one or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, pre-eclampsia or placental insufficiency; or
- c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation

36.62 Prolonged activated partial thromboplastin time (APTT)

36.63 The laboratory may also instigate investigation of an unexplained prolongation of the APTT that fails to shorten by the addition of normal plasma, suggesting an inhibitor of coagulation. Commonly this is due to a lupus anticoagulant, but often of no immediate clinical significance.

36.64 Heritable (congenital) thrombophilia (anti-thromobin, proteins C and S, factor V Leiden and the prothrombin gene anomaly F2G20210A, that may be associated with venous thrombosis.

- Do not offer thrombophilia testing to patients who have had provoked DVT or PE.
- Do not offer thrombophilia testing to patients who are continuing anticoagulation treatment.
- Consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE, if it is planned to stop anticoagulation treatment.
- Do not routinely offer thrombophilia testing to first-degree relatives of people with a history of DVT or PE and thrombophilia.

36.65 Thrombophilia testing indications

- Unexplained venous thrombosis in the individual at an early age (<40), especially if from an apparent thrombosis prone family (more than two other symptomatic family members).
- Adults who develop skin necrosis in association with oral vitamin K antagonists are tested for protein C and S deficiency when VKA treatment is withdrawn.
- Neonates and children with purpura fulminans should be tested urgently for protein C and S deficiency.
- Women with a previous venous event due to a minor provoking factor (e.g. travel, HRT/Infertility/Foetal loss) should be tested and may be considered for prophylaxis if a thrombophilia is found.

- Testing is not indicated in patients with arterial thrombosis.
the acute phase reaction and also anticoagulants. These tests rarely affect acute management, but if needed, screening can be done after 2-3 months, even on warfarin. Required samples: three (blue) citrated + one (gold) clotted tube.

36.67 These anomalies are identified in 5-7% of the normal Caucasian population and carry varying risks for thrombosis and re-thrombosis, such that they should not be considered in isolation when deciding on the duration of anticoagulation for an individual.

36.68 Samples not thought suitable or unclear will be stored and will be reported as:
36.69 "The clinical details on this request do not fulfill the current recommended criteria for Lupus anticoagulant investigation, the sample will not be processed. Sample stored - Please supply full clinical details to the laboratory (x2502) or discuss clinical indication with Consultant Haematologist you wish to proceed"

36.70 Pregnancy associated venous-thrombo-embolism:
(Further information on this subject is available via the Trust’s document library)

36.71 One in 1-2,000 pregnancies may be complicated by venous thrombo-embolism (VTE), particularly during around delivery and in the post-partum period.

In clinically suspected DVT or PE, treatment with low molecular weight heparin should be given until diagnosis established; stop treatment only if VTE ruled out.

- DVT – Compression duplex ultrasound; if negative and high level clinical suspicion – repeat in one week
- Iliac vein thrombosis – Magnetic resonance venography or conventional contrast venography (consult radiologist)
- Pulmonary thrombo-embolism – chest X-ray and, if –ve, compression duplex Doppler. If both –ve and persistent clinical suspicion – ventilation-perfusion (V/Q) scan or computed tomography pulmonary angiogram (CTPA)

36.72 Treatment of DVT/PE in pregnancy

- Dalteparin or Enoxaparin LMWH subcutaneously, titrated against weight
- twice daily schedule (maternal pharmacokinetics)
- using prefilled syringes, as multidose vials because contain preservative:

<table>
<thead>
<tr>
<th>LMWH</th>
<th>&lt;50kg</th>
<th>51-69kg</th>
<th>70-89kg</th>
<th>&gt;90kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>5000units b.d</td>
<td>7500units am</td>
<td>10000units am</td>
<td>10000units b.d</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>40mg bd</td>
<td>60mg bd</td>
<td>80mg bd</td>
<td>100mg bd</td>
</tr>
</tbody>
</table>

36.73 Additional actions for DVT

- Elevate leg
- Graduated elastic compression stockings*

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- Involve tissue viability team as needed
- Encourage mobilisation

36.74 Iliac vein VTE
- Consider use of temporary inferior vena cava filter

36.75 Massive PE
- Unfractionated heparin intravenously, as per section 2.3
- Consider thrombolysis, as per section 2.8

36.76 Any diagnosed thromboembolic disease:
- Continue anticoagulation throughout pregnancy and the puerperium
- NB. Oral anticoagulants are contraindicated in pregnancy (but can be used in the puerperium [6 weeks post-partum])

36.77 *Post thrombotic syndrome is particularly common following pregnancy related DVT, with progression to varicose venous insufficiency, such that women may be encouraged to use compression stockings for at least two years and also as prophylaxis in further pregnancies.

36.78 Such cases can be discussed with a Haematology Consultant and can be referred for follow-up in the joint Haematology Obstetric Clinic.

36.79 **Pregnancy in patients on warfarin:**
36.80 Organogenesis occurs during the 6th to 12th weeks of gestation, exposure to warfarin during this period carrying the greatest risk of embryopathy. Abnormalities may occur even if exposure only starts after 12 weeks and so warfarin is generally avoided throughout pregnancy. Patients should be advised of this risk. Pregnancy is best planned and confirmed before 6 weeks gestation to allow liaison on switching to heparin prophylaxis. This can be urgently arranged with the Haematology Department.

36.81 Thromboprophylaxis during pregnancy, labour and after vaginal delivery

36.82 The Trust guidance is available on the intranet, with respect to that from the Royal College of Obstetricians and Gynaeologists: Thrombosis and Embolism during Pregnancy and the Puerperium, Reducing the Risk (Green-top 37).

36.83 For women with a personal history of VTE or other specified risk, advice may be obtained from either the Consultant Obstetrician or Haematologists, or by referral to the monthly Joint Haematology Obstetric Clinic (Department of Haematology)

36.84 With respect to caesarean section see Trust document library.
36.85 The investigation, management and prevention of venous thrombosis in children

36.86 A rational basis for the investigation and management of children age 1 month–16 years with VTE, including cerebral venous thrombosis (CVT), is outlined in the British Committee for Standards in Haematology (2011) guideline: The investigation, management and prevention of venous thrombosis in children.

37 Surgery/invasive procedures in anticoagulated patients:

37.57 Anti-platelet agents (aspirin, clopidogrel, dipyridamole, prasugrel, ticlopidine and Ticagrelor).

37.58 The following is recommendations for patients who are assessed as at risk for thrombosis and so due either heparin or rivaroxaban thrombo-prophylaxis for elective or emergency surgery.

37.59 Guidance for elective surgery

37.60 These drugs inhibit platelet function and whilst ideally best avoided in the 7 days prior to surgery, however, usually these drugs are for a medical indication e.g. significant vascular ischaemia and then the need for continuing therapy should be considered with their clinician or cardiologist as often the indication(s) are complex, such that universal rules cannot be written. If the drug is continued this should be at a minimum dose/schedule with close attention given to any undue surgical haemorrhage, with general guidance:

- Single agent aspirin may generally continue, especially if 75mg, whilst larger doses can be empirically be reduced to 75mg for the surgery.
- Single agent clopidogrel (usually for ischaemic stroke prophylaxis) can be stopped one week pre-operatively and if tolerant and necessary replaced with aspirin 75mg.
- Dual Aspirin and clopidogrel or prasugrel or ticagrelor for cardiovascular disease should not be stopped without discussion with the patient’s clinician or cardiologist. Some patients may be able to stop clopidogrel.
- If patient is to undergo elective surgery and anti-platelet effect is not required Ticagrelor (Brilique®) should be discontinued 7 days prior to surgery. Use of Ticagrelor indicates recent cardiac event so should not be stopped without consultation with cardiology. Prescribing Ticagrelor alongside strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, nefazodone, ritonavir, and atazanavir) is contraindicated, and any such co-administration may lead to a substantial increase in exposure to ticagrelor.
- Patients who have had previous ischaemic stroke or TIA can be switched from on clopidogrel or dipyridamole to aspirin.
• Where a decision in elective orthopaedic hip or knee venous surgery thromboprophylaxis not to use rivaroxaban, aspirin is not supported by NICE 2010 and so heparin should be administered

• Prior to discharge consider advising on recommencing previous therapy.

37.61 **Guidance for emergency surgery**

37.62 **Clopidogrel** is a pro-drug. The active metabolite circulates for approximately 18 hours after the most recent dose and permanently inhibits any platelets present during this time (whether endogenous or transfused).

• Platelet therapy during this time is unlikely to be helpful.

• If possible, emergency surgery is best delayed for at least 24 hours after the last dose of clopidogrel.

Ischaemic stroke:

• stop drug(s)

• **Document time of last dose**

• operate 24 hours post last dose and restart 24 hours post op if haemostasis achieved

Coronary artery stents:

• **seek advice from cardiologists**

37.63 **Vitamin K antagonists eg warfarin**

37.64 The thrombotic risk is dependent on the underlying indication for anticoagulation and the patient's general health. Surgery increases the risk for venous thrombosis, but not arterial thrombosis. Generally procedures require discontinuation of warfarin.

37.65 "Bridging" anticoagulation describes the administration of a short-acting anticoagulant, consisting of subcutaneous (SC) low-molecular-weight heparin (LMWH) or IV unfractionated heparin (UFH), over the pre and post-operative periods during interruption of VKA therapy when the international normalized ratio (INR) is below the therapeutic range. With LMWH for surgeries at high risk of haemorrhage post-operatively a preventative dose may be appropriate (appendix 2)

37.66 In patients with chronic AF routine bridging is not required unless patients are at high risk for arterial embolism with a mitral mechanical heart valve, or have had embolic stroke, systemic embolism or TIA within the previous 12 weeks

37.67 Once the INR is <2.0 the patient may proceed to surgery/investigation.

37.68 General recommendations are made. For patients with mechanical heart valves the per-operative care needs to be planned with their Cardiologist, who will specify the required anticoagulation schema. Specific management may be also needed, for example in cases of recurrent thrombosis in association with
adenocarcinoma or thrombophilia, when there is a particularly high risk of venous thrombosis. Advice can be obtained from Anticoagulant Service/DVT Clinic or the Consultant Haematologists.

<table>
<thead>
<tr>
<th>Clinical indication</th>
<th>Pre-operatively once INR sub-therapeutic and continued post-operatively until INR therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute venous thrombosis Within first 3 months</td>
<td>iv UF or sc LMW therapeutic (bridging) dose heparin (see Appendix 2)</td>
</tr>
<tr>
<td>After 3 Months on continuing warfarin</td>
<td>sc LMW heparin prophylactic dose as in patient</td>
</tr>
<tr>
<td>Recurrent venous thrombosis</td>
<td>sc LMW heparin prophylactic dose as in patient</td>
</tr>
<tr>
<td>Acute arterial embolism Within first month</td>
<td>iv UF therapeutic dose heparin</td>
</tr>
<tr>
<td>After first month</td>
<td>sc LMW heparin prophylactic dose as in patient</td>
</tr>
<tr>
<td>AF and, or MS without previous thrombosis. Low risk surgery</td>
<td>sc LMW heparin prophylactic dose as in patient</td>
</tr>
<tr>
<td>Moderate/high risk surgery</td>
<td>sc LMW heparin prophylactic dose as in patient</td>
</tr>
<tr>
<td>AF and, or MS with previous thrombosis, or considered high risk*</td>
<td>sc LMW therapeutic (bridging) dose or IV UF heparin (see Appendix 2)</td>
</tr>
<tr>
<td>Mechanical heart valve</td>
<td>Consult patient’s Cardiologist</td>
</tr>
</tbody>
</table>

37.69 *In patients with chronic AF, risk stratification for thrombotic events can be based on the CHADSVASC$_2$ score, validated in a non peri-operative setting and this may be applicable in the peri-operative setting to define those patients at higher risk. Patients should be considered for bridging if they have three or more of the following risk factors:

- Congestive Cardiac failure
- Hypertension (>140/90mmHg or on medication)
- Age >75 years
- Diabetes Mellitus

37.70 For complex cases of venous thrombo-embolism for example recurrent thrombosis or where a patient has had thrombosis despite prophylaxis, advice can be obtained from Anticoagulant Service/DVT Clinic or the Consultant Haematologists
Surgery/invasive procedures in warfarin patients general protocol:
- Patients should be on a stable warfarin dose
- Warfarin should be omitted for at least 5 days “pre-operatively”
- INR should be checked on the pre-operative/operative day
- Where indicated, once the INR is subtherapeutic commence heparin, either as daily low molecular weight preparation (LMW) or unfractionated heparin (UF), as per the above table:
  - **sc LMW prophylactic dose dalteparin** should be prescribed at the higher-dose schedule ie 5,000 units sc nocte commencing on the pre-procedure eve or when more intensive heparin cover is required either:
    - **sc LMW therapeutic dose dalteparin daily**, as per Appendix 2 provided renal function is adequate (creatinine clearance >= 30 ml/min in which case substitute enoxaparin as per appendix 1, or
    - **iv UF heparin**:
      - **pre-op** - prescribe as per section 2.6
      - the infusion should be discontinued 6 hours pre-operatively
      - **post-op** - provided haemostasis is satisfactory, restart 48 hours post-operatively without a loading dose at the pre-operative rate.
  - If a patient requires urgent surgery, given its short half-life, iv UF heparin may be the option of choice.
    - provided there is no excessive post-operative bleeding warfarin can be restarted at the usual dose once the patient can take oral medication.
    - Heparin is discontinued once the INR is therapeutic

37.71 For patients with mechanical heart valves, where the Cardiologist has indicated a requirement for per-operative cover with heparin:
- Patients should be on a stable warfarin dose
- Warfarin should be omitted for at least 5 days “pre-operatively”
- INR should be checked on the pre-operative/operative day
- Where indicated, once the INR is subtherapeutic commence heparin as:
  - **sc LMW therapeutic dose dalteparin daily** as per Appendix 2, provided renal function is adequate (creatinine clearance >= 30 ml/min in which case substitute enoxaparin as per appendix 1, or
  - **iv UF heparin**:
    - **pre-op** - prescribe as per section 2.6.
    - the infusion should be discontinued 6 hours pre-operatively
    - **post-op** - provided haemostasis is satisfactory, restart 48 hours post-operatively, without a loading dose at the pre-operative rate, or
  - Restart warfarin at the usual dose once the patient can take oral medication.
  - Heparin is discontinued once the INR is therapeutic
37.72 Alternately, in specific cases it may be preferable to continue with warfarin (e.g. patients with previous heparin induced thrombocytopaenia, or when the risk of bleeding is low):
- Patients should be on a stable warfarin dose
- The warfarin dose is titrated for 2 days pre-operatively against the INR test ratio to attain a target of 2-2.5 pre-op (as per BNF section 2.8.2).
- If there is no post-operative bleeding warfarin can be started at the usual dose on the post-operative evening then dosed as per daily INR.

37.73 Not all surgery will require anticoagulant dose modification, eg dental surgery and minor oral/maxillofacial procedures:
- For stably anticoagulated patients on oral vitamin K antagonist anticoagulants (eg Warfarin), a check INR is recommended 72 hours prior to dental surgery
- Oral anticoagulants should not be discontinued in the majority of patients requiring out-patient dental surgery including dental extraction with a stable INR in the therapeutic range 2.0-4.0. For stable anticoagulated patients prescribed a single dose of antibiotics as prophylaxis against endocarditis, there is no necessity to alter their anticoagulant regimen.
- Bleeding risk may be minimised by
  - the use of oxidised cellulose (Surgicel) or collagen sponges and sutures and
  - 5% tranexamic acid, 10mls of a 5% solution as a mouthwash, used four times a day for 2 days. Tranexamic acid mouthwash is not readily available in most primary care dental practices, but can be ordered through community pharmacies.
- Such patients taking should not be prescribed non-selective NSAIDs or COX-2 inhibitors as analgesia following dental surgery.

37.74 Urgent reversal of warfarin to enable surgery/invasive procedures:
- For surgery that requires reversal of warfarin and that can be delayed for 6–12 hours, the INR can be corrected by giving intravenous vitamin K.
- If a patient’s pre-operative INR is >1.5-2.0, then give a titrated dose ie 500mcg-2mg of vitamin K, intra-venously, which will reduce the INR generally within 3-4 hours.
- Such doses of vitamin K will not generally make patients resistant to the post-operative re-introduction of warfarin,
- For surgery that requires reversal of warfarin and which cannot be delayed, for vitamin K to have time to take effect the INR can be corrected by giving PCC and intravenous vitamin K.
- Fresh frozen plasma, is a low potency product and is not recommended for the reversal of warfarininisation
- PCC should not be used to enable elective or non-urgent surgery (2C).
• restart warfarin once the patient can take oral medication,
  o if preoperatively they were within their target range at the usual dose
  o if preoperatively they were outside their target range, or there are circumstances eg medication that might potentiate warfarin, adjust the dose.

37.75 Patients on acenocoumarol and surgery/invasive procedures
• For the minority of patients on acenocoumarol (Sinthrome ®) this has a half life of 8-11 hours and should broadly be managed as above other than for the timing of omission prior to elective surgery of or procedures for whom acenocoumarol should be omitted for at least 3-4 days “pre-operatively”

37.76 Direct oral anticoagulants (apixaban, Edoxaban, dabigatran elixate and rivaroxaban) and surgery/ invasive procedures
These agents are direct inhibitors of coagulation. Apixaban and rivaroxaban inhibit activated factor X (anti-Xa), with maximum concentrations appearing 2 - 4 hours after tablet intake and in the presence of adequate stable renal function, mean half-lives of about 7-14 hours. For dabigatran inhibits activated factor II (anti-IIa), with the peak plasma concentration and anticoagulant effect achieved within 2-3 h of oral administration and a mean half-life between 12-17 hours.

37.77 With respect to elective and emergency surgery or invasive procedures, the issues are the safe timing of the procedure from discontinuation of the drug, the timing and dose for post-operative re-introduction of drug and the advisability of other anticoagulation such as LMWH for temporary prophylaxis of venous and or arterial thrombosis.

37.78 SPC licensed product information, available from the EMC website, is limited to pre-procedure and the following Trust guidance is derived from these together with expert opinion including that of the European Heart Rhythm Association Practical Guide (2013) as follows:

37.79 Summary:
37.80 Discontinuation of novel oral anticoagulants (apixaban, dabigatran elixate and rivaroxaban) prior to an elective procedure.

• Assess the surgery or intervention for risk of bleeding (see Appendix 3 Classification of Bleeding Risk Associated with Procedure)
• For procedures with a low risk for haemorrhage interruption of drug may not be necessary, rather as per current practice for coumarin therapy
• Since patients with renal impairment may exhibit elevated concentrations of these drugs, it may be beneficial to check serum creatinine several days prior to elective surgery and calculate the CrCl
• If an invasive procedure or surgical intervention is required, apixaban, dabigatran elixate, or rivaroxaban should be stopped at least 24 hours or more before the intervention, based on the clinical complexity of surgery, the risk for haemorrhage and renal function, specific derived guidance for timing is suggested as follows:
Apixiban, Rivaroxaban, Dabigatran and Edoxaban

Normal renal function and low risk bleeding procedure - Stop ≥ 24 hours before
Normal renal function and high risk bleeding procedure – Stop ≥48 hours before

For patients with impaired renal function refer to the following table:

<table>
<thead>
<tr>
<th>Renal Function (CrCl/ min)</th>
<th>Estimated half-life (hours)</th>
<th>Low Bleeding risk procedure</th>
<th>High Bleeding risk procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>13</td>
<td>24 hours</td>
<td>48 hours</td>
</tr>
<tr>
<td>&gt;50 to &lt;80</td>
<td>15</td>
<td>24-48 hours</td>
<td>48-72 hours</td>
</tr>
<tr>
<td>&gt;30 to &lt;50</td>
<td>18</td>
<td>48-72 hours</td>
<td>96 hours</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>9</td>
<td>24 hours</td>
<td>48 hours</td>
</tr>
<tr>
<td>&lt;30</td>
<td></td>
<td>48 hours</td>
<td>72 hours</td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>8</td>
<td>24 hours</td>
<td>48 hours</td>
</tr>
<tr>
<td>&lt;30</td>
<td></td>
<td>48 hours</td>
<td>72 hours</td>
</tr>
<tr>
<td>Edoxaban</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>12</td>
<td>24 hours</td>
<td>48 hours</td>
</tr>
<tr>
<td>&lt;30</td>
<td></td>
<td>48 hours</td>
<td>72 hours</td>
</tr>
</tbody>
</table>

For patients with AF and risk factors, or VTE within 3 months, following discontinuation of dabigatran at 96 hrs (and wash out of the drug), consider for therapeutic bridging with LMWH. For those patients with renal impairment ie creatinine clearance < 80 ml/min, therapeutic bridging should be with attenuated dose enoxaparin administered from 48 to 24 hours pre-operation or procedure

37.81 Urgent surgery

- Assess the interval since the last dose of medication and renal function
- If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
- For patients taking Dabigatran only Praxbind® can be used for urgent reversal (see section 33.54)
- Consider a coagulation screen and for Dabigatran a thrombin time, to estimate the presence of a therapeutic dose
- In the event of unexpected haemorrhage follow guidance as per section 33.13

37.82 Recommencing apixaban, dabigatran elixate, or rivaroxaban post procedure
37.83 Evidence is currently limited however on the basis of pharmacokinetics and experience with heparin therapy it is suggested that:

- For procedures with immediate and complete haemostasis, apixaban, dabigatran elixate, or rivaroxaban can be resumed 6-12 h after the intervention, including after atraumatic spinal/epidural anaesthesia or clean lumbar puncture (i.e. non-bloody tap).
- For many surgical interventions, however, full dose anticoagulation should be deferred to at least 48 hrs post-procedure, as within the first 48-72 hrs the bleeding risk could outweigh the risk of cardio-embolism, or venous thrombosis.
- Routine thromboprophylaxis may be considered 6–8 h after the operation and continued until the apixaban, dabigatran elixate, or rivaroxaban is re-introduced. LMW heparin will generally be appropriate, but there is licensed a lower dose schedule for elective hip and knee replacement surgery for each drug.
- For patients at high risk of cardiac or venous thrombo-embolism, full dose anticoagulation can be re-introduced from 48 hrs post-procedure, provided no significant ongoing haemorrhage (which for rivaroxaban can be split into a bd schedule).
- For patients not at high risk of cardiac or venous thrombo-embolism and provided no significant ongoing haemorrhage, full dose anticoagulation can be re-introduced from 5 days post-procedure, whilst in the interim LMW heparin thromboprophylaxis considered.
- Patients at risk for bleeding or patients at risk of excessive anticoagulation, are those with renal impairment (CrCl <50 ml/min), who should be treated with caution, with as necessary monitoring of renal function.

37.84 Fondaparinux and Surgery

37.85 Patients who are to undergo coronary artery bypass graft (CABG) surgery

- In STEMI or UA/STEMI patients should not be given Fondaparinux during the 24 hours prior to procedure and may be restarted 48 hours post-operatively.

37.86 Patients who are to undergo other surgery or invasive procedures

- Patients should not be given Fondaparinux during the 24 hours prior to procedure. Fondaparinux can be restarted at least 6 hours post-operatively if haemostasis is secure and bleeding risk is low.

38 Investigation and management of venous thrombosis at unusual sites

38.1 Management of Thrombosis related to Central Venous Catheters (CVCs)

38.1.1 Central Venous Catheters are widely used for fluid resuscitation, administration of medications, transfusion therapy and blood sample acquisition. Catheter associated Thrombosis is associated with a number of complications including development of PE, recurrent thrombosis and post-thrombotic syndrome. Whilst some patients with upper limb thrombus related to CVC may be asymptomatic the presence of both pain and swelling at the site may be predictive for thrombosis.

38.1.2 The incidence of symptomatic catheter associated thrombosis of the upper extremity is about 4% in cancer patients for whom indwelling CVCs are commonly used as a means of delivering chemotherapy and supportive care.
38.1.3 Imaging should be by contrast venography and/or linography in cases of suspected catheter associated thrombosis. Contrast venography is able to demonstrate the central vasculature and therefore should also be considered in all cases of non-CVC related (idiopathic) upper limb thrombosis as it may help support decision for thrombolysis and longer term management. The routine use of D-dimer is not advocated in patients with suspected upper limit thrombosis.

38.1.4 The aim of treatment for catheter related DVT is to improve symptoms of the acute thrombosis, restore lumen patency and prevent recurrence of VTE. Treatment with anticoagulation is recommended as per the guidance for treatment of lower limb DVT. Treatment should be for a minimum of 3 months and should continue as long as the catheter remains in place.

38.2 Guidance on the acute treatment of CVC related thrombosis in cancer patients:

- Patients should be anticoagulated with therapeutic dose low molecular weight heparin only (See Section 15) without removal of the catheter if the central venous catheter is functional and required for ongoing therapy.
- Anticoagulation should be continued for a minimum of 3-6 months and treatment should be extended for patients with ongoing risk factors and where the catheter remains in place.
- Non-functional, infected, or incorrectly positioned catheters should be removed and the patient subsequently anticoagulated with low molecular weight heparin.
- A short duration of anticoagulation (3 to 5 days), if clinically practical, is recommended prior to removal of a central venous catheter.
- If therapeutic anticoagulation cannot be safely administered due to active risk of haemorrhage then the CVC should be removed without anticoagulation.
- Anticoagulation is preferable to thrombolysis for the acute management of catheter associated thrombosis. Consideration of clot-directed thrombolysis should be reserved for cases of massive clot burden and/or refractory thrombosis.

38.3 Guidance on the acute treatment of CVC related thrombosis in non-cancer patients:

- Patients should be anticoagulated with treatment dose low molecular weight heparin (see section 15) switching to VKA eg Warfarin. The Central venous catheter should not be removed if it is functional and required for ongoing therapy (tunnelled lines only).
- Generally temporary (non-tunnelled) CVC should be removed and if required re-sited in line with local policies and procedures for the management of CVC.
- Anticoagulation should be continued for a minimum of 3-6 months and treatment should be extended for patients with ongoing risk factors and where the catheter remains in place.

38.4 Guidance on the management of other unusual venous thrombosis, specifically in the cerebral and sinus circulation, retinal vein, upper limb, IVC, abdominal, genitourinary system and also superficial vein thrombosis of the lower limb is available from the British Committee for Standards in Haematology website www.bcsvguidelines.com.
39 **Guidance on travel and venous thrombosis**
This is available on the intranet Trust Document Library.

40 **Clinical governance.**

40.57 Audit of defined criteria is recommended to monitor local practice, which can be specialty specific and best done as part of a rolling programme. Suggested criteria for audit could include:

40.58 Venous thrombo-embolism prophylaxis.

40.1 **Risk assessment, prophylaxis and documentation** in accordance with the NICE Quality Standards (available via the NICE website as the ‘VTE prevention quality standard’):

1. All patients, on admission, receive an assessment of VTE and bleeding risk using the clinical risk assessment criteria described in the national tool.
2. Patients/carers are offered verbal and written information on VTE prevention as part of the admission process.
3. Patients provided with anti-embolism stockings have them fitted and monitored in accordance with NICE guidance.
4. Patients are re-assessed within 24 hours of admission for risk of VTE and bleeding.
5. Patients assessed to be at risk of VTE are offered VTE prophylaxis in accordance with NICE guidance.
6. Patients/carers are offered verbal and written information on VTE prevention as part of the discharge process.
7. Patients are offered extended (post hospital) VTE prophylaxis in accordance with NICE guidance.

The incidence of VTE in hospital patient groups

The haemorrhagic risk with prophylaxis

Patient information

Therapeutic anticoagulation

Heparinisation for Venous thrombo-embolic disease (DVT and PE), cardiac arterial disease and Stroke Thrombolysis

For low molecular and unfractionated heparin: Dosing, monitoring and adverse events

Warfarin: compliance with loading schedule, days to target INR, adverse events
Use of Graduated Elastic Compression Stockings

Use of Inferior vena caval (IVC) filters.

Complications of therapeutic anticoagulation.

Bleeding: Adequacy of reversal

Heparin induced thrombocytopenia (HIT).

Discharge of patients on anticoagulants, education, the Therapeutic anticoagulation discharge pro-forma

The DoH Anticoagulant Therapy Record

Liaison with primary care.

Special circumstances.

Pregnancy: Diagnosis of VTE, therapy and thromboprophylaxis during pregnancy and labour.

Surgery/invasive procedures in-patients on anticoagulants (including anti-platelet agents).

41 Dissemination and Implementation

41.57 This guidance is available through the Trust intra-net and internet, the update being communicated to all clinical staff members.

41.58 Training for medical staff is undertaken for the induction of F1/2 doctors, with additional teaching sessions and competency assessment. Nurse teaching is also undertake.
## 42 Monitoring compliance and effectiveness

| Element to be monitored | VTE risk assessment as per national CQUIN process  
|                        | VTE assessment and appropriate prescription rolling pharmacy audit  
|                        | Pharmacy audit of INR’s >6  
|                        | Speciality and Divisional audits |
| Lead                   | Dr MD Creagh Thrombosis Lead and Pharmacy safety pharmacists |
| Tool                   | Business Unit collation of CQUIN data  
|                        | Pharmacy audits  
|                        | Speciality audits and collation of data to the Thrombosis Prevention and Anticoagulation Committee |
| What tool will be used to monitor/check/observe/assess/inspect/authenticate that everything is working according to this key element from the approved policy? | Attach the tool to the policy or no one will know what you are monitoring. |
| Frequency              | CQUIN monthly data collection  
|                        | Monthly Pharmacy audits  
| How often is the need to monitor each element? |  |
| How often is the need to complete a report? |  |
| How often is the need to share the report? |  |
| Individualise the timeframe(s) |  |
| Reporting arrangements  | Thrombosis Prevention and Anticoagulation Committee  
|                        | Who or what committee will the completed report be sent to. |
| How will each report be interrogated to identify the required actions and how thoroughly should this be documented in e.g. meeting minutes. | The lead or committee is expected to read and interrogate the report to identify deficiencies in the system and act upon them  
| Consider stating this responsibility in committee terms of reference |  |
| Acting on recommendations and Lead(s) | Which committee, department or lead will undertake subsequent recommendations and action planning for any or all deficiencies and recommendations within reasonable timeframes?  
| Required actions will be identified and completed in a specified timeframe |  
| Consider stating this responsibility in committee terms of reference |  |
| Change in               | How will system or practice changes be implemented the lessons |
practice and lessons to be shared

Possible wording to use for this column. Required changes to practice will be identified and actioned within … (state a specific time frame). A lead member of the team will be identified to take each change forward where appropriate. Lessons will be shared with all the relevant stakeholders.

43 Updating and Review

43.57 When significant new guidance or licensing of medications occurs, revision to the guidance will be considered by the Thrombosis Prevention and Anticoagulation Steering Group and as necessary updated ahead of the planned review.

44 Equality and Diversity

44.57 This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the 'Equality, Diversity & Human Rights Policy' or the Equality and Diversity website.

44.2 Equality Impact Assessment
The Initial Equality Impact Assessment Screening Form is at Appendix 8.
Appendix 1: Licensed use of enoxaparin (Clexane®) LMWH in severe chronic renal failure.

1. A dosage adjustment is required for patients with severe but chronic stable renal impairment (creatinine clearance < 30 ml/min), according to the following tables, since enoxaparin exposure is significantly increased in this patient population:

<table>
<thead>
<tr>
<th>Dosage adjustments for therapeutic dosage ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard dosing schedule</strong></td>
</tr>
<tr>
<td><strong>Severe chronic renal impairment schedule</strong></td>
</tr>
<tr>
<td>Venous thrombosis 1.5 mg/kg once daily</td>
</tr>
<tr>
<td>Acute ST-segment elevation Myocardial Infarction:</td>
</tr>
<tr>
<td>IV bolus of 30mg plus a 1mg/kg SC dose followed by 1mg/kg SC twice daily</td>
</tr>
<tr>
<td>Acute STEMI in patients ≥ 75 years of age 0.75mg/kg SC twice daily without initial bolus</td>
</tr>
<tr>
<td>Arterial disease 1 mg/kg twice daily</td>
</tr>
<tr>
<td>Pre-operative “bridging” 1.5 mg/kg once daily</td>
</tr>
<tr>
<td>Post-operative “bridging” 0.75mg/kg twice daily</td>
</tr>
</tbody>
</table>

For obese patients >150kg it is suggested that a risk assessment should be made and that it may be reasonable to limit the total daily dose to 150mg.

2. Dosage adjustments for prophylactic dosage ranges

<table>
<thead>
<tr>
<th>Standard dosing</th>
<th>Severe renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg once daily</td>
<td>20 mg once daily</td>
</tr>
<tr>
<td>20 mg once daily</td>
<td>20 mg once daily</td>
</tr>
</tbody>
</table>

3. The recommended dosage adjustments do not apply to the haemodialysis indication.

4. **Monitoring**: Risk assessment and clinical monitoring are the best predictors of the risk of potential bleeding. Routine anti-Xa activity monitoring is usually not required. However, anti-Xa activity monitoring might be considered in those patients treated with LMWH who also have either an increased risk of bleeding (such as those with renal impairment, elderly and extremes of weight) or are actively bleeding.

5. Refer to the SMC on the EMC website for further details.
Appendix 2: LMW heparin bridging anticoagulation during interruption of vitamin K antagonists eg warfarin, for patients requiring more intensive maintenance of anticoagulation peri-invasive procedure.

General indications:
AF: High risk for arterial embolism with a mitral mechanical heart valve, MS or chronic atrial fibrillation with embolic stroke, systemic embolism or TIA within the previous 12 weeks
VTE: if within the previous 12 weeks or post-operatively despite prophylaxis should be considered for bridging therapy with treatment dose LMWH

### Peri-procedural anticoagulation regimen

<table>
<thead>
<tr>
<th>Day</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>-7 to -10</td>
<td>Assess for peri-procedure bridging anticoagulation,</td>
</tr>
<tr>
<td></td>
<td>Classify patients as undergoing high-bleeding-risk or non-high bleeding risk procedure (see table below)</td>
</tr>
<tr>
<td>-7</td>
<td>Review anti-platelet drugs</td>
</tr>
<tr>
<td></td>
<td>Review non-steroidal anti-inflammatory medication</td>
</tr>
<tr>
<td>-5</td>
<td>Stop warfarin (or phenindione, NB for sinthrome stop day -4 day)</td>
</tr>
<tr>
<td>-2 ( or If a recorded INR has fallen below target)</td>
<td>Start dalteparin <strong>200</strong> units/kg once daily in morning (see section 15. Dalteparin schedule) <strong>Maximum 18,000 units once daily.</strong></td>
</tr>
<tr>
<td>-1</td>
<td>Last pre-procedural dose of dalteparin administered not less than 24 hours pre surgery or procedure (inc epidural*)</td>
</tr>
</tbody>
</table>

**Non-high bleeding risk procedure** provided haemostasis secured otherwise delay

<table>
<thead>
<tr>
<th>Day</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Assess post procedural haemostasis if secured resume previous maintenance dose of warfarin on evening of or day after procedure, provided patient able to take oral therapy</td>
</tr>
<tr>
<td></td>
<td>No dalteparin</td>
</tr>
<tr>
<td>+1</td>
<td>dalteparin (prophylaxis)</td>
</tr>
<tr>
<td></td>
<td>5000 units SC once daily</td>
</tr>
<tr>
<td>+2 and +3</td>
<td>dalteparin (therapeutic)</td>
</tr>
<tr>
<td></td>
<td><strong>100</strong> units/kg <strong>twice</strong> daily</td>
</tr>
<tr>
<td></td>
<td>(to facilitate withdrawal of heparin if significant bleeding)</td>
</tr>
<tr>
<td>+4 onwards</td>
<td>INR testing</td>
</tr>
<tr>
<td></td>
<td>Stop dalteparin if INR therapeutic, or if needs consider switch to 200 units/kg once daily if discharged before INR is therapeutic</td>
</tr>
<tr>
<td>+7 to +10</td>
<td>INR testing</td>
</tr>
</tbody>
</table>

**High bleeding risk procedure** provided haemostasis secured otherwise delay

<table>
<thead>
<tr>
<th>Day</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dalteparin (prophylaxis)</td>
</tr>
<tr>
<td></td>
<td>5000 units SC once daily</td>
</tr>
<tr>
<td></td>
<td>dalteparin (prophylaxis)</td>
</tr>
<tr>
<td></td>
<td>5000 units SC once daily</td>
</tr>
<tr>
<td></td>
<td>dalteparin (prophylaxis)</td>
</tr>
<tr>
<td></td>
<td>5000 units SC once daily</td>
</tr>
</tbody>
</table>

**INR testing**

Stop dalteparin if INR therapeutic

INR testing

INR testing

Stop dalteparin if INR therapeutic

INR testing
*If an epidural is to be sited then consideration should be given to use of a standard dalteparin 5,000 unit prophylactic dose on the pre-operative eve.

General reported risks (over 10-18 day post-procedure period):

Non-high-bleeding-risk procedure:
- thromboembolic events c 0.4%,
- major bleeding episodes c 0.7%

Increased wound-related blood loss (precluding post-procedural dalteparin) c 5.9%.

High-bleeding-risk procedure:
- major bleeding episodes c 1.8%.

Adapted from Douketis JD, Johnson JA, Turpie AG. Arch Int Medicine 2004;164:1319

Table: Post-procedure bridging with dalteparin (non-high bleeding risk procedures), based on 100 units per kg twice daily

<table>
<thead>
<tr>
<th>Bodyweight to nearest kg</th>
<th>Anti – Xa units TWICE daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 46 kg</td>
<td>4500 units</td>
</tr>
<tr>
<td>46 – 56 kg</td>
<td>5000 units *</td>
</tr>
<tr>
<td>57 – 68 kg</td>
<td>6250 units</td>
</tr>
<tr>
<td>69 – 82 kg</td>
<td>7500 units *</td>
</tr>
<tr>
<td>83 – 100 kg</td>
<td>8750 units</td>
</tr>
</tbody>
</table>

*prefilled syringes are available for these doses. Other doses can be given using the 10,000 unit graduated syringe
### Appendix 3 continued table: Classification of Bleeding Risk Associated with Procedure

<table>
<thead>
<tr>
<th>Bleeding Risk Category</th>
<th>Surgical or other Invasive Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>Abdominal aortic aneurism repair</td>
</tr>
<tr>
<td></td>
<td>Bilateral knee replacement</td>
</tr>
<tr>
<td></td>
<td>breast cancer surgery</td>
</tr>
<tr>
<td></td>
<td>Head and neck cancer surgery</td>
</tr>
<tr>
<td></td>
<td>Intra abdominal cancer surgery</td>
</tr>
<tr>
<td></td>
<td>Kidney biopsy</td>
</tr>
<tr>
<td></td>
<td>Laminectomy</td>
</tr>
<tr>
<td></td>
<td>Transurethral prostate resection</td>
</tr>
<tr>
<td></td>
<td>Urogynaecological cancer surgery</td>
</tr>
<tr>
<td><strong>Non High (surgical procedure)</strong></td>
<td>Abdominal hernia repair</td>
</tr>
<tr>
<td></td>
<td>Abdominal hysterectomy</td>
</tr>
<tr>
<td></td>
<td>Axillary node dissection</td>
</tr>
<tr>
<td></td>
<td>Bowel polypectomy</td>
</tr>
<tr>
<td></td>
<td>Bowel resection</td>
</tr>
<tr>
<td></td>
<td>Cholecystectomy</td>
</tr>
<tr>
<td></td>
<td>Dental surgery</td>
</tr>
<tr>
<td></td>
<td>Dilation and curettage</td>
</tr>
<tr>
<td></td>
<td>Endarterectomy or carotid bypass</td>
</tr>
<tr>
<td></td>
<td>Eye surgery (including Cataract)</td>
</tr>
<tr>
<td></td>
<td>Haemorrhoidal surgery</td>
</tr>
<tr>
<td></td>
<td>Hydrocele repair</td>
</tr>
<tr>
<td></td>
<td>Orthopaedic surgery inc foot and hand surgery, hip or knee replacement and shoulder surgery Pacemaker insertion</td>
</tr>
<tr>
<td></td>
<td>Skin cancer excision</td>
</tr>
<tr>
<td><strong>Non High Risk Non Surgical Procedure</strong></td>
<td>Arthroscopy</td>
</tr>
<tr>
<td></td>
<td>Biopsy (prostate, bladder, thyroid, breast, lymph node, pancreas, myocardial or thyroid)</td>
</tr>
<tr>
<td></td>
<td>Bronchoscopy +/- biopsy</td>
</tr>
<tr>
<td></td>
<td>Central venous catheter removal</td>
</tr>
<tr>
<td></td>
<td>Cornary angiography +/- Percutan-eous intervention</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal endoscopy +/- biopsy</td>
</tr>
<tr>
<td></td>
<td>Non coronary angiography</td>
</tr>
</tbody>
</table>
**Appendix 4: Estimating the pre-test probability of Heparin induced thrombocytopenia (HIT): the 'four T's'.**

<table>
<thead>
<tr>
<th>Points (0, 1, or 2 for each of 4 categories: maximum possible score = 8)</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>&gt; 50% fall or platelet nadir 20 - 100 x 10⁹/l</td>
<td>30 50% fall or platelet nadir 10 19 x 10⁹/l</td>
<td>fall &lt; 30% or platelet nadir &lt; 10 x 10⁹/l</td>
</tr>
<tr>
<td>Timing* of platelet count fall or other sequelae</td>
<td>Clear onset between d 5–10; or less than 1 d (if heparin exposure within past 100 d)</td>
<td>Consistent with immunization but not clear (e.g. missing platelet counts) or onset of thrombocytopenia after d 10</td>
<td>Platelet count fall too early (without recent heparin exposure)</td>
</tr>
<tr>
<td>Thrombosis or other sequelae (e.g. skin lesions)</td>
<td>New thrombosis; skin necrosis; post heparin bolus acute systemic reaction</td>
<td>Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven</td>
<td>None</td>
</tr>
<tr>
<td>Other cause for thrombocytopenia not evident</td>
<td>No other cause for platelet count fall is evident</td>
<td>Possible other cause is evident</td>
<td>Definite other cause is present</td>
</tr>
</tbody>
</table>

**Pretest probability score: 6 8 = High; 4 5 = Intermediate; 0 3 = Low**

*First day of immunizing heparin exposure considered d 0; the day the platelet count begins to fall is considered the day of onset of thrombocytopenia (it generally takes 1 3 d more until an arbitrary threshold that defines thrombocytopenia is passed.


- In making a diagnosis of HIT the clinician's estimate of the pre-test probability of HIT together with the type of assay used and its quantitative result (ELISA only) should be used to determine the post-test probability of HIT. Grade C Level IV.
- Clinical decisions should be made following consideration of the risks and benefits of treatment with an alternative anticoagulant. Grade C level IV
- For patients with strongly suspected or confirmed HIT heparin should be stopped and full dose anticoagulation with an alternative such as lepirudin or danaparoid commenced (in the absence of a significant contraindication). Grade B level III
Appendix 5: Royal Cornwall NHS Trust: Oral Anticoagulant Discharge pro-forma
<table>
<thead>
<tr>
<th>Target INR</th>
<th>Acceptable INR range</th>
<th>Clinical indication</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>2.0-3.0</td>
<td>Calf DVT - post-op no persistent risk factors</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calf DVT – non-surgical 1st event provoked proximal DVT or PE, 2nd provoked DVT and, or PE</td>
<td>3 months, at least 3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unprovoked 1st event PE</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent unprovoked DVT and, or PE while not on warfarin</td>
<td>3 months, then consider risk/benefit of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DVT/PE with inherited thrombophilia</td>
<td>long-term</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antiphospholipid syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatic mitral valve disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mural thrombus, cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>bio-prosthetic valves</td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>2.5-3.5</td>
<td>Cardioversion</td>
<td>3 weeks before and 4 weeks after cardioversion</td>
</tr>
<tr>
<td>3.5</td>
<td>3.0-4.5</td>
<td>Recurrent DVT and PE, whilst on therapeutic warfarin</td>
<td>Long-term</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mechanical prosthetic valves (but also subject to Cardiologist’s decision)</td>
<td>Long-term</td>
</tr>
</tbody>
</table>

DO NOT FAX THIS SIDE TO THE GP!

Written by: Anticoagulation Policy Steering Group
Royal Cornwall Hospitals Trust, Truro.
Appendix 6: Rivaroxaban in orthopaedic prophylaxis and antiplatelet therapy

**Rivaroxaban (Xarelto)**

### Indications for Rivaroxaban
- Total hip replacement
- Total knee replacement
- Partial knee replacement
- Hip Resurfacing
- Revision knee surgery
- Revision hip surgery

If surgery completed during morning then give at 2200 hours.
If surgery completed in afternoon then give dose at 0600 hrs next day.

### Dosage
- Single daily dose of 10mg OD
- Treatment duration TKR 2 weeks & THR 5 weeks
- If dose is missed, rivaroxaban should be given immediately and then continue the following day with once daily intake.
- Can be taken with or without food

### For patients with epidurals prescribe as follows
- Dalteparin 5000 units 2200 hrs post surgery
- Dalteparin 5000 units 2200 hrs day 2
- Rivaroxaban 10mg 2200 hrs day 3
- Continue Rivaroxaban until pack is empty

### AES (TED) stockings
All patients to receive TEDs but discontinue after discharge unless immobile or non weight bearing

### Contraindications to Rivaroxaban
- Patients on Warfarin
- Patients who continue on Aspirin/Clodigogral (cardiac intervention within 12 months) eg stenting
- Acute acute gastro-intestinal, or cerebral bleeding.
- Interacting drugs – can reduce effectiveness or increase risk of bleeding (see below "Interactions with medicinal products")
- Clinically significant active bleeding.
- Severe renal failure (eGFR <15ml/min). Use with caution if eGFR 15-29ml/min as increased risk of bleed due to higher plasma concentrations.
- Severe hepatic impairment & hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Pregnancy & lactation
- Patients under 18 years
- Hypersensitivity to the active substance or to any of the excipients

### For patients with contraindications to Rivaroxaban
- Dalteparin 5000 units 2200 hrs post surgery
- Daily until discharge

Make sure you send the patient home with Chemical prophylaxis as per Trust Thrombosis Prevention and Anticoagulation Policy (TPAP)

### Interactions medicinal products
- The use of rivaroxaban is not recommended in patients receiving concomitant systemic treatment with strong CYP3A4 inhibitors & P-450 inhibitors and HIV protease inhibitors. This interaction can lead to increased levels of rivaroxaban & therefore increased risk of bleeding. Examples: ketoconazole, iraconazole, voriconazole, posaconazole and ritonavir. Fluconazole is expected to have less effect on rivaroxaban exposure and can be co-administered with caution.

- The concomitant use of rivaroxaban with strong CYP3A4 inducers may lead to reduced rivaroxaban plasma concentrations and therefore effectiveness. Examples: rifampicin, phenytoin, carbamazepine, phenobarbital and St John’s Wort.

- Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as NSAIDs, acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents. Furocoumarin would be the NSAID of choice if necessary. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered.

For more detailed information on rivaroxaban, see the summary of product characteristics at www.medicines.org.uk/emc/

For more detailed information on rivaroxaban, see the summary of product characteristics at www.medicines.org.uk/emc/

And Trust Thrombosis Prevention and Antiocoagulation Policy (TPAP)

http://intra.cornwall.nhs.uk/DocumentsLibrary/RoyalCornwall Hospitals Trust Thrombosis Prevention and Anticoagulation Policy (TPAP)

Rivaroxaban protocol by R Kincaid and M Daoud 2011 version 2
DOES YOUR PATIENT NEED RIVAROXABAN?

Do they take warfarin, aspirin, clopidogrel, or dipyridamole?

**Aspirin**
- 150mg daily or greater
- Previous cardiology intervention?
  - NO: Stop 7 days prior to surgery unless advised by cardiologist
  - YES: Continue as advised by cardiologist; consult anaesthetist & surgeon if in doubt

**Clopidogrel**
- 75mg
- Aspirin only
- Aspirin and Dipyridamole
  - • Stop pre-op.
  - • Re-start post-op
  - • Start rivaroxaban post-op

**Warfarin**
- DO NOT GIVE RIVAROXABAN
  - • Stop warfarin pre-op.
  - • Check INR on Admission.
  - • Back to warfarin post-op with LMWH until INR therapeutic – see anticoagulation policy for further info.
  - • Home on warfarin ONLY

**Clopidogrel only**
- • Consult cardiology
  - • Stop both pre-op.
  - • Re-start Asp, only post-op
  - • Start Rivaroxaban
  - • Home on Asp & Rivaroxaban only.
  - • Re-start Dip after Riv completed.

**Aspirin**
- • Consult cardiology
  - • Stop pre-op.
  - • Re-start Asp, only post-op
  - • Start Rivaroxaban
  - • Home on Asp & Rivaroxaban only.
  - • Re-start Dip after Riv completed.

Further info (for patient on aspirin)
- Diabetes – Can stop
- AF, Controlled – Can stop
- TIA can stop if not recent/recent

Previous stroke – anaesthetist to review clopidogrel
- After MI/stenting – do not stop (at least one year post)
- intolerance to aspirin – individual decision

---

Xarelto (rivaroxaban) protocol by R Kincaid and M Daoud June 2011 version 2

---
### Appendix 7. VTE risk assessment tool for non-weight bearing patient patients with Lower limb immobility in POP or airboot

<table>
<thead>
<tr>
<th>Date:</th>
<th>Dept / Ward:</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please circle all the risks listed below that apply to you and return the completed form to your nurse or doctor:

- Achilles Tendon rupture or repair
- Previous history of leg clots (DVT) or lung clots (PE)
- Pregnant or within 6 weeks of delivery
- Complex surgery of the lower leg or fracture of the pelvis within last 6 weeks
- Active cancer
- History of blood clots in close family member (mother/father/brother/sister)
- Overweight (BMI >30kg/m²) - please ask nursing staff if you are unsure of your BMI
- Unable to walk before the injury
- Age over 60 years old
- Abdominal (tummy) surgery within last 6 weeks
- Varicose veins
- Taking the Oral Contraceptive Pill or Hormone Replacement Therapy
- Any inflammatory bowel disease (Crohn’s disease or Ulcerative Colitis)

**Total Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>Recommendation</th>
<th>Tick action</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>Mobilisation as able - no prophylaxis required</td>
<td></td>
</tr>
</tbody>
</table>
| 3 or more | LMWH daily until cast removed and fully weight bearing  
eGFR >30ml/min - Dalteparin 5,000 units S/C once daily  
eGFR <30ml/min - Enoxaparin 20mg S/C once daily |            |

**Contra-indications:** To be completed by supervising health care professional

- Do not offer VTE prophylaxis with LMWH if the patient has any of the following
  - Concurrent use of oral anticoagulation (inc. Warfarin, Rivaroxaban, Apixaban or Dabigatran)
  - Acquired or inherited bleeding disorder (eg haemophilia)
  - Thrombocytopenia (platelet count < 75x10⁹/l)
  - Uncontrolled hypertension (>230/120mm/hg)
  - Active bleeding from any source

Care Plan activated by:  Sign  Print  Designation
Care Plan shared with parents:  Sign  Print  Designation
### Appendix 8. Governance Information

<table>
<thead>
<tr>
<th>Document Title</th>
<th>Thrombosis Prevention Investigation And Management Of Anticoagulation Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Issued/Approved:</td>
<td>February 2016</td>
</tr>
<tr>
<td>Date Valid From:</td>
<td>February 2016</td>
</tr>
<tr>
<td>Date Valid To:</td>
<td>February 2019</td>
</tr>
<tr>
<td>Directorate / Department responsible (author/owner):</td>
<td>Desmond Creagh, Consultant Haematologist</td>
</tr>
<tr>
<td>Contact details:</td>
<td>01872 252503</td>
</tr>
<tr>
<td>Brief summary of contents</td>
<td>This document provides all staff with clinical guidance in the prevention, management and treatment of venous thromboembolism of adult patients when in hospital</td>
</tr>
<tr>
<td>Suggested Keywords:</td>
<td>Anticoagulation, thrombosis, warfarin, haemorrhage, heparin, discharge, thromboembolism, VTE, pulmonary embolism, PE, deep vein thrombosis, DVT</td>
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<tr>
<td>Target Audience</td>
<td>RCHT</td>
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<tr>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Executive Director responsible for Policy:</td>
<td>Medical Director</td>
</tr>
<tr>
<td>Date revised:</td>
<td>16th Jan 2015</td>
</tr>
<tr>
<td>This document replaces (exact title of previous version):</td>
<td>Thrombosis Prevention Investigation And Management Of Anticoagulation Guidance v8</td>
</tr>
<tr>
<td>Approval route (names of committees)/consultation:</td>
<td>Thrombosis prevention and anticoagulant steering group</td>
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<td></td>
<td>CSSC Governance DMB</td>
</tr>
<tr>
<td>Divisional Manager confirming approval processes</td>
<td>Sally Kennedy, Divisional Director CSSC</td>
</tr>
<tr>
<td>Name and Post Title of additional signatories</td>
<td>Not Required</td>
</tr>
<tr>
<td>Name and Signature of Divisional/Directorate Governance Lead confirming approval by specialty and divisional management meetings</td>
<td>{Original Copy Signed}</td>
</tr>
<tr>
<td></td>
<td>Name: Janet Gardner, Governance Lead CSSC</td>
</tr>
<tr>
<td>Signature of Executive Director giving approval</td>
<td>{Original Copy Signed}</td>
</tr>
<tr>
<td>Publication Location (refer to Policy on Policies – Approvals and Ratification):</td>
<td>Internet &amp; Intranet ✓ Intranet Only</td>
</tr>
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<td>Document Library Folder/Sub Folder</td>
<td>Clinical / Haematology</td>
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## Links to key external standards

<table>
<thead>
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<tr>
<td><strong>NHSLA Risk Management Standard Criterion 4.8</strong></td>
</tr>
<tr>
<td><strong>NPSA</strong></td>
</tr>
<tr>
<td>- Actions that can make anticoagulant therapy safer Safety alert 18 (March 2007).</td>
</tr>
<tr>
<td>- Reducing treatment dose errors with low molecular weight heparins (2010/RRR014)</td>
</tr>
<tr>
<td><strong>NICE</strong></td>
</tr>
<tr>
<td>- Venous thromboembolism: Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital clinical guideline 92</td>
</tr>
<tr>
<td>- Venous thrombo-embolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing clinical guideline 144.</td>
</tr>
<tr>
<td>Electronic medicines compendium <a href="http://www.medicines.org.uk/emc">http://www.medicines.org.uk/emc</a></td>
</tr>
<tr>
<td>- Update to NICE clinical guideline CG92 Reducing the risk in adults admitted to hospital chapter 24 Stroke</td>
</tr>
<tr>
<td>- Update to NICE clinical guideline 144 Nov 2015 – Nice quality standard 29 statement 4 use of compression hosiery <a href="https://www.nice.org.uk/guidance/CG144/chapter/Recommendations#treatment-2">https://www.nice.org.uk/guidance/CG144/chapter/Recommendations#treatment-2</a></td>
</tr>
<tr>
<td><strong>RCHT:</strong></td>
</tr>
<tr>
<td>- Management of Acute Coronary Syndromes</td>
</tr>
<tr>
<td>- Thrombolysis for myocardial infarction</td>
</tr>
<tr>
<td>- Policy for the use of anti-embolism stockings</td>
</tr>
<tr>
<td>- Thrombosis Prevention (Venous) and Treatment of Venous Thromboembolism Policy</td>
</tr>
<tr>
<td><strong>Department of Health</strong></td>
</tr>
<tr>
<td>- Venous thrombo-embolism (VTE) risk assessment tool 2010</td>
</tr>
<tr>
<td><strong>The British Society for Haematology Committee for Standards in Haematology (BCSH) Haemostasis and Thrombosis Task Force guidance:</strong></td>
</tr>
</tbody>
</table>
Safety indicators for inpatient and outpatient oral anticoagulant care, British Journal of Haematology 2007; 136(1) 26-9
Guidelines for the management of patients on oral anticoagulants requiring dental surgery 2007. BCSH approved document

Guideline on the management of bleeding in patients on antithrombotic agents (2012)

Royal College of Obstetricians and Gynaecologists. Green top Clinical Guidelines
Hormone Replacement Therapy and Venous Thrombo-embolism (19) 2004
Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management (28)2007
Thrombosis and Embolism during Pregnancy and the Puerperium, Reducing the Risk (37) 2009

Scottish Intercollegiate Guidelines Network (SIGN).
Prevention and management of venous thromboembolism December 2010 (publication no. 122.)

The American College of Chest Physicians
- The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

International Society for Thrombosis and Haemostasis – Scientific Sub-Committee on Haemostasis and Malignancy
- Catheter associated deep vein thrombosis of the upper extremity in cancer patients: guidance form the SCC of the ISTH

Thrombosis Canada
- Guidance on central Venous Catheter-related Deep Vein Thrombosis

New England Journal of Medicine
Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation, Douketis et al June 2015

Training Need Identified?
- Dissemination through Trust communication, Medical meetings and mandatory training
<table>
<thead>
<tr>
<th>Date</th>
<th>Version</th>
<th>Summary of Changes</th>
<th>Changes Made by</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 2010</td>
<td>4</td>
<td>Reformat per NICE</td>
<td>Desmond Creagh, Chair of Thrombosis Prevention and Anticoagulation Steering Group</td>
</tr>
<tr>
<td>Nov 2012</td>
<td>5</td>
<td>Reformat per Trust standard. Complete revision of content to include best practice guidance.</td>
<td>Desmond Creagh, Chair of Thrombosis Prevention and Anticoagulation Steering Group</td>
</tr>
<tr>
<td>June 2014</td>
<td>7</td>
<td>P63 : Management of Thrombosis related to Central Venous Catheters (CVCs)</td>
<td>Desmond Creagh, Chair of Thrombosis Prevention and Anticoagulation Steering Group</td>
</tr>
<tr>
<td>March 2015</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P5: (7) Glossary, inclusion of the term DOAC (Direct Oral Anticoagulant) to reflect usage of this term throughout the guidance

P6: (8.7 + 8.8) Inclusion/amendments to guidance for treatment of patients with End Stage Renal Failure with treatment dose LMWH

P8: (8.21) Change of Title to DOAC

P9: (8.30) Amendments to the licenses for use of Apixaban

P9: (8.31) Amendments to the licences for use of Dabigatran

P18: (10.8) Amendments to prophylaxis table – recommendations for VTE prophylaxis in patients with stroke

P20: (10.19) Amendments to guidance for patients in lower limb plaster casts

P25: (14.8) Amendments reflecting removal of Dalteparin multi-dose ampoules form the Trust

P27: (15.0) Amendments to table to reflect use of pre-filled syringes of Dalteparin

P29: (18.5) additional guidance for treatment of new VTE with DOACS including dosing tables for Rivaroxaban, Apixaban and Dabigatran

P31 (23.0) Revision/update of section for anti-platelet therapy in Acute coronary syndrome in line with RCHT pathway for chest pain and acute coronary syndrome

P32 (24.0) Revision/update of section for anti-Thrombotic therapy in Acute coronary syndrome in line with RCHT pathway for chest pain and acute coronary syndrome

P36 (31.3) Amendments to table showing approved INR range for recurrent VTE and mechanical heart valves

P38 (33.1) Amendments to wording re reversal of VitK antagonists with PCC in patients with head injury

P52 (34.7) Revision of section on Argabatran including tables for administration and dosing of argabatran in HIT

P53-54 (35.0 and 35.4) – updates to section on patient information including patient information booklets in DOACS

P58-59 (37.0) updates to section on anti-platelet therapy in elective surgery to include guidance on Ticagrelor

P64 (37.24) revision to discontinuation of Dabigatran for elective surgery wording

Andrew McSorley
Lead Anticoagulation Nurse/Thrombosis practitioner
| Dec 2015 | P8 (8.22) Update to licensed drug indications for DOAC's (table)  
P10 (8.37-8.41) Addition of Edoxaban as licensed treatment option for VTE  
P10-11 (8.42) Update to table for drug interactions and contra-indications to include Edoxaban  
P18 (10.8) insertion of link to IPC protocol in stroke (within table)  
P18 (10.8) addendum to table recommending standard prophylaxis for patients with decompensated liver disease  
P29-30 (18.5) Update to title and section on direct oral anticoagulants to include Edoxaban including addendum for first line choice of Rivaroxaban or Apixaban in VTE  
P33 (27.2) Addendum recommending use of unfractioned heparin only in areas with appropriately trained staff  
P38 (33 & title page) Expansion of title to complications of therapeutic anticoagulation ‘including bleeding’  
P41 (33.21-33.22) inclusion of additional section for management of bleeding with fondaparinux  
P42 (33.33-33.34, 33.36 and algorithm p43) Addendum to actions with regard to Vit K use with recommendations for repeat INR post administration  
P49 (33.53) Removal of wording ‘in liaison with on-call haematologist’ as no longer required  
P59 (37.26) Addendum re Ticagrelor outlining potential interactions with CYP3A4 inhibitors  
P60 (37.32 and appendix 2) update/amendments to section on bridging anticoagulation in chronic AF |
| June 2016 | P10 (8.35) Amendment to include availability of Praxbind for the reversal of Dabigatran Exetilate  
P13 (8.62-8.66) Removal of section regarding supply of compression hosiery for PTS as duplicated in section 19  
P18 (10.8) Addendum to table for consideration of IPC in medical patients contra-indicated to both AES/LMWH  
P19 (10.9) Addendum to table for consideration of IPC in surgical patients contra-indicated to both AES/LMWH  
P24 (14.1) Addendum to advise against the use of D-dimer screening in pregnancy or inpatients  
P30 (19.0-19.4) Amendment to advice regarding supply of compression hosiery for PTS following results of SOX trial and NICE 144 update 2015  
P47-48 (33.51-33.56) Amendments and addendum to section of DOAC related bleeding to include the introduction of Praxbind for Dabigatran reversal  
P60 (37.69) addendum for consideration of peri-op bridging in patients with multiple risk factors  
P63 (37.84-37.86) Addendum guidance for management of Fondaparinux in Surgery  
P64 (37.80) Amendments to guidance for stopping DOACS in cases of non-emergency/elective surgery  
P64 (37.81) Addendum on the use of Praxbind for the reversal of Dabigatran in urgent surgery  
P80 (Appendix 7) – Document addition: copy of RCHT POP VTE risk assessment tool | Andrew McSorley  
Lead Anticoagulation Nurse/Thrombosis practitioner

Andrew McSorley  
Lead Anticoagulation Nurse/Thrombosis practitioner
### Appendix 9. Initial Equality Impact Assessment Screening Form

<table>
<thead>
<tr>
<th>Thrombosis prevention, investigation and management guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Directorate and service area:</strong> Medical, Nursing, Midwifery and AHP</td>
</tr>
<tr>
<td><strong>Name of individual completing assessment:</strong> Dr MD Creagh</td>
</tr>
<tr>
<td><strong>Telephone:</strong> 01872 252524</td>
</tr>
</tbody>
</table>

| 1. Procedure Aim* | To update Trust guidance for the Prevention and treatment of arterial and venous thrombo-embolism |
| 2. Procedure Objectives* | This guidance is intended to provide necessary information to enable the treatment and prevention of thrombosis. |
| 3. Procedure – intended Outcomes* | This guidance provides information on the risks and prevention of VTE in the setting of hospital in-patients and the management of venous thrombosis, together with reference to other areas of clinical practice and Trust guidance, such as ischaemic heart and cerebral disease and also special circumstances such as pregnancy. |
| 4. How will you measure the outcome? | Refer to ‘Monitoring Compliance’ section. |
| 5. Who is intended to benefit from the Procedure? | Patients |
| 6a. Is consultation required with the workforce, equality groups etc. around this procedure? | No |
| b. If yes, have these groups been consulted? | |
| c. Please list any groups who have been consulted about this procedure. | |

#### 7. The Impact

Please complete the following table.

<table>
<thead>
<tr>
<th>Are there concerns that the policy could have differential impact on:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Equality Strands:</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Sex</strong> (male, female, transgender / gender reassignment)</td>
</tr>
<tr>
<td><strong>Race / Ethnic communities /groups</strong></td>
</tr>
</tbody>
</table>

---

Thrombosis Prevention Investigation And Management Of Anticoagulation Guidance

Page 89 of 90
Disability - Learning disability, physical disability, sensory impairment and mental health problems | ✓ |
---|---
Religion / other beliefs | ✓ |
Marriage and civil partnership | ✓ |
Pregnancy and maternity | ✓ |
Sexual Orientation, Bisexual, Gay, heterosexual, Lesbian | ✓ |

You will need to continue to a full Equality Impact Assessment if the following have been highlighted:
- You have ticked “Yes” in any column above and
- No consultation or evidence of there being consultation - this excludes any policies which have been identified as not requiring consultation. or
- Major service redesign or development

8. Please indicate if a full equality analysis is recommended. | Yes | No ✓ |

9. If you are not recommending a Full Impact assessment please explain why.

Signature of policy developer / lead manager / director | Date of completion and submission |
---|---

Names and signatures of members carrying out the Screening Assessment
1.  
2.  

Keep one copy and send a copy to the Human Rights, Equality and Inclusion Lead, c/o Royal Cornwall Hospitals NHS Trust, Human Resources Department, Knowledge Spa, Truro, Cornwall, TR1 3HD

A summary of the results will be published on the Trust’s web site.

Signed ________________  
Date ________________