Anticoagulation and Thrombolysis for the Interventionalist

Sharon Jackson
Middlemore Hospital
An outline

- The problem with renal patients
- Anticoagulants in renal failure/ Novel Oral Anticoagulant drugs
- Peri-procedural haemostasis
- Peri-procedural management of the patient on anticoagulants
- Clotted grafts and catheters
  - Drug options to prevent them
  - Thrombolysis
The problem

Patients with renal failure are at increased risk of both thrombosis and haemorrhage
Chronic Kidney disease is a procoagulant state

**Endothelial factors:**
- Increased levels of VWF
- Increased levels of thrombomodulin
- Oxidative stress and reduced NO synthesis
- Increased levels of PAI-1

**Extrinsic factors:**
- Uremic toxins,
- Anaemia

**Platelet factors:**
- Increased platelet stimulation
- Contact with artificial circuit
- Hyperfibrinogenemia
- Release of growth factors that reduce blood flow in the vascular access

**Plasma factors:**
- Increased levels of thrombin
- Reduced levels and activity of antithrombin
- Reduced levels of protein C and S
- Increased levels of tissue factor
- Antiphospholipid antibodies

**Jalal DI et al; Semin Throb Hemost 2010**
Thrombosis in chronic renal disease

- Higher incidence of arterial and venous thrombosis compared to general population
- 6-fold higher risk for PE in dialysis patients
- Renal vein thrombosis and vascular access thrombosis are particularly problematic
- DVT reported in up to 15% of patients with nephrotic syndrome
- Multiple risk factors: inflammation, infection, immobility, reduced levels of endogenous anticoagulants, endothelial dysfunction, rEPO
### Pathophysiology of bleeding in renal impairment

<table>
<thead>
<tr>
<th>Defect</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelets</strong></td>
<td></td>
</tr>
<tr>
<td>Adhesion</td>
<td>Altered arachidonic acid metabolism</td>
</tr>
<tr>
<td>Secretion</td>
<td>Abnormal Ca(^{2+}) mobilisation</td>
</tr>
<tr>
<td>Aggregation</td>
<td>Decreased ADP, epinephrine, 5-HT production</td>
</tr>
<tr>
<td></td>
<td>Decreased GPIb, GPIIb-IIIa receptor function</td>
</tr>
<tr>
<td></td>
<td>Decreased Fibrinogen binding to activated plts</td>
</tr>
<tr>
<td></td>
<td>Inhibitor in uremic plasma (eg urea, guanidine-succinate)</td>
</tr>
<tr>
<td>Interaction</td>
<td>Decreased vWF activity</td>
</tr>
<tr>
<td></td>
<td>Inhibitor in uremic plasma</td>
</tr>
<tr>
<td></td>
<td>Increased Release of prostacyclin and nitric oxide</td>
</tr>
<tr>
<td><strong>RBC haematocrit</strong></td>
<td>Anaemia</td>
</tr>
<tr>
<td></td>
<td>Altered blood rheology</td>
</tr>
<tr>
<td></td>
<td>RBCs impact on platelets</td>
</tr>
<tr>
<td></td>
<td>Reduced clearance of nitric oxide</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Medications</td>
</tr>
<tr>
<td></td>
<td>Antiplatelet and anticoagulant therapy</td>
</tr>
<tr>
<td></td>
<td>Iron deficiency, malnutrition, inflammation</td>
</tr>
<tr>
<td></td>
<td>Post-operative bleeding</td>
</tr>
</tbody>
</table>

Major bleeding in HD patients

- Retrospective review of 255 pts from Jan 2002 – Jan 2004 (1028 person years of exposure)
- 25/26 major bleeds were upper or lower GI bleed; 1 = CNS

<table>
<thead>
<tr>
<th>Treatment</th>
<th># patients</th>
<th>Major bleed</th>
<th>Incidence rate</th>
<th>Hazard model for time to 1st bleed (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>178</td>
<td>4</td>
<td>0.8%</td>
<td>Reference</td>
</tr>
<tr>
<td>Warfarin</td>
<td>89</td>
<td>15</td>
<td>3.1%</td>
<td>4.1 (1.05 – 14.6)</td>
</tr>
<tr>
<td>ASA</td>
<td>107</td>
<td>12</td>
<td>4.4%</td>
<td>5.7 (1.8 – 18.0)</td>
</tr>
<tr>
<td>ASA + Warfarin</td>
<td>50</td>
<td>5</td>
<td>6.3%</td>
<td>8.2 (2.2 – 30.7)</td>
</tr>
<tr>
<td>Total</td>
<td>255</td>
<td>26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CJASN 2008;3:105-110
Anticoagulant Sites of Action

- Unfractionated Heparin
- Low Molecular Weight Heparin
- Direct Factor Xa Inhibitors
- Warfarin
- Direct Thrombin (IIa) Inhibitors

Fibrin Clot

Courtesy of Dr. J Ansell.
**LMWH dose adjustment in renal failure**

Highest MW – may be less dependent upon renal elimination  
Closest anti-Xa:IIa activity compared to heparin

<table>
<thead>
<tr>
<th>Agent</th>
<th>Average MW (daltons)</th>
<th>Anti Xa: IIa ratio</th>
<th>Dose adjustment CrCl &lt; 30 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>15,000</td>
<td>1:1</td>
<td>No</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>6,500</td>
<td>1.9:1</td>
<td>No</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>5,600</td>
<td>2.0 – 2.7:1</td>
<td>?</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>4,500</td>
<td>2.7 – 4.1:1</td>
<td>Yes (50%)</td>
</tr>
<tr>
<td>Nadropran</td>
<td>4,300</td>
<td>3.2 – 3.7:1</td>
<td>Yes (no guidelines)</td>
</tr>
</tbody>
</table>

In-hospital major Bleeding according to renal status

- Prospective, multicentre, observational registry of 11,881 ACS pts
- 40% with CrCl < 60 mL/min given LMWH (primarily enoxaparin)

No significant difference between UFH and LMWH wrt bleeding for CrCl < 30 ml/min

Collett JP et al Eur Heart J 2005;26:2285-93
Anticoagulation in Hospitalized Patients With Renal Insufficiency*: A Comparison of Bleeding Rates With Unfractionated Heparin vs Enoxaparin

CHEST. 2004;125(3):856-863. doi:10.1378/chest.125.3.856

Major Bleeding

26.3/1000 person-days UFH

20.7/1000 person-days enoxaparin
<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Vit K epoxide reductase</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Oral bioavailability</strong></td>
<td>99%</td>
<td>6 – 7%</td>
<td>60 - 80%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>T (max)</strong></td>
<td>72 – 96 h</td>
<td>2 h</td>
<td>2 – 4 h</td>
<td>3 h</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>40 h</td>
<td>14 – 17 h</td>
<td>5 – 9 h healthy 9 – 13 h elderly</td>
<td>8 – 15 h</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>INR – adjusted</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>QD</td>
<td>QD or BID</td>
<td>QD or BID</td>
<td>BID</td>
</tr>
<tr>
<td><strong>Metabolism / Elimination</strong></td>
<td>Cytochrome P450</td>
<td>80% renal 20% biliary</td>
<td>66% renal 33% biliary</td>
<td>25% renal 75% biliary</td>
</tr>
<tr>
<td><strong>Antidote or treatment of bleeding</strong></td>
<td>Vit K + PCC</td>
<td>Standard of care (consider PCC or rVIIa)</td>
<td>Standard of care (consider PCC or rVIIa)</td>
<td>Standard of care (consider PCC or rVIIa)</td>
</tr>
<tr>
<td><strong>Coag Assay</strong></td>
<td>PT / INR</td>
<td>TT is extremely sensitive</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>CYP 2C9, 1A2, &amp; 3A4</td>
<td>Potent P-gp inhibitors / inducers; PPIs decrease absorp</td>
<td>Potent P-gp inhibitors / inducers; CYP34A inhibitors</td>
<td>Potent P-gp inhibitors / inducers; CYP3A4 inhibitors</td>
</tr>
</tbody>
</table>
IN THE CORONER'S COURT
AT CHRISTCHURCH

IN THE MATTER OF

THE CORONERS ACT 2006

AND

IN THE MATTER OF

An inquest into the death of
John MacDonald

Before:
Coroner S.P. Johnson

Date of Hearing
16 May 2012

Date of Finding
17 July 2012

Appearances
Senior Constable Paul Martin for Police
Greg Brogden for Canterbury District
Health Board
Jenny Gibson for Dr Richard Troughton

RESERVED FINDINGS OF CORONER S.P. JOHNSON

These Findings should be read in conjunction with my Certificate of Findings, dated 17 July 2012.

INTRODUCTION
Trial patient (ROCKET-AF) on scooter in bike lane hit by car turning left

Told ambulance officers he was in rivaroxaban trial – carried wallet card and alert bracelet – ambulance officer had not heard of rivaroxaban

EC medical officer asked if he was on warfarin: “not sure”

INR was 1.3 – assessed as having no significant coagulopathy from warfarin

Haematologist called – agreed INR made it improbable patient was on therapeutic warfarin – was unaware of possibility of other anticoagulant
Patient bled total of 5 litres into chest cavity

No prothrombinex or Novo-7 used (or plasma)

Post-mortem anti-Xa level came back as 0.6 – i.e. equivalent to therapeutic enoxaparin - while INR was only 1.3.
Lessons

- Normal baseline coagulation screen does not imply normal haemostatic function!
- Importance of prominent documentation when a patient is receiving a NOAC
Anticoagulant Options

- Drugs with no significant renal clearance
  - Unfractionated heparin (UFH)
  - Warfarin
  - Direct Thrombin Inhibitors: argatroban
  - Factor Xa inhibitors: apixaban

- Drugs with significant dependence on renal clearance
  - Low molecular weight heparins (LMWHs)
  - Pentasaccharide: fondaparinux
  - Heparinoids: Danaparoid
  - Direct Thrombin Inhibitors: lepirudin, bivalirudin, dabigatran
  - Factor Xa inhibitors: rivaroxaban
Consensus guidelines for haemostatic management of patients requiring interventions
VESSEL INJURY

Platelet Release Reaction

Platelet Fusion

Primary Haemostatic Plug

Thromboxane A2, ADP

Tissue Factor

Platelet Aggregation

Blood Coagulation Cascade

Thrombin

Fibrin

Reduced Blood Flow

Serotonin

Collagen Exposure

Platelet Phospholipid

Stable Haemostatic Plug

Reduced Blood Flow

vasoconstriction

VESEL INJURY
Pre-intervention assessment of coagulation status

- INR/PR
- APTT
- Platelet count
- Haemoglobin

HISTORY: “The best screening test for operative bleeding is a good history. Patients with a negative bleeding history do not require routine coagulation screening prior to surgery”

British Society of Haematology guideline 2008
Lack of data

Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence based review.

- 25 studies but only one clinical trial
- Procedures included bronchoscopy with biopsies, liver biopsy, femoral angiography, liver biopsy, kidney biopsies, paracentesis, lumbar puncture
- Elevated coagulation parameters provide little or no predictive value for bleeding complications from image guided interventions

Segal JB Dzik WH. Transfusion 2005: 45:1413-1425
Nephrostomy tube placement

- 7/160 patients had abnormal PT or aPTT
- No bleeding complications observed
- No screening coagulation studies necessary before nephrostomy tube placement

Does an abnormal PFA-100 predict bleeding after renal biopsy?

- 56 patients undergoing PKB under ultrasound guidance
- PFA-CEPI abnormal in 9% and PFA-CADP abnormal in 14.3% participants
- 19% of patients developed post biopsy haematoma on ultrasound, 9% macroscopic haematuria and 7% required PRBC transfusion
- PFA closure times showed no association with any of the bleeding complications

Islam N, 2010; Clin Nephrol 73(3) 229-37
## Procedures with Low risk of Bleeding: Easily detected and controllable

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Preprocedure laboratory testing</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis access</td>
<td>INR: For patients on warfarin or with known liver disease</td>
<td>INR&gt;2: Threshold for treatment</td>
</tr>
<tr>
<td>Central line removal</td>
<td>APTT: For patients on heparin</td>
<td>APTT: No consensus</td>
</tr>
<tr>
<td>PICC line placement</td>
<td>Platelet count: Not routinely recommended</td>
<td>Hct: No recommended threshold for transfusion</td>
</tr>
<tr>
<td></td>
<td>Haematocrit: Not routinely recommended</td>
<td>Platelets; Transfusion if counts &lt;50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plavix; Do not withhold</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin: Do not withhold</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DDAVP: Not indicated</td>
</tr>
</tbody>
</table>

Patel IJ et al; J Vasc Interv Radiol 2012;23:727-736
## Procedures with moderate risk of Bleeding

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Preprocedure laboratory testing</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography</td>
<td>INR: Recommended APTT: in patients on UH Platelet count and Hct: not routinely recommended</td>
<td>INR: Correct above 1.5 APTT: Correct for values &gt; 1.5 times normal Platelet: Transfuse if platelets &lt; 50 Plavix: Withold for 5 days Aspirin: Do not withhold DDAVP: Not indicated</td>
</tr>
<tr>
<td>Venous interventions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tunnelled central venous catheter</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Procedures with significant bleeding risk: Difficult to detect or control

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Preprocedure laboratory testing</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal biopsy</td>
<td>INR</td>
<td>INR: Correct above 1.5</td>
</tr>
<tr>
<td>Nephrostomy tube placement</td>
<td>APTT if on heparin</td>
<td>APTT: Reverse heparin for values &gt; 1.5 x control</td>
</tr>
<tr>
<td></td>
<td>Platelet count</td>
<td>Platelets&lt; 50: transfuse</td>
</tr>
<tr>
<td></td>
<td>Haemoglobin</td>
<td>Plavix: Withold for 5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin: Withold for 5 days</td>
</tr>
</tbody>
</table>

Patel IJ et al; J Vasc Interv Radiol 2012;23:727-736
Transfusion and Reversal Guidelines

Fresh Frozen Plasma 12-15 ml/kg
Prothrombinex 25-50 U/kg
Cryoprecipitate 1 unit /20 kg
Protamine 1 mg/100U heparin
## Desmopressin for uremic platelet dysfunction

### DDAVP and improved platelet function in renal failure

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Sample size &amp; characteristics</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manucci et al (1983)</td>
<td>Retrospective double blind, placebo controlled</td>
<td>Patients with chronic renal failure receiving haemodialysis with poor history of bleeding and bleeding time &gt; 10 min (n=12)</td>
<td>One dose (0.3 μg/kg i.v.) DDAVP vs placebo One dose (0.3 μg/kg i.v. DDAVP</td>
<td>Bleeding time normalized in 5:12 patients 1 hr post infusion &amp; 1:12 patients 8hr post infusion</td>
</tr>
<tr>
<td>Kohler et al (1989)</td>
<td>Prospective randomized double blind, placebo controlled</td>
<td>Patients receiving haemodialysis for indication of unknown etiology with bleeding time &gt; 15 min (n = 8)</td>
<td>One dose (0.4 μg/kg i.v.) DDAVP</td>
<td>Bleeding time reduced in 7:8 patients and normalized in 2:8 patients. Significant increase in concentration of von Willebrand factor</td>
</tr>
<tr>
<td>Watson &amp; Keoth (1982)</td>
<td>Prospective single centre</td>
<td>Patients with chronic renal failure &amp; bleeding time &gt; 12 min (n=12); 4 receiving haemodialysis, 3 receiving peritoneal dialysis</td>
<td>One dose (0.4 μg/kg i.v.) DDAVP</td>
<td>Bleeding time normalized in 6:12 patients 1 h post infusion, 3:12 patients 2 hr post infusion, but 0:5 patients 24 h post infusion</td>
</tr>
</tbody>
</table>
Anticoagulation management in patients on Warfarin / LMWH / heparin
Balancing the risks of bleeding vs thrombosis
If antithrombotic therapy is interrupted before surgery, is “bridging Anticoagulation” needed?

The need for bridging is driven by patients' estimated risk for thromboembolism (TE):

- In **high-risk patients**, the need to prevent TE will dominate management irrespective of bleeding risk; the potential consequences of TE may justify bridging.
- In **moderate-risk patients**, a single perioperative strategy is not dominant and management will depend on individual patient risk assessment.
- In **low-risk patients**, the need to prevent TE will be less dominant and bridging may be avoided.
- In **all patients**, judicious use of postoperative bridging is needed to minimizing bleeding that would have the undesired effect of delaying resumption of antithrombotic therapy after surgery.
## Perioperative Risk Stratification

<table>
<thead>
<tr>
<th>Thrombosis Risk</th>
<th>Mechanical Heart Valve</th>
<th>Atrial Fibrillation</th>
<th>VTE</th>
<th>Bridge</th>
</tr>
</thead>
</table>
| **HIGH** (>10% per annum risk of event) | - Mitral valve  
- Older aortic valve (tilting disc)  
- Recent (<6 mo) stroke or TIA | - CHADS$_2$ 5-6  
- Recent (<3 mo) stroke or TIA  
- Rheumatic valvular HD | - VTE < 3 mo  
- Severe thrombophilia | Yes (1C)  
LMWH preferred over heparin (2C) |
| **MODERATE** | - Bileaflet aortic valve + one of: a fib, stroke, TIA, HT, DM, CHF, > 75 | CHADS$_2$ 3-4 | - VTE < 3 mo  
- Recurrent VTE  
- Active cancer | Full dose or prophylactic dose or no bridge (2C) |
| **LOW** (<5% per annum risk of event) | - Bileaflet aortic valve & no risk factors for stroke | CHADS$_2$ 0-2 and No prior stroke/TIA | - VTE > 12 mo  
& no other risk factors | No bridge or prophylactic LMWH (2C) |

Chest 2012
Risk Stratification for Bleeding

High bleeding-risk surgeries/procedures include:

- Urologic surgery/procedures: nephrectomy or kidney biopsy (untreated tissue damage after TURP and endogenous urokinase release)
- Pacemaker or ICD implantation (separation of infraclavicular fascia and no suturing of unopposed tissues may lead to hematoma)
- Colonic polyp resection, especially >1-2 cm sessile polyps (bleeding occurs at transected stalk after hemostatic plug release)
- Vascular organ surgery: thyroid, liver, spleen
- Bowel resection (bleeding may occur at anastomosis site)
- Major surgery involving considerable tissue injury: cancer surgery, joint arthroplasty, reconstructive plastic surgery
- Cardiac, intracranial or spinal surgery (small bleeds can have serious clinical consequences)
Temporary Discontinuation of Warfarin:
INR Decay with Target Range 2-3

- N= 22 patients; serial INRs done at 2.7 and 4.7 days after D/C
  (Ann Intern Med 1995;122:40-2)
Choosing the Best Bridging Medication

- Depends on patient characteristics:
  - Recent bleed or increased risk of bleeding
  - Renal function
  - Actual body weight
  - Pre-op INR
  - Baseline coagulation tests
  - History of Heparin-Induced Thrombocytopenia

- Available data, clinical experience, and Douketis advocate bridging with LMWH if possible

- In prophylactic doses LMWH has NOT been shown to increase the risk of bleeding complications, irrespective of the degree of renal impairment

Garcia D et al, Chest 2012;141,2,supp
Moderate and High risk

**LMWH**

**Therapeutic dose**
- Enoxaparin 1 mg/kg sc od
- Dalteparin 100u/kg sc od
- Tinzaparin 175U/kg sc od

Usually for 3 days pre-op

Last dose 24 hours before procedure. Consider dose reduction to:
- Enoxaparin 40 mg sc

**UFH**

Recommended if CrCl<30 ml/min

Admit and start infusion 2 days prior to surgery

Discontinue 6 hours before procedure
IV Heparin:
- Stop infusion 4 to 6 hours before procedure
- Usually delay resumption until at least 24 hours post procedure
- Resume without a bolus dose
- SC dosing 250 IU/kg bd (Garcia D et al, Chest 2012;141,2,supp)
Perioperative Administration of Bridging

- **Recommendation**: In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we suggest administering the last preoperative dose of LMWH approximately 24 h before surgery *instead of* 12 h before surgery (Grade 2C).

- **Recommendation**: In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high bleeding-risk surgery, we suggest resuming therapeutic-dose LMWH 48-72 h after surgery *instead of* resuming LMWH within 24 h after surgery (Grade 2C).

**Chest 2012**
How to Bridge with LMWH
(Circulation 2004;110:1658-63)

- **Day - 5**: Full dose OD or BID or prophylactic dose OD
- **Day - 3**: Stop LMWH (or ½ dose in am - impractical)
- **Day - 1**: INR > 1.5 Vit K 1mg po
- **Day 0**: Restart depends on adequate hemostasis
- **Day +1 or 2**: Stop LMWH when INR therapeutic
# Mechanical Heart Valve
(Please discuss with the preassessment anaesthetist)

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
<th>Therapeutic Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk</strong></td>
<td>Any mechanical mitral valve, Older (ball and cage / tilting) aortic valve, Recent stroke within 6 months or TIA</td>
<td>1mg / kg BD</td>
</tr>
<tr>
<td><strong>Moderate Risk</strong></td>
<td>Bileaflet aortic valve prosthesis with any other cardiovascular condition or diabetes</td>
<td>1mg / kg BD</td>
</tr>
</tbody>
</table>

### Atrial Fibrillation

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
<th>Therapeutic Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk</strong></td>
<td>CHADS$_2$ Score of &gt;4, Recent stroke / TIA within 3 months, Rheumatic valve disease</td>
<td>1mg / kg BD</td>
</tr>
<tr>
<td><strong>Moderate Risk</strong></td>
<td>CHADS$_2$ Score of ≥2</td>
<td>Prophylactic clexane 40 mg OD</td>
</tr>
<tr>
<td><strong>Low Risk</strong></td>
<td>CHADS$_2$ Score of 0-2, No previous stroke or TIA, Normal heart</td>
<td>No clexane</td>
</tr>
</tbody>
</table>

### Venous Thromboembolism (VTE)

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
<th>Therapeutic Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk</strong></td>
<td>Recent VTE within 3 months, Severe thrombophilia (predisposing to blood clots – Protein S &amp; C, Antiphospholipid)</td>
<td>1mg / kg BD</td>
</tr>
<tr>
<td><strong>Moderate Risk</strong></td>
<td>Recurrent VTE, VTE within 3-12 months</td>
<td>1mg / kg BD</td>
</tr>
<tr>
<td><strong>Very High Risk</strong></td>
<td>Acute arterial or venous thrombotic event (current or within 6 weeks), Thromboembolic event whilst taking warfarin</td>
<td>Speak to preassessment anaesthetist – may require expert help</td>
</tr>
<tr>
<td><strong>Moderate Risk</strong></td>
<td>Patients taking warfarin for recurrent stroke</td>
<td>Prophylactic clexane 40 mg OD</td>
</tr>
<tr>
<td><strong>Moderate Risk</strong></td>
<td>Dilated cardiomyopathy, Cardiac failure(other causes), Left ventricular aneurysm</td>
<td>Prophylactic clexane 40 mg OD</td>
</tr>
</tbody>
</table>

### CHADS$_2$ Score for patients in AF:

- Score 1 point for each co-morbid condition except Stroke or TIA:
  - Congestive cardiac failure
  - Hypertension
  - Age >75
  - Diabetes
  - Stroke
  - TIA
- (Stroke or TIA at any time scores 2)
## Important Safety Points

### Renal failure – eGFR < 30

- Therapeutic dosing with 1mg/kg OD am only
- Only 40mg the day before surgery
- Use lean body weight for dosing

<table>
<thead>
<tr>
<th>Days before surgery</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stopping Warfarin</strong></td>
<td>Omit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>When to take clexane injections (TICK)</strong></td>
<td>08:00</td>
<td>✓</td>
<td>✓</td>
<td>✔</td>
<td>40mg</td>
</tr>
<tr>
<td></td>
<td>18:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
"BRIDGING" STRATEGY

-7
-5
-3
-1
+1
+2
+3
+5

Hold Warfarin

Start full Dose LMWH

Prophylactic Dose LMWH

Resume full dose LMWH

Resume Warfarin

J.D. Douketis, Thrombosis Research; 108 (2003) 3-13
Bridging therapy in patients with renal impairment

<table>
<thead>
<tr>
<th>CrCl 30-50 ml/min (n=274)</th>
<th>CrCl 20-29 ml/min (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding (ANY) 6.5%</td>
<td>12.1</td>
</tr>
</tbody>
</table>

- 3 Major bleeds and 27 minor bleeds
- Mean time between last enoxaparin dose and procedure 27 hours

Hammerstingl C Thromb Haemost 2009; 101:185-1090
Emergency Interventions in the Anticoagulated Patient

- D/C all anticoagulants
- If INR >2.5: Prothrombinex +/- Vit K
- Have blood cross matched
- Consider PRBC transfusion to “augment hematocrit” especially in pts with cardiac disease
- Watch for volume overload, dilutional thrombocytopenia and coagulopathy
Prothrombininex dosing

25 to 50 IU/kg

FFP not required
Antiplatelet Agents

- Thromboxane A₂ inhibitors
  - Acetylsalicylic Acid (ASA)

- ADP-receptor antagonists (thienopyridines)
  - Clopidogrel (Plavix)

- Phosphodiesterase Inhibitors
  - Dipyrimadole (Persantin)

- Glycoprotein IIb/IIIa blockers
  - Abciximab
  - Tirofiban
  - Eptifibatide
Risk of thrombosis

- **Low risk**
  - Primary prevention of CAD (e.g., DM, HTN)

- **Intermediate risk**
  - Secondary prevention of CAD

- **High risk**
  - Recent MI or stroke
  - Coronary stents
    - Drug eluting lumen (sirolimus or paclitaxel > bare metal lumen)
Management for elective interventions

- **Low risk**
  - Temporary interruption is safe
  - Stop drug 7 days prior to procedure
  - Restart when adequate haemostasis

- **Intermediate risk**
  - Assess risks of discontinuation prior to stopping

- **High risk**
Patients With Coronary Stents requiring a procedure

- **Recommendation:** In patients with a coronary stent who are receiving dual antiplatelet therapy and require surgery, we recommend deferring surgery for at least 6 weeks after placement of a bare-metal stent and for at least 6 months after placement of a drug-eluting stent instead of undertaking surgery within these time periods (Grade 1C).

- **Recommendation:** In patients who require surgery within 6 weeks of placement of a bare-metal stent or within 6 months of placement of a drug-eluting stent, we suggest continuing dual antiplatelet therapy around the time of surgery instead of stopping dual antiplatelet therapy 7-10 days before surgery (Grade 2C).
Peri-procedure Anticoagulation: General Points

- In resuming treatment after procedure, it takes:
  - 2-3 days for anticoagulant effect to begin after starting warfarin
  - 3-5 h for peak anticoagulant effect after starting LMWH
  - minutes for an antiplatelet effect to begin after starting ASA
  - 3-7 days for peak inhibition of platelet aggregation after starting a maintenance dose of clopidogrel

- Some procedures done out-of-hospital and potential thromboembolic or bleeding complications occur during the initial 2 wks patient is at home
  - Close patient follow-up during early postop period allows early detection and treatment of complications
Vascular Access Thrombosis

Inherited Risk factors
- Prothrombin gene mutation
- Gene polymorphisms of:
  - Transforming Growth factor β
  - Nitric Oxide Synthase
  - Plasminogen Activator Inhibitor 1
  - Angiotensin Converting Enzyme
  - MTHF Reductase

Acquired Risk factors
- Diabetes
- AF
- Hypertension
- Low serum albumin
- APL
- Erythropoietin
- Malnutrition
Endothelial Cell Injury
Hypertension
Oxidative Stress
Inflammation
Diabetes
Uremic Toxins
Bio-incompatibility of artificial membranes
Activated platelets
Increased levels of circulating TNFα
Intimal fibromuscular hyperplasia

Hypercoagulability
Platelet hyper-reactivity
Decreased tPA
Prothrombin 20210 polymorphisms
Anticardiolipin antibodies
Hyperhomocysteinemia

Stasis
Poor inflow
Poor outflow
Hypotension
Poor conduit
Hypovolemia
Low-dose aspirin
## Antiplatelet drugs and prevention of thrombosis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>Control</th>
<th>Graft type</th>
<th>N</th>
<th>Duration</th>
<th>Thrombosis rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Aspirin 1 g alternate days</td>
<td>Placebo</td>
<td>AVF</td>
<td>92</td>
<td>28 days</td>
<td>4% aspirin vs 23% control</td>
</tr>
<tr>
<td>Andrassy et al 1974</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>75mg tds or aspirin 325mg od or Dipyridamole &amp; aspirin</td>
<td>Placebo</td>
<td>AVG</td>
<td>107 (84 type I, 23 type II)</td>
<td>72 months</td>
<td>DPD 17% Aspirin 80% Both 25% Placebo 40% Type II. 80-100%</td>
</tr>
<tr>
<td>Sreedhara 1994</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAC study</td>
<td>Dipyridamole 200mg bd &amp; aspirin 25mg</td>
<td>Placebo</td>
<td>AVG</td>
<td>649</td>
<td>1 year</td>
<td>25 % patency with D/A cf. 23% placebo</td>
</tr>
<tr>
<td>Group et al 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thienopiridines</td>
<td>Clopidogrel (300mg loading – 75 mg maintenance)</td>
<td>Placebo</td>
<td>AVG</td>
<td>877</td>
<td>6 weeks</td>
<td>12.2% vs 19.5% **</td>
</tr>
<tr>
<td>DAC study 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimarchi 2006</td>
<td>Clopidogrel 75mg</td>
<td>Placebo</td>
<td>AVG</td>
<td>24</td>
<td>3 years</td>
<td>8% vs 92% **</td>
</tr>
<tr>
<td>Kaufman et al 2003</td>
<td>Clopidogrel 75mg &amp; aspirin 325mg</td>
<td>Placebo</td>
<td>AVG</td>
<td>200</td>
<td>Stopped 7 months</td>
<td>HR 0.81 in favour of combined</td>
</tr>
</tbody>
</table>
“An aspirin a day will help prevent a heart attack if you have it for lunch instead of a cheeseburger.”
Coagulation cascade

Exposed collagen

Tissue factor

Factor IXa

Factor VIIa

Factor Xa

Thrombin

Fibrinogen

Factor Va

Calcium Phospholipids

Factor VIIIa

PGL₂

Endothelial cells

Smooth muscle

warfarin
Figure 2. Survival curve for patients allocated to warfarin or placebo.

Crowther M A et al. JASN 2002;13:2331-2337
# Oral warfarin to prevent thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Warfarin early</th>
<th>Warfarin late</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>81</td>
<td>63</td>
</tr>
<tr>
<td>TCC thrombosis/malfunction</td>
<td>12%</td>
<td>52%</td>
</tr>
<tr>
<td>BFR(ml/min)</td>
<td>305 +/- 34</td>
<td>246 +/- 42</td>
</tr>
</tbody>
</table>

Coli L, 2006 J Vasc Access 7(3) 118-22

Warfarin with target INR 1.4-1.9: 73% graft loss compared to 61% with Placebo

BUT Significant increase in Major Haemorrhage

PLASMINOGEN

- tPA
- Urokinase

PLASMIN

- α2-antiplasmin, α2-macroglobulin

FIBRIN

- Thrombin-activatable fibrinolysis inhibitor (TAFI)

FIBRIN DEGRADATION PRODUCTS
Plasminogen → Plasmin + α2 Plasmin inhibitor → Inactive complex

Plasminogen Activator + PAI-1 → Inactive complex

PAI-1

Plasminogen Activator

Plasmin

α2 Plasmin inhibitor

Fibrin Degradation Products

Thrombolysis
# Principal Biologic Effects of Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Effect</th>
<th>Event</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical benefit</td>
<td>Thrombolysis</td>
<td>Degradation of fibrin in the thrombus</td>
</tr>
<tr>
<td>Side effect</td>
<td>Systemic Lytic state</td>
<td>Degradation of plasma fibrinogen by circulating plasmin</td>
</tr>
<tr>
<td>Complication</td>
<td>Bleeding</td>
<td>Degradation of fibrin in haemostatic plugs</td>
</tr>
<tr>
<td>Enzymatic efficiency for clot lysis</td>
<td>Fibrin specificity</td>
<td>Potential antigenicity</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>High</td>
<td>Minimal</td>
</tr>
<tr>
<td>Tissue plasminogen activator</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Urokinase</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Tenecteplase (Metalyse)</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>
Prevention of Dialysis Catheter Lumen Occlusion with rt-PA versus Heparin

Hemmelgarn B, et al. NEJM 2011;364:303
## Thrombolyis with tPA

<table>
<thead>
<tr>
<th>Author / year</th>
<th>Dwells</th>
<th>Catheters</th>
<th>N</th>
<th>Success Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zacharias, 2003</td>
<td>164</td>
<td>66</td>
<td>30</td>
<td>88</td>
</tr>
<tr>
<td>Daelhaigh, 2000</td>
<td>56</td>
<td>28</td>
<td>22</td>
<td>88</td>
</tr>
<tr>
<td>Crowther, 2000</td>
<td>42</td>
<td>23</td>
<td>23</td>
<td>88</td>
</tr>
<tr>
<td>Paulsen, 1993</td>
<td>18</td>
<td>18</td>
<td>8</td>
<td>83</td>
</tr>
<tr>
<td>O’Mara, 2001</td>
<td>62</td>
<td>25</td>
<td></td>
<td>58</td>
</tr>
<tr>
<td>Davies, 2004</td>
<td>57</td>
<td>38</td>
<td>20</td>
<td>85</td>
</tr>
</tbody>
</table>
Thrombolytic therapy for catheter thrombosis

Reteplase 88% +/- 4%
Alteplase 81% +/- 37%
Tenecteplase 41% +/- 5%

Adverse events extremely rare
No serious adverse bleeding events reported

Hilleman D, Pharmacotherapy 2011: 31(10) 1031-40
Fibrinolysis for Haemodialysis Catheters

- Contraindications:
  - Hypersensitivity
  - Relative Contraindications related to increased risk of bleeding
    - Recent severe bleeding
    - Recent major trauma/surgery (<10 days)
    - Acute pericarditis/pancreatitis/bacterial endocarditis
    - Ulcerative GI disease
    - Recent stroke/intracranial neoplasm
    - On warfarin
    - APTT > 38
    - Platelet count < 100
    - Systolic hypertension
Thrombosed AVFs and AVGs

TPA or urokinase infusions with balloon angioplasty
Pulse Spray Pharmacomechanical Thrombolysis

Technical success rates of 60-95%
Patency rates at 12 months variable
Incidence of PE after percutaneous intravascular thrombolysis of thrombosed haemodialysis AVG

<table>
<thead>
<tr>
<th>Author</th>
<th>PSPMT with UK</th>
<th>PE after PSPMT with UK</th>
<th>PSPMT with HS</th>
<th>PE after PSPMT with HS</th>
<th>PMT</th>
<th>PE after PMT</th>
<th>Symptom PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swan 1995</td>
<td>22</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Petronis 1999</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
<td>9</td>
<td>0</td>
<td>0</td>
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<td>Smits 1996</td>
<td>11</td>
<td>3</td>
<td></td>
<td></td>
<td>12</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Kinney 2000</td>
<td>11</td>
<td>2</td>
<td>14</td>
<td>9</td>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

Calderon K, 2010 Seminars Dialysis 23;5;522
Urokinase

- **Local Instillation:**
  - Dissolve in saline to 5000U/ml. Instill volume sufficient to fill lumen and lock for 20 to 60 minutes

- **Systemic infusion:** 250,000 U Urokinase powder/100 mls normal saline over 2 hours

- If heparin has been given it should be discontinued and the aPTT should be less than twice the normal control value before urokinase is initiated

- For systemic administration a 3 to 5 fold prolongation of the TT measured 4 hours after initiation of therapy is considered sufficient

- Restart heparin infusion once the aPTT is less than twice the normal control value
Concomitant Anticoagulation

- No direct evidence to support use of any anticoagulation regimen over another

- Current consensus is for full dose therapeutic level heparin when using UK

- Subtherapeutic heparin with APTT < 1.5x control with TPA, RPA or TNK
  - Bolus 60IU/kg followed by infusion 12IU/kg/hr (max 1000IU/hr)
Clot Busters
Advantages and limitations of NOA

**Advantages**
- Fixed dosing
- Monitoring of anticoagulant effect not required
- Few drug interactions than warfarin

**Limitations**
- Measurement of anticoagulant effect not available
- Lack of specific antidote
- Some drug interactions
- Dose adjustments required in renal / hepatic dysfunction
Testing for Dabigatran Anticoagulant Effect

- INR relatively insensitive (only supratherapeutic doses give INR approx 2.0)
- Echis ratio more sensitive than INR
- APTT moderately sensitive but curve flattens off higher doses, and may remain elevated after all drug gone
- Thrombin time (TT) very (too!) sensitive with linear response curve – may take 10 days to normalise
- Drug level testing by modified dilute TCT available at ACH, MMH.
- Prolonged clotting tests may be multifactorial
Perioperative Management

- For minor procedures e.g. dental surgery, may not need to be discontinued.
- Other procedures = plan ahead (not reversible!)
- Timing of discontinuation dependent on patient’s renal function.
<table>
<thead>
<tr>
<th>Renal function (CrCl, mL/min)</th>
<th>Half-life of dabigatran (hours)$^a$</th>
<th>Timing of discontinuation after last dose of dabigatran before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>13 (11-22)</td>
<td>24 hours</td>
</tr>
<tr>
<td>&gt; 50 to ≤ 80</td>
<td>15 (12-34)</td>
<td>24 hours</td>
</tr>
<tr>
<td>&gt; 30 to ≤ 50</td>
<td>18 (13-23)</td>
<td>At least 2 days (48 hours)</td>
</tr>
<tr>
<td>≤ 30'</td>
<td>27 (22-35)</td>
<td>2-5 days</td>
</tr>
</tbody>
</table>

Protocol: Perioperative Management of Patients on Dabigatran

Background

Dabigatran is an oral thrombin inhibitor approved for use in atrial fibrillation and prevention of venous thromboembolism post major orthopaedic surgery.

Dabigatran has many advantages over warfarin but there is little international experience in managing dabigatran perioperatively.

In addition, dabigatran:

- Cannot be readily reversed
- There is no established blood test
- There are no proven guidelines for perioperative management.

Purpose

The purpose of this protocol is to provide a clear and unambiguous pathway for the perioperative management of patients on dabigatran.

The aims of the protocol are that:

- risks to patients are identified and assessed
- appropriately directed actions are taken to minimise adverse outcomes
- ongoing monitoring informs ongoing actions and provides continued improvement of this pathway

Scope

All patients on dabigatran requiring surgery – acute or elective.
Acute Surgical Patients taking Dabigatran

Assess Theatre priority as per agreed Theatre Acuity Guidelines

**LIFE THREATENING CONDITIONS**
- Uncontrolled haemorrhage, ruptured AAA

**ORGAN THREATENING CONDITIONS**
- Torsion of testis, ischaemic limb, fasciotomy, ruptured bowel

**NON CRITICAL, BUT URGENT**
- Appendicitis, compound fractures, acute bowel obstruction, open wounds

**NON CRITICAL, ACUTE BUT NOT URGENT**
- Fractured NOF, closed reduction fractures, incision of superficial abscess

**ACUTE EPISODE NO ADVERSE CONSEQUENCE**

**ACUTE ARRANGED**

**PRIORITY 1**
- Stop dabigatran
- Consider SMO Haematology consultation regarding limited reversal options
- Consider blood products (platelets or FFP) if concomitant factors (e.g. antithrombotic agents or liver disease) present

**PRIORITY 2**
- Step dabigatran & if possible (risk/benefit) delay surgery for extra 24 hours (total 48hrs)
- Consult with SMO Haematology if major blood loss or bleeding risk

**PRIORITY 3**
- Neuroaxial anaesthesia contraindicated
  - Consult SMO Anaesthesia regarding other regional anaesthesia forms

**PRIORITY 4**
- Send blood for TCT and Dabigatran assay (with time of last dose if known)

**PRIORITY 5**
- Proceed to surgery

**PRIORITY 6**
- Apply flowchart for elective patients
### Elective Surgery Overview

<table>
<thead>
<tr>
<th>Step</th>
<th>Task</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Determine Bleeding Risk</td>
<td>Identify the type of procedure planned for the patient.</td>
</tr>
<tr>
<td>2</td>
<td>Determine Patient Risk</td>
<td>Identify and assess the patient factors which may affect the risk to the patient. Consult relevant SMOs as directed by the algorithm.</td>
</tr>
<tr>
<td>3</td>
<td>Required Actions</td>
<td>From the Bleeding and Patient Risks determine necessary dabigatran washout period, necessary monitoring and surgery implications.</td>
</tr>
</tbody>
</table>

### Bleeding Risk Determination

#### Assessment of Procedure Type to Determine Bleeding Risk/Implications

- **Determine Procedure Type**
  - Minor surgery on superficial compressible site
  - Gynaecological surgery
  - Breast surgery
  - Laparoscopic surgery
  - Arthroscopic surgery
  - Upper limb orthopaedic surgery including shoulder joint replacement
  - Spinal surgery
  - Intracranial surgery
  - Airway surgery
  - Thyroid surgery
  - Prostate surgery
  - Plastic surgery free flaps
  - All Jehovah’s Witness patients
  - Patients for neuraxial anaesthesia (hip and knee arthroplasty, laparotomies)
  - Pelvic surgery
# Dabigatran Risk Assessment and Actions

<table>
<thead>
<tr>
<th></th>
<th>Monitoring</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGH Patient Factor Risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOW Bleeding Risk</td>
<td>Withhold dabigatran the evening before and morning of surgery</td>
<td>Surgery can proceed</td>
</tr>
<tr>
<td>Moderate Bleeding Risk</td>
<td>Four full days without dabigatran prior to surgery</td>
<td>Collect blood on induction and send for baseline APTT, TCT and dabigatran level. Surgery can proceed before blood results are available</td>
</tr>
<tr>
<td>HIGH Bleeding Risk</td>
<td>Seven full days without dabigatran prior to surgery</td>
<td>Check TCT and dabigatran assay level the night before and morning of surgery. Ideally these patients should NOT be first on the list. Surgery cannot proceed until results are checked. Proceed if TCT normal OR serum dabigatran assay is less than 0.01mmol/L.</td>
</tr>
</tbody>
</table>
### Pharmac guidelines: Testing and Perioperative Management of Dabigatran

<table>
<thead>
<tr>
<th>Renal function (CrCl, mL/min)</th>
<th>Half-life of dabigatran (hours)a</th>
<th>Timing of discontinuation after last dose of dabigatran before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>13 (11-22)</td>
<td>Standard risk of bleeding: 24 hours</td>
</tr>
<tr>
<td>&gt; 50 to ≤ 80</td>
<td>15 (12-34)</td>
<td>High risk of bleeding: 2-4 days</td>
</tr>
<tr>
<td>&gt; 30 to ≤ 50</td>
<td>18 (13-23)</td>
<td>At least 2 days (48 hours)</td>
</tr>
<tr>
<td>≤ 30'</td>
<td>27 (22-35)</td>
<td>4 days</td>
</tr>
</tbody>
</table>
Rivaroxaban

Effect on Lab tests:

- Very little!
  - Only measureable when drug conc high
  - Modest elevation of PR eg 1.2 (depends on thromboplastin; some more sensitive to factor X inhibition)
  - Possibility of “INR-riva” cf “INR-VKA”
- Need to specifically test for anti-Xa activity
  - Would need to calibrate anti-Xa test for rivaroxaban as well as for enoxaparin and heparin
Rivaroxaban

- Anti-Xa (like enoxaparin)
- 7 hour half-life (i.e. similar to enoxaparin)

Registered uses:
- VTE prophylaxis in elective knee and hip joint replacement
- Prevention of stroke and other ATE in patients with non-valvular AF
- Treatment of DVT and prevention of PE