Anticoagulants and their use

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Therapeutic haemostatic agents

Summary of mechanisms of action: factor targets

AT = antithrombin; LMWH = Low molecular weight heparin; UFH = unfractionated heparin

What do I need to know?

- Frequently used anticoagulants
  - Names
  - Mechanisms of action
  - Understand differences in pharmacokinetics
- VTE prophylaxis
  - How to use risk assessment tool
  - Prescribe chemical and mechanical prophylaxis
- How to start anticoagulation
  - Monitoring and adjusting heparin, warfarin and clexane dosing
- What can go wrong?
- Where to find guidance
Frequently used anticoagulants

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade names</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH: Enoxaparin, Dalteparin</td>
<td>Clexane, Fragmin</td>
</tr>
<tr>
<td>LMWH: low molecular weight heparin</td>
<td></td>
</tr>
<tr>
<td>(Unfractionated) Heparin</td>
<td>Marevan, Coumadin</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Pradaxa</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Xarelto</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Eliquis</td>
</tr>
</tbody>
</table>

Indications: UFH

- Treatment of venous thrombosis – IV infusion
- Prophylaxis (prevention) of venous or arterial thrombosis – subcutaneous injection
- Early secondary prophylaxis of thrombosis following myocardial ischaemia
- Haemodialysis, cardiopulmonary bypass to prevent thrombosis in filters/pumps
- Disseminated Intravascular Coagulation – some cases

ADVANTAGES:
- Short half life
- Fully reversible with protamine
- Can be used in renal impairment

Clinical use of UFH (unfractionated heparin)

- IV infusion or intermittent s/c injection since poor oral absorption
- Immediate onset of action
- Half life varies with dose 1-5 hours
- Metabolism:
  - Degradation primarily via reticuloendothelial system
  - Mononuclear phagocytes – liver
  - Small amount eliminated unchanged via kidney
  - CAN use in renal impairment
- Does NOT cross the placenta
- Specific antagonist (reversal): protamine sulphate
- 1mg/100u heparin, maximum 50mg dose

Laboratory monitoring

- Using APTT
  - Aim 1.5-2 x normal for IV infusions
  - Measured 4-6 hours after start and any rate changes
  - In steady state, measured daily
- Clinical monitoring and daily FBC essential
Side effects of UFH

- Increased bleeding rate proportional to APTT
- Osteoporosis, fractures with prolonged use
- Elevated hepatic transaminases
- Hyperkalaemia
- Allergy — rare
- Heparin induced thrombotic thrombocytopenia syndrome (HITTS)

Complications: HITTS

- Heparin induced thrombotic thrombocytopenia syndrome
- Clinical Dx primarily
- Incidence 0.5 – 3%
- Mediated by antibodies to heparin-platelet factor 4 complex
- Onset day 5-14 (1st Rx) or earlier (repeat Rx)
- Progressive fall in platelets
- 4Ts score

HITTS

- Hypercoagulable state
- High risk thrombosis
  - Including unusual sites and sites of pre-existing pathology
  - Eg: sagittal sinus, adrenals
  - Often multifocal
- Mortality 20-30%

HITTS pathophysiology
HITTS management

- Stop heparin immediately
- DO NOT give platelets
- Delay starting warfarin until platelet count recovers
- Start alternative anticoagulant in interim
  - Danaparoid
  - Direct thrombin inhibitor
- Testing available to confirm the diagnosis
- Negative testing does not preclude the diagnosis

Low Molecular Weight Heparins (LWMH)

- Metabolism: Primarily renal clearance
- Contraindicated with Creatinine Clearance < 20ml/min
- Primarily acts via ATIII to inactivate Xa
- Less non specific plasma protein binding than UFH
- Pharmacokinetics dose dependent and weight adjusted
- Lab monitoring only required in selected pts
  - Chronic renal failure, pregnancy, body wt extremes, high risk bleeding or recurrence
  - Use anti Xa assay
  - Must advise lab of specific LMWH in use eg enoxaparin = clexane
- Does NOT cross placenta
- Protamine reverses only 60% of effect

Warfarin mechanism of action

Vitamin K dependent factors: Factor II (prothrombin), VII, IX, X, Protein C, Protein S
- Gla-rich tail domains anchor factors to membranes
- Vitamin K essential cofactor for carboxylation (and activation) of glutamic acid residues on factors II, VII, IX, X, Protein C and S
- Time required for each cofactor to reach a new steady state depends on each factors individual rate of clearance
  - VII – 7 hrs Prot C – 8 hrs
  - IX – 24 hrs Prot S – 30 hrs
  - X – 36 -48 hrs II – 60 hrs
- Full effect therefore takes 3 days
Warfarin

- Near complete oral bioavailability
- 99% plasma protein bound
- Crosses placenta - teratogenic
- Active form not found in breast milk
- T ½ 40 hours, duration action 2-5 days
- Metabolism: Oxidation and glucuronidation in liver
- Increased sensitivity
  - Old age, reduced body weight
  - Impaired cardiac or liver function

Warfarin dosing

- Dosage
  - Great variability between pts, 0.5-15mg daily
- Monitoring
  - PT converted to INR (International normalised ratio), Usual target range 2-3
  - Test initially day 3, then every 3 days till stable
  - Long term monitoring at least every 4 weeks
  - Increase frequency if medication changes, unwell, diet changes

Warfarin drug and food interactions

- Drug and other interactions are prodigious
- Any substance or condition is potentially dangerous if it alters:
  - uptake or metabolism of Vit K or warfarin
  - synthesis, function or clearance of any factor or cell involved in clotting
  - integrity of any epithelial surface

Warfarin interactions

- Decreased effect
  - Reduced absorption: Cholestyramine
  - Increased volume of distribution and short half life: Nephrotic syndrome
  - Increased metabolic clearance due to hepatic enzyme induction: Barbiturates, rifampin, phenytoin, chronic alcohol
  - Ingestion of Vit K rich foods or supplements

- Increased effect
  - Decreased metabolism: phenylbutazone, metronidazole, allopurinol, cimetidine, amiodarone, acute intake of alcohol
  - Relative deficiency of vitamin K: Inadequate diet, loss of intestinal microbial agents due to antibiotics, cephalosporins inhibit Vit K epoxide
  - Low levels of coagulation factors
  - Liver disease, congestive heart disease

Brands of warfarin – Coumadin® vs Marevan® (not interchangeable, not bioequivalent)
*Initiation for new patients = Coumadin®
Starting warfarin

GUIDELINE for HOME ANTICOAGULATION
- This guideline is valid only if the patient is clinically stable, has no severe conditions, and INR is within the target range.
- Monitoring is necessary for the duration of treatment and after changing warfarin dose.
- In case of side effects, readjustment of dose may be necessary.

<table>
<thead>
<tr>
<th>Treatment day</th>
<th>Warfarin dose</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age &lt; 50 yrs; OR Weight &gt; 80 kg; OR Chronic or moderate illness</td>
<td>5 mg</td>
</tr>
<tr>
<td>2</td>
<td>Age &gt; 50 yrs; OR Weight &lt; 80 kg; OR Chronic or moderate illness</td>
<td>5 mg</td>
</tr>
<tr>
<td>3</td>
<td>INR &lt; 2.0</td>
<td>5 mg</td>
</tr>
<tr>
<td>4</td>
<td>INR = adjusted warfarin dose according to physician's advice</td>
<td></td>
</tr>
</tbody>
</table>

LMWH is co-prescribed

- Therapeutic doses (adjust as per CrCl) until INR is >2.0 for two consecutive days

<table>
<thead>
<tr>
<th>Normal dosing (Cr Cl &gt; 30 mL/min)</th>
<th>Renal Impairment (Cr Cl &gt; 10 mL/min)</th>
<th>Renal Impairment (Cr Cl &lt; 10 mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twice daily regimen: Enoxaparin (Cassenda®) 1 mg/kg SC daily (max. 150 mg per day) Dalteparin (Fragmin®) 100 units/kg SC daily max. 7,500 units SC daily</td>
<td>Enoxaparin (Cassenda®) 1 mg/kg SC once daily Dalteparin (Fragmin®) 100 units/kg SC once daily</td>
<td>Use unfractionated heparin</td>
</tr>
<tr>
<td>Once daily regimen: Enoxaparin (Cassenda®) 1.5 mg/kg once daily Dalteparin (Fragmin®) 200 units/kg once daily max. 2,500 units/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Warfarin side effects

- Bleeding
  - Exponential rise in bleeding risk with INR
  - Minimise risk with monitoring
  - Excessive bleeding risk with INR > 5
  - Major bleeding 1-3%/year
  - Intracranial bleeding 0.1-0.5%/year
  - Incrasing risk with age, concomitant serious illness, atherosclerosis, NSAIDs, alcohol abuse, renal disease, liver disease, past history of bleeding
  - After stroke, bleeding risk 8%/year
- Skin necrosis – rare
- Teratogenic

Warfarin requires monitoring

- The anticoagulant effect of VKAs is optimized when therapeutic doses are maintained within a very narrow range.
- INR = International normalized ratio, VKA = vitamin K antagonist.
Warfarin reversal guideline

- Vitamin K reverses effect
  - If given orally, can use IV formulation rather than tablets for flexible dosing
  - To temporarily reverse warfarin use low dose Vit K 0.5-2.5mg
  - Avoids resistance once warfarin is reinstituted
- PCC (prothrombin complex concentrate: II, IX, X, VII)
  - First choice for immediate reversal
  - Also Vit K to sustain this reversal
  - Contraindications: acute thrombosis, DIC
- FFP can be used, but requires much larger volumes
  - Less effective

New drugs: NOACs

- Use generic names (do NOT use trade names – many health professionals are not yet used to them.)
- Some patients have been doubly anti-coagulated because of this.
- Doses depend on indication
- Are not monitored with blood test routinely
- Not clearly reversible
- Should only be initiated by a consultant

NOAC Advantages

- Selectively inhibit thrombin or factor Xa
- Rapid onset of action, no bridging
- Wide therapeutic window
- Predictable PK, limited hepatic metabolism
- Few drug and no food interactions
- Fixed dosing without monitoring
- Pt and Dr convenience
- More cost-effective?
  - No routine monitoring
  - Fewer SAEs requiring hospitalisation

Limitations of NOACs

- Renal elimination: dose reduction or contra-indicated in CKD
- Relatively short t1/2
  - Rapid decline in effect if doses missed
- Limited availability assays to measure drug levels
- Absence validated monitoring strategies for special circumstances
  - Pts presenting with adverse events
  - Failure of therapy vs poor compliance
  - Timing of urgent surgery, ARF
- No specific antidotes available for major bleeds
- Potential for overuse
- High acquisition cost cf VKA
## Comparative characteristics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Warfarin</th>
<th>Dabigatran etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>VK K epoxide reductase</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>&gt; 95%</td>
<td>6.5%</td>
<td>80%</td>
<td>66% approx</td>
</tr>
<tr>
<td>Time to Cmax</td>
<td>72-96 hrs</td>
<td>1-2 hrs</td>
<td>2.5-4 hrs</td>
<td>3 hrs</td>
</tr>
<tr>
<td>Half-life</td>
<td>40 h</td>
<td>9-13 h</td>
<td>7-11 h</td>
<td>8-15 h</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Routine</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dosing</td>
<td>Once daily, INR adjusted</td>
<td>Fixed, once or twice daily</td>
<td>Fixed, once or twice daily</td>
<td>Fixed, twice daily</td>
</tr>
<tr>
<td>Elimination</td>
<td>None</td>
<td>80% renal</td>
<td>67% renal, 18% faecal</td>
<td>25% renal, 56% faecal</td>
</tr>
<tr>
<td>Potential drug interactions</td>
<td>CYP 2C9, 3A4, 1A2 inhibitors, dietary vit K</td>
<td>Potent p-gp inhibitors</td>
<td>Potent CYP 3A4 and p-gp inhibitors</td>
<td>Potent CYP 3A4 inhibitors</td>
</tr>
</tbody>
</table>

## Effects of NOACs on coagulation assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT/INR</td>
<td>Routinely required</td>
<td>Not routine</td>
<td>Not routine</td>
<td>Not routine</td>
</tr>
<tr>
<td>APTT</td>
<td>Mild/no prolongation</td>
<td>Prolonged but non-linear</td>
<td>Minimal or no affect</td>
<td>Minimal or no affect</td>
</tr>
<tr>
<td>TT</td>
<td>Markedly prolonged even at low drug concentrations</td>
<td>Not affected</td>
<td>Not affected</td>
<td></td>
</tr>
</tbody>
</table>

## NOAC indications in Australia

<table>
<thead>
<tr>
<th>Clinical indication</th>
<th>Warfarin</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>VK prophylaxis following elective hip or knee surgery</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>VTTE prophylaxis in asymptomatic medical at-risk population</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>VTTE prophylaxis for surgery following hip fracture, major orthopaedic or non-orthopaedic procedures</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>VTTE treatment</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Thromboprophylaxis for non-vascular axial fibrillation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Thromboprophylaxis for patients with signaibous valve disease* and axial fibrillation</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Thromboprophylaxis for patients with mechanical prosthetic cardiac valve replacement</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* Mild aortic valve, prosthetic heart valve or mitral valve regurgitation
** Excluding patients with active cancer or antiphospholipid syndrome

## Interpreting NOAC drug concentrations

6 blind people and an elephant
NOACs and perioperative setting

• Urgency of surgery – delay if practical
• Which NOAC and what dose
• Assess renal function
• Type of surgery or procedure
• Other bleeding risks
• No antidotes yet
• Ongoing thrombotic risk

Low bleeding risk surgery: NOACs

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Half life</th>
<th>Creatinine Clearance</th>
<th>Time of last dose pre-operative</th>
<th>Time of first post-operative dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>12-17 hr</td>
<td>≥ 50 ml/min</td>
<td>24 hrs</td>
<td>24 hrs, usual dose</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>13-23 hr</td>
<td>30-49ml/min</td>
<td>48-72 hrs</td>
<td>24 hrs, usual dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>5-9 hr</td>
<td>≥ 50 ml/min</td>
<td>24 hrs</td>
<td>24 hrs, usual dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>9-13 hr</td>
<td>30-49ml/min</td>
<td>48 hrs</td>
<td>24 hrs, usual dose</td>
</tr>
<tr>
<td>Apixaban</td>
<td>7-8 hr</td>
<td>≥ 50 ml/min</td>
<td>24 hrs</td>
<td>24 hrs, usual dose</td>
</tr>
<tr>
<td>Apixaban</td>
<td>17-18 hr</td>
<td>30-49ml/min</td>
<td>48 hrs</td>
<td>24 hrs, usual dose</td>
</tr>
</tbody>
</table>

- 2-3 drug half lives between last dose and surgery
- Expect residual anticoagulant effect < 12-25%
- Severe renal impairment – consider assays for anticoagulant effect

Tran et al, IMJ 2014, 44:525-536

High bleeding risk surgery: NOACs

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Half life</th>
<th>Creatinine Clearance</th>
<th>Time of last dose pre-operative</th>
<th>Time of first post-operative dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>12-17 hr</td>
<td>≥ 50 ml/min</td>
<td>48-72 hrs</td>
<td>48-72 hrs, usual dose</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>13-23 hr</td>
<td>30-49ml/min</td>
<td>96 hrs</td>
<td>48-72 hrs, usual dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>5-9 hr</td>
<td>≥ 50 ml/min</td>
<td>48-72 hrs</td>
<td>48-72 hrs, usual dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>9-13 hr</td>
<td>30-49ml/min</td>
<td>72 hrs</td>
<td>48-72 hrs, usual dose</td>
</tr>
<tr>
<td>Apixaban</td>
<td>7-8 hr</td>
<td>≥ 50 ml/min</td>
<td>48-72 hrs</td>
<td>48-72 hrs, usual dose</td>
</tr>
<tr>
<td>Apixaban</td>
<td>17-18 hr</td>
<td>30-49ml/min</td>
<td>72 hrs</td>
<td>48-72 hrs, usual dose</td>
</tr>
</tbody>
</table>

- 4-5 drug half lives between last dose and surgery
- Expect residual anticoagulant effect < 3% - 6%
- Severe renal impairment – consider assays for anticoagulant effect
- Don’t forget VTE prophylaxis, prior to resuming NOAC
- In high thromboembolic risk patients consider lower NOAC doses from 24 hours: dabigatran 75mg daily, rivaroxaban 10mg daily, apixaban 2.5mg BD

Tran et al, IMJ 2014, 44:525-536
HELP!!!! ...my patient is bleeding on a NOAC...

Don’t PANIC!

How can I ‘reverse’ NOACs?

<table>
<thead>
<tr>
<th>Renal function (Creatinine clearance)</th>
<th>Half-life (hours)</th>
<th>Timing of discontinuation after last dose of dabigatran before surgery</th>
<th>A. of bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>&lt; 50</td>
<td>24 hours</td>
<td>2-4 days</td>
</tr>
<tr>
<td>30 to &lt; 50</td>
<td>&gt; 30</td>
<td>2-5 days</td>
<td>&gt; 5 days</td>
</tr>
<tr>
<td></td>
<td>&lt; 30</td>
<td>at least 24 hours (48 hours)</td>
<td></td>
</tr>
</tbody>
</table>

The future: Antidotes in clinical development

Bleeding on NOACs

- Haemodialysis for dabigatran
- NOT oral Xa agents
- If feasible in severe bleeding, possibly for moderate bleeding
- Especially if renal impairment and excess dabigatran present

Tran et al, BMJ 2016, 355:i4535
Warkentin et al, Blood 2012; 119:2172
Stegler et al, Crit Care Nurse 2013; 32:29
Warkentin et al, Ann Pharmacother 2012; 46:241
Wychowski et al, Ann Pharmacother 2012; 46:10
The Impact of VTE

• More than 14,000 Australians develop a VTE per year
• More than 5,000 of them will die as a direct result
• VTE causes 7% of all hospital deaths

VTE causes more deaths than bowel Ca and breast Ca

Hospitalisation

• Hospitalisation = ↑ risk of VTE
• ~ 50% of VTE cases occur during or soon after hospitalisation
  – 24% (surgery)
  – 22% (medical illness)
• Incidence 100 times greater in hospitalised patients than community residents

Mechanical Prophylaxis

• Devices that increase blood flow velocity in leg veins, reducing venous stasis.
• They include:

<table>
<thead>
<tr>
<th>Device</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graduated Compression Stockings (GCS)</td>
<td>Provide graduated compression, which is firmest at the ankle. Used mainly for ambulant patients</td>
</tr>
<tr>
<td>Anti-embolic Stocking</td>
<td>Standard compression throughout. Used for bedbound or non-ambulant patients</td>
</tr>
<tr>
<td>Intermittent Pneumatic Compression Device (IPC)</td>
<td>Inflatable garment wrapped around legs which is inflated by pneumatic pump. Enhances venous return</td>
</tr>
<tr>
<td>Foot Impulse Device (FID)</td>
<td>Stimulates legs veins to mimic walking and reduce stasis. Used for immobilised patients</td>
</tr>
</tbody>
</table>
Contraindications

Case 1: Samantha Stosur

- 32 yo female
- Presents with acute onset right leg pain and swelling
- Doppler USS shows occlusive femoral vein thrombus
- What is the diagnosis?
- What baseline tests should be performed?
- Prescribe anticoagulation for this patient
- Weight 70kg, Creat 75 micromol/L, Height 172cm
Check the guideline

LMWH is the treatment of choice for most patients with established DVT or PE.
- For uncomplicated distal DVT (distal to the popliteal vein), the once daily LMWH regimen is indicated.
- For DVT extending above (proximal to) the popliteal vein either once daily or twice daily LMWH regimens are acceptable.
- For PE either once daily or twice daily LMWH regimens are acceptable.
- If a LMWH is administered for more than 5 days, platelets should be monitored second daily for at least the next 2 weeks.

Twice daily regimens:
- For patients who are not taking any other anticoagulants (Class IIa)
- For patients who are taking other anticoagulants (Class III)
- Monitor Anti Xa levels
- Reduce Clexane dosing to 70 mg (1 mg/kg) daily
- Consider delaying warfarin commencement

SS continued

Patient receives warfarin 10mg, then 5mg and 5mg
- On day 4 the INR is 1.7, write up the next dose
- On day 6 the INR is 2.0, write up the next dose
  - When will you retest INR?
  - When will you cease Clexane?
- On day 7 INR is 1.6
  - What may be the causes?
- How do you organize this for outpatients?

How would your management change if you discovered:
- The patient was pregnant?
  - Continue LMWH, do not warfarinise during pregnancy
  - Monitor Anti Xa levels
- The patient was found to have a breast cancer?
  - Continue LMWH rather than warfarinising
- The patient had creatinine clearance of 28 mL/min?
  - Reduce Clexane dosing to 70 mg (1 mg/kg) daily
  - Check Anti Xa levels
  - Consider delaying warfarin commencement
Case 2: Nicholas Kyrigos

- 65yo male with mechanical mitral valve
- Presents with an acute bowel obstruction and rectal mass on CT scan
- Warfarin is reversed and he proceeds to bowel resection
- He has acute renal failure with CrCl 20 mL/min
- Weight 80kg
- What anticoagulation would you prescribe postoperatively?

Heparin protocols - starting

NK continued

- 5 hours after starting IV heparin, the APTT is > 160 sec
  - What questions must you ask?
  - What would you prescribe next?
  - When should you repeat the APTT?
- 6 hours later the APTT is 52 sec
  - What would you prescribe now?
- 6 hours later the APTT is 95 sec
  - What would you prescribe next?
  - When should you repeat the APTT?
And adjusting – take blood for APTT when requested (on time)

<table>
<thead>
<tr>
<th>APTT (sec)</th>
<th>Goal</th>
<th>Recheck</th>
<th>Rate change</th>
<th>Next APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 - 13</td>
<td>18</td>
<td>3 hours</td>
<td>Increase 50%</td>
<td>30</td>
</tr>
<tr>
<td>14 - 17</td>
<td>30</td>
<td>6 hours</td>
<td>Increase 100%</td>
<td>60</td>
</tr>
<tr>
<td>18 - 20</td>
<td>60</td>
<td>6 hours</td>
<td>No change</td>
<td>60</td>
</tr>
<tr>
<td>21 - 23</td>
<td>120</td>
<td>6 hours</td>
<td>Decrease 50%</td>
<td>60</td>
</tr>
<tr>
<td>&gt; 23</td>
<td>180</td>
<td>6 hours</td>
<td>Decrease 100%</td>
<td>30</td>
</tr>
</tbody>
</table>

Note: Elderly patients may require more diluted than younger adults.

Case 3: Dawn Fraser

87yr old lady on Warfarin for AF
Hx of IHD, AF, CRF, DM
Presents with Decreased GCS
CT shows ICH
INR 7
What's next...
What questions do you ask?

NK continued

- Document APTT & what you want the infusion rate to be in the notes.
- Communicate with the nurse
- (Prescribe actual infusion rate on IV fluid order)

DF continued

[Table or diagram related to Case 3 and Warfarin therapy options]
DF continued

INR ≥ 1.5 with life threatening (critical organ) bleeding

INR ≥ 2.0 with clinically significant bleeding (not life threatening).

Any INR with minor bleeding

Cease warfarin therapy and administer:
• vitamin K1 (phytonadione) 5 – 10 mg IV
• and Prothrombinase -VF 50 - 150 IU
• and fresh frozen plasma 100 – 300 ml.
• If Prothrombinase -VF is unavailable, administer fresh frozen plasma 15 ml/kg.

Case 4: Lleyton Hewitt

54yr old gentleman
Severe nausea, vomiting, diarrhoea
Recent travel to Indonesia
Usually healthy
BP 90/60
Bili 20 ALT 240 AST 200 GGT 220 ALT 155
PT 20sec APTT 38sec INR 1.8
Management plan?

Ignore INR!

What is INR?
What is it used for?
How does correcting INR help the patient?

If not on Warfarin, INR is USELESS!

Who can help me?

• Your registrar
• The pharmacists
• The nurses (if they question something you’ve charted – check with someone else)
• Consultant
• Haematology registrar pager: 27150 Mob: 0409392151
• Consultant haematologist
• Anti-coagulation guidelines
The short answer...

Guidelines

Guidelines for Anticoagulation (Adult)
Approved for use in the following hospital/unit: Westmead, Blacktown Mt. Druitt, Auburn

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1. Thrombolipoprotein
2. Thrombotic Thrombocytopenia
3. Treatment of Deep Vein Thrombosis (DVT) or Pulmonary Embolus (PE)
4. Low Molecular Weight Heparin (DVT PE)
5. Oral Anticoagulation – Warfarin
6. LMWH Monitoring and Reversal
7. Unfractionated Heparin: Treatment of DVT/PE

Questions...

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