SAFE PRESCRIBING & ADMINISTRATION OF MEDICINES IN SCOTTISH HOSPITALS

TUESDAY 1 OCTOBER 2013
RCPE Symposium

Royal College of Physicians of Edinburgh
Representing physicians, maintaining standards.
Managing the Risks Associated with Anticoagulant Therapy

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NHS Greater Glasgow and Clyde
Background

- Identified as “high risk” medicines
- Wide range of indications for anticoagulation
  - For example:
    - Prevention and treatment of venous thromboembolism
    - Prevention and treatment of stroke and systemic embolism
    - Acute coronary syndromes
    - Treatment of intra-ventricular thrombus
    - Maintenance of catheter patency
    - Prevention of extracorporeal thrombosis
    - Prevention of heart valve thrombosis
- Wide range of possible patient demographics
- Multiple possible reasons for adverse outcomes
- Novel agents becoming available
Anticoagulation: Benefit vs. Risk

Benefit
- Indication
- Confidence in diagnosis
- Assessment of risk of thromboembolism
- Are validated tools available?
- Are they being used

Risk
- Assessment of risk of haemorrhage
- Risk of other ADRs
- Are validated tools available?
- Are they being used
Available anticoagulants

- Parenteral
  - Unfractionated Heparin (UFH)
  - Factor Xa inhibitors
    - Low Molecular Weight Heparins (LMWHs)
      - Enoxaparin
      - Dalteparin
      - Tinzaparin
      - Fondaparinux
      - Danaparoid
  - Direct thrombin inhibitors
    - Bivalarudin
    - Argatroban

- Oral
  - Vitamin K Antagonists (VKAs)
    - Warfarin
    - Acenocoumarol
    - Phenindione
  - Direct thrombin inhibitors
    - Dabigatran
  - Factor Xa inhibitors
    - Rivaroxaban
    - Apixaban
Mechanisms of action

Tissue Injury

XII  XIIa

XI  XIIa

IX  IXa

VII-TF

Prothrombin (II)

Thrombin (IIa)

Xa

Fibrinogen

Fibrin

Clot

Fibrinogen

Fibrin

Clot

TF

VII

Xa Inhibitors

Heparin (ATIII)

Ila Inhibitors

VKAs

XII

XI

IX

X

VKAs
Unfractionated Heparin: Benefits

• Rapid onset of action
  • Especially if IV bolus given
• Short half-life
  • Quick offset of action
• Reversible
  • Rapid offset of action
Unfractionated Heparin: Risks

- No fixed dose for full anticoagulant effect
  - Inter-patient variability
- Monitoring required
  - Guidance on interpretation
- Unfamiliarity with use
  - Rarely used as first line anticoagulant
- Often used for “non-therapeutic” reasons
  - Inadvertent anticoagulation
- Multiple formulations
UFH Formulations

- Heparin Sodium
  - 10 units/ml 5ml
  - 100 units/ml 2ml
  - 1000 units/ml 2ml, 5ml, 10ml, 20ml
  - 5000 units/ml 1ml, 5ml
  - 25000 units/ml 0.2ml, 1ml, 5ml
- Heparin Calcium
  - 25000 units/ml 0.2ml

- Are they all needed?
- What are the risks?
UFH Monitoring and Dose Adjustment

• Do prescribers know:
  • when to use?
  • how to monitor?
  • how to interpret findings?
  • How to adjust doses?

• Is guidance readily available?
• Is supporting documentation available?
LMWH: Benefits

- Once or twice daily administration
- No venous access required
- Fixed, weight based dosing
- No routine monitoring required
- Can be self-administered
- Reduced risk of needle-stick injuries
LMWH: Risks

- Indication based dosing
  - VTE vs ACS
- Weight based dosing
  - Extremes of weight
- Renal elimination
  - Dose adjustment
  - Choice of agent
- Combination treatment
  - Bleeding risk e.g. antiplatelets
Fondaparinux

Benefits
• Daily dosing
• Fixed dosing
• No HIT

Risks
• Unfamiliarity
• Indication based dosing
  • VTE vs ACS
• Renal elimination
  • CI if Clcr<20ml/min
VKAs

• Mainstay of medium / long-term therapy
  • Most common: 3 months to lifelong
• Extensive experience of their use
  • May depend on setting / services
• Problems well known
  • Bleeding
  • Non-bleeding ADRs
• Treatment intensity flexible E.g.
  • recurrent events on treatment
  • mechanical MVR
VKAs: Risks

- Loading doses variable
  - Pre-treatment INR
  - Age
    - Age adjusted Fennerty nomogram
  - Inter-patient variability
  - Maintenance dose
  - INR fluctuation
  - Interactions
    - Drug-Drug
    - Drug-Food
- Frequent monitoring
  - Time in therapeutic range
    - nOACS
VKAs: Documentation

• Protocols for initial dosing and subsequent adjustment
• Documentation to record:
  • Reason for anticoagulation / target INR
  • ‘Daily’ INRs
  • Daily doses
  • Plans for other antithrombotics
    • parenteral anticoagulants
    • antiplatelets
Transfer

• Different systems in primary care for follow-up
• Documentation to communicate:
  • Reason for anticoagulation / target INR
  • Recent INRs
  • Recent doses
  • Plans for other antithrombotics
    • Antiplatelets
  • Plans for follow-up
Anticoagulation of Adult Patients with Acute DVT or PE

INITIAL TREATMENT: start immediate treatment with Low Molecular Weight Heparin (LMWH)

Dalteparin is the LMWH of choice across NHSGGC for treatment of VTE unless the patient is pregnant or has specific contraindications to dalteparin.

Continue with dalteparin until:

- The diagnosis is disproved or
- the diagnosis is confirmed and the dalteparin has been over-lapped with warfarin for 4 - 6 days and the INR has been > 2 for two consecutive days.
- Dalteparin does not require laboratory monitoring (APPT is inappropriate, though if significant renal impairment or exceptionally low or high BMI, consider assessing anti-factor Xa activity 4 hours following dose of dalteparin)
- If still receiving dalteparin on day 6, measure platelet count to monitor for Heparin Induced Thrombocytopenia and repeat every 2 - 3 days while dalteparin continues (until day 14).

Follow on Treatment: using warfarin

- Commence oral anticoagulant (warfarin) on day objective confirmation of DVT or PTE is obtained
- Warfarin may not be appropriate for pregnant patients, patients with cancer or intravenous drug users – see Therapeutics Handbook for detailed guidance
- For most patients who require to quickly achieve an INR of 2-3, the age-adjusted Fennerty regimen is suitable.
- Perform baseline INR, and repeat INR daily for first 4 days.
<table>
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<tr>
<th>Day</th>
<th>INR</th>
<th>≤50 Years</th>
<th>51-65 Years</th>
<th>66-80 Years</th>
<th>&gt;80 Years</th>
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<td>7.5</td>
<td>6</td>
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<td>3.5-4.5</td>
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<td>2.6-3.0</td>
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<td>9.0-13.0</td>
<td>7.5-11.0</td>
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<td>1.5</td>
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<td>1.0-2.0</td>
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<td>0.5-1.5</td>
<td>0.5-1.0</td>
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<td>&gt;4.5</td>
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</tbody>
</table>

- Omit today’s dose then:
- ≤50 Years 1.0-2.0
- 51-65 Years 0.5-1.5
- 66-80 Years 0.5-1.5
- >80 Years 0.5-1.0

Withhold warfarin until INR < 3.0, then restart on 0.5-1.0 mg.
### Reversal of Anticoagulant Therapy

#### Reversal of LMWH
If patient is bleeding, give protamine sulphate by slow (5mg/min) IV injection to a maximum of 50mg in one dose.
If patient is continuing to bleed, consider fresh frozen plasma and further protamine – contact Duty Haematologist to discuss

#### Reversal of Warfarin

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Life-threatening bleeding (eg intracranial or major gastrointestinal bleed)</td>
</tr>
<tr>
<td>1</td>
<td>Stop warfarin</td>
</tr>
<tr>
<td>2</td>
<td>Give vitamin K₁ 5mg intravenously. Repeat if necessary</td>
</tr>
<tr>
<td>3</td>
<td>Give intravenous Prothrombin Complex Concentrate (Beriplex)</td>
</tr>
<tr>
<td>B</td>
<td>Less severe bleeding (eg haematuria, epistaxis)</td>
</tr>
<tr>
<td>1</td>
<td>Stop warfarin for 1-2 days</td>
</tr>
<tr>
<td>2</td>
<td>Give vitamin K₁ 0.5mg intravenously</td>
</tr>
<tr>
<td>3</td>
<td>Reassess</td>
</tr>
<tr>
<td>C</td>
<td>High INR but no bleeding</td>
</tr>
<tr>
<td>1</td>
<td>Stop warfarin and monitor INR. Restart warfarin when INR &lt; 5.0</td>
</tr>
<tr>
<td>2</td>
<td>Consider giving vitamin K₁ 0.5mg IV or 2mg orally if INR &gt; 8.0 or other risk factors for bleeding</td>
</tr>
</tbody>
</table>
GREATER GLASGOW & CLYDE ANTICOAGULATION SERVICE (GCAS)

PATIENT DETAILS
Name
Address
Hospital No (if known)
D.O.B.
CHI No.

CONSULTANT DETAILS
Name
Referring Ward and Hospital

GP DETAILS (or stamp)
Name
Address
Post Code
Tel No.

<table>
<thead>
<tr>
<th>INDICATION FOR ANTICOAGULATION</th>
<th>INR Target (range)</th>
<th>Recommended Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calf vein thrombosis</td>
<td>2.5 (2-3)</td>
<td>At least 3 months</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>2.5 (2-3)</td>
<td>6 months</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>2.5 (2-3)</td>
<td>6 months</td>
</tr>
<tr>
<td>Recurrent DVT and/or PE</td>
<td>2.5 (2-3)</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Recurrent DVT and/or PE while on warfarin (INR range 2-3)</td>
<td>3.5 (3-4)</td>
<td>Indefinite</td>
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<tr>
<td>Atrial fibrillation or high risk arrhythmias (see guidelines)</td>
<td>2.5 (2-3)</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Atrial fibrillation, awaiting cardioversion</td>
<td>2.5 (2-3)</td>
<td>Until further notice</td>
</tr>
<tr>
<td>Aortic mechanical prosthetic valve</td>
<td>2.5 (2-3)</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Mitral mechanical prosthetic valve</td>
<td>3.0 (2.5-3.5)</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Bioprosthetic heart valves (selected patients)</td>
<td>2.5 (2-3)</td>
<td>3 months</td>
</tr>
<tr>
<td>Cardiomyopathy, mural thrombus or akinetic segment</td>
<td>2.5 (2-3)</td>
<td>Indefinite</td>
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</table>

Other indications / target / duration (please specify)

Is the patient already on an anti-platelet agent (eg aspirin, dipyridamole, clopidogrel)? Yes ☐ No ☐
If yes should the antiplatelet agent be continued while on warfarin? Yes ☐ No ☐
If yes, please specify agent(s), dose and duration: ________________________________

Is patient referral for induction or ongoing monitoring? (Please circle which applies)
**OTHER RELEVANT INFORMATION**

<table>
<thead>
<tr>
<th>Other drug therapy</th>
<th>Daily warfarin maintenance dose prior to this admission:</th>
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<tbody>
<tr>
<td></td>
<td>Date warfarin treatment started:</td>
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<td>Anticoagulant clinic appointment date, time and Clinic:</td>
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**Other relevant factors - Please circle Yes or No for EACH condition:**

<table>
<thead>
<tr>
<th>Active Malignancy</th>
<th>Abnormal LFTs</th>
<th>Peptic Ulcer</th>
<th>Recent GI Bleed</th>
<th>Likely Poor Compliance</th>
<th>Alcohol above safe limits</th>
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<tbody>
<tr>
<td>YES / NO</td>
<td>YES / NO</td>
<td>YES / NO</td>
<td>YES / NO</td>
<td>YES / NO</td>
<td>YES / NO</td>
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</table>

**RESULTS AND TREATMENT RECORD (record 6 most recent results)** - *Shaded boxes – inpatients only*

<table>
<thead>
<tr>
<th>Date</th>
<th>LMWH (Drug &amp; Dose)</th>
<th>Prescriber's signature</th>
<th>Time given</th>
<th>Administered by</th>
<th>INR</th>
<th>Warfarin dose mg 18.00 hr</th>
<th>Prescriber's signature</th>
<th>Administered by</th>
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**Referring Doctors signature** ................................................................. (Must be completed) **Print name** .................................................................

**Date of referral** .................................................................................
Novel Oral AntiCoagulants (nOACS)

- Not widely used
- Place in therapy still being defined
- Restricted range of indications
  - VTE prevention and treatment
  - Stroke /systemic embolism prevention in AF
- Defined doses
- No routine monitoring required
nOACS: Risks

- Lack of experience
  - Awareness that they are anticoagulants
- No standard information
- Not readily reversible
  - Clinical relevance unknown
- No monitoring
  - Benefit and risk
  - Adherence
  - Efficacy
  - Effect on routine coagulation indices
- Some dose adjustments required
  - Desired outcome (dabigatran)
  - Renal function / age / weight
- Different interactions with other medicines
Conclusions

• Risk associated with anticoagulation well known
• Systems available to minimise risk
• Compliance with good practice can be an issue
• Newer agents may pose different risks