Drug interactions with warfarin

- Where possible avoid interacting drugs
- Monitor patients on interacting drugs
- Pharmacodynamic interactions
  - Through changes affecting drug-receptor complex
  - Increases risk of bleeding without increasing INR
- Pharmacokinetic interactions
  - Due to handling and time course of drug through body
  - Will alter INR

Drugs interact with warfarin: pharmacokinetics

Pharmacokinetic interactions

Alter the plasma concentration of warfarin, resulting in a change in the INR
- Absorption
- Distribution
- Metabolism
  ✓ extensively metabolised via cytochrome P450 system

Drug interactions that increase the INR

- Absorption - malabsorption of vitamin K
  - antibiotics, laxatives
- Distribution - displacement of warfarin binding from serum albumin
  - sulphonamides, phenylbutazone
- Metabolism - liver enzyme inhibition
  - cimetidine, amiodarone, metronidazole, fluconazole, ciprofloxacin

Drug interactions that decrease the INR

- Absorption:
  - Reduced absorption of warfarin - colestyramine
- Metabolism:
  - Liver enzyme induction - barbiturates, rifampicin, carbamazepine

Drugs interact with warfarin: pharmacodynamic
### Pharmacodynamic interactions

Increase the risk of bleeding without altering the plasma concentration of warfarin, for example:

- Anti-platelet drugs
  - clopidogrel
  - aspirin in low doses
  - dipyridamole
- NSAIDs

### Drug interactions with warfarin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on INR</th>
<th>Mechanism of Action</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Chronic alcoholics decrease INR</td>
<td>Stimulates hepatic enzymes</td>
<td>Advise patients about safe levels of alcohol. Assess anti-coagulants if warfarin appropriate. Monitor closely.</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Increase INR</td>
<td>Inhibits cytochrome concerned with metabolism of prothrombinogen: elimination reduced, anticoagulant effects prolonged.</td>
<td>Reduce dose by one third to one half. Monitor weekly. Effects persist for 6 –16 weeks after stopping amiodarone.</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Increase INR for doses 2 – 4g daily</td>
<td>Pharmacodynamic potentiation so low dose increases risk of bleeding</td>
<td>Advise patients to avoid aspirin containing products.</td>
</tr>
</tbody>
</table>

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<tr>
<td>Trimethoprim</td>
<td>Increase INR</td>
<td>May inhibit the metabolism of warfarin</td>
<td>Monitor closely.</td>
</tr>
<tr>
<td>Antidepressants - SSRIs</td>
<td>Increase or decrease INR</td>
<td>Pharmacodynamic interaction – increased risk of bleeding</td>
<td>Be aware of risk of bleeding if used concomitantly.</td>
</tr>
<tr>
<td>Antidepressants - Tricyclics</td>
<td>Increase or decrease INR</td>
<td>Not understood. May inhibit metabolism or slow GI motility</td>
<td>Monitor closely when commence and stopped.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Decrease INR</td>
<td>Warfarin metabolism increased. Elimination increased.</td>
<td>Warfarin dose may need doubled is patient stabilised. Monitor weekly initially.</td>
</tr>
<tr>
<td>Carbimazole</td>
<td>Decrease INR</td>
<td>Decrease in metabolism of clotting factors</td>
<td>Warfarin dose may need increased</td>
</tr>
<tr>
<td>Cortisosteroids</td>
<td>Increase or decrease INR</td>
<td>Mechanism not clear</td>
<td>Monitor closely, dose reduction may be required.</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Increase INR</td>
<td>Leads to increased warfarin activity possibly due to diazepam affecting thrombin formation</td>
<td>Monitor closely, switch to analgesics as start and stop therapy and alcohol.</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Increase INR</td>
<td>Not well understood</td>
<td>Dose may need to be reduced by one third to one half.</td>
</tr>
<tr>
<td>Imidazole anti-fungals</td>
<td>Increase INR</td>
<td>Effect on liver enzymes</td>
<td>Monitor closely. Avoid oral/vaginal preparations if possible.</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>Increase INR</td>
<td>Increase in metabolism of clotting factors</td>
<td>Warfarin dose reduced and closely monitored.</td>
</tr>
<tr>
<td>PPIs – esomeprazole, omeprazole and pantoprazole</td>
<td>Increase INR</td>
<td>Effect on liver enzymes</td>
<td>Monitor closely.</td>
</tr>
<tr>
<td>Statins</td>
<td>Increase INR</td>
<td>Effects CYP2C9 enzyme system</td>
<td>Monitor closely start of treatment, changes and increase in dose.</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Increase INR</td>
<td>Warfarin &amp; tamoxifen compete for same metabolizing systems</td>
<td>Patients may need dose of warfarin halved.</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Increase INR</td>
<td>Unknown</td>
<td>Closely monitor, may be required for patients who need a strong pain relif</td>
</tr>
</tbody>
</table>
**Drug interactions with warfarin**

- Influenza vaccination
  - Serious bleeding in a few patients
  - Mechanism of action is not understood
  - Care with IM route of administration
- Oseltamivir and zanamivir
  - Reports to MHRA of increases in INR
  - Mechanism of interaction unclear
  - Increased INR due to ‘flu symptoms rather than anti-virals?

**Herbal remedy and vitamin interactions with warfarin**

<table>
<thead>
<tr>
<th>Herbal Remedy/Vitamin</th>
<th>Effect</th>
<th>Potential Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfalfa</td>
<td>Decrease INR</td>
<td>Contains large amounts of Vitamin K.</td>
</tr>
<tr>
<td>Bilberry</td>
<td>Increased INR of bleeding</td>
<td>Mechanism unclear but used as an anti-inflammatory – avoid concomitant use.</td>
</tr>
<tr>
<td>Chamomile</td>
<td>Increased INR</td>
<td>May increase risk of bleeding, thought to be a constituent of coumarins.</td>
</tr>
<tr>
<td>Chondroitin sulphate</td>
<td>Increased INR</td>
<td>Anticoagulant or antithrombotic effects have been described.</td>
</tr>
<tr>
<td>Cod Liver Oil</td>
<td>Increased risk of bleeding</td>
<td>High in docosahexaenoic acid (DHA) and eicosapentaenoic (EPA), both of which can inhibit platelet aggregation.</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>Decrease in INR</td>
<td>Reduces anticoagulant effect as structurally similar to Vitamin K.</td>
</tr>
<tr>
<td>Devil’s claw</td>
<td>Increased risk of bleeding</td>
<td>May enhance the anticoagulant effect, used to reduce inflammation.</td>
</tr>
<tr>
<td>Dong Quai</td>
<td>Increased risk of bleeding</td>
<td>Increased risk of bleeding due to inhibition of COX and platelet aggregation.</td>
</tr>
</tbody>
</table>

**Herbal remedy and vitamin interactions with warfarin**

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<tr>
<td>Evening Primrose Oil</td>
<td>Increased risk of bleeding</td>
<td>Potential antiplatelet effect, may increase risk of bruising and bleeding.</td>
</tr>
<tr>
<td>Fenugreek</td>
<td>Increased risk of bleeding</td>
<td>Potential antiplatelet effect, may increase risk of bleeding.</td>
</tr>
<tr>
<td>Feverfew</td>
<td>Increased risk of bleeding</td>
<td>May increase risk of bleeding, used to treat pain and arthritis.</td>
</tr>
<tr>
<td>Flaxseed Oil</td>
<td>Increased risk of bleeding</td>
<td>May decrease platelet aggregation and increase bleeding.</td>
</tr>
<tr>
<td>Garlic</td>
<td>Increased risk of bleeding</td>
<td>Has antiplatelet effects.</td>
</tr>
<tr>
<td>Ginkgo Biloba</td>
<td>Increased risk of bleeding</td>
<td>In vitro evidence suggests inhibits platelet aggregation.</td>
</tr>
<tr>
<td>Ginger</td>
<td>Increased risk of bleeding</td>
<td>Inhibits platelet aggregation.</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Increased INR</td>
<td>Contains coumarin.</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>Increased INR</td>
<td>Mechanism unclear.</td>
</tr>
</tbody>
</table>

**Drugs that can increase the risk of VTE**

- Combined hormonal contraceptives
- Hormone replacement therapy
- Tamoxifen
-Raloxifene
- Clozapine and olanzapine (very rare side-effect)

- Prevents
- Starts
- Dose change
Initiating warfarin therapy

- Assess patient’s coagulation status
  - Baseline INR
  - Indication for treatment
  - Identify appropriate INR target range
  - Proposed duration of treatment

- Recorded in patient’s case records and oral anticoagulant therapy book

Rapid anticoagulation

- Indicated for acute thromboembolism or following a heart valve replacement:
  - Heparin (LMWH) and warfarin administered on day 1

- Warfarin prescribed using either:
  - ‘Fennerty’ induction regimen – 10mg warfarin daily with monitoring and titration depending on the INR to achieve and maintain therapeutic range
  OR
  - 5mg dose or single 10mg dose followed by 5mg doses in elderly (>60 years), liver disease, cardiac failure or at risk of bleeding

- Heparin continued for at least 5 days and withdrawn when INR in therapeutic range for two consecutive days

Slow-loading anticoagulation

- Indicated for atrial fibrillation
- 2mg, 3mg or 5mg daily
- Safe and achieves anticoagulation within 3-4 weeks

Monitoring

- Induction and initial stabilisation
  - Daily INR measurements
  - Thereafter dictated by INR values
- 4-6 weeks post-stabilisation
  - Weekly monitoring
  - Gradually increasing to 4-8 weekly
- If INR well stabilised
  - 12 weekly INR monitoring

Over anticoagulation

High INR may be caused by:

- Inappropriately high dose of warfarin
- Drug interaction
- Alcohol
- Intercurrent Illness
- Reduction in vitamin K intake or decreased synthesis of vitamin K factors
- Increased clearance of vitamin K dependant clotting factors
Presentation of over anticoagulation

- Bruising
- Bleeding
- Haematuria
- Blood in stools
- Nose bleeds
- Bleeding gums

Treatment of over anticoagulation (1)

Major bleeding:
- Stop warfarin
- Give phytonadione (vitamin K) 5-10mg slow intravenous injection
- Give Prothrombin Complex Concentrate, e.g. Octaplex® or Beriplex® 30-50 units/kg

Minor bleeding:
- Stop warfarin
- Urgent INR
- Give phytonadione (vitamin K) orally or by slow intravenous injection
- Check INR in 24 hours or sooner if clinical deterioration

Treatment of over anticoagulation (2)

No bleeding but INR > 5.0

- INR > 8.0
  - Stop warfarin and give phytonadione (vitamin K) orally or by slow intravenous injection.
  - Check INR in 24 hours or sooner if clinical deterioration.
- INR 5.0 – 8.0
  - If the patient has a low/moderate risk of bleeding - stop warfarin and recheck INR, restart warfarin when INR < 5.0.
  - If patient is at high risk of bleeding - stop warfarin and consider phytonadione (vitamin K) orally. If given, check INR in 24 hours

Treatment of over anticoagulation (3)

Bleeding with therapeutic or sub-therapeutic INR

- Investigate possible underlying causes.
  - There is often a reason for gastrointestinal bleeding in patients on oral anticoagulant therapy, particularly in the elderly.
  - Not acceptable to dismiss bleeding as occurring due to anticoagulant therapy without appropriate investigation.

Under anticoagulation

Low INR may be caused by

- Inappropriately low dose of warfarin or non-compliance
- Drug interaction
- Alcohol
- Intercurrent Illness
- Increase in vitamin K intake
- Decreased clearance of vitamin K dependant clotting factors

Risks associated with under anticoagulation

- Increased risk of further VTE, especially if patient has had a DVT/PE in past four weeks
- In patients with a mechanical heart valve, increased risk of a clot forming around valve and stroke
- In patients with atrial fibrillation, increased risk of stroke
DVT patients
- Symptoms of DVT may reoccur, e.g. pain, swelling in leg.
- May develop PE – signs may be pain in chest, shortness of breath – potentially fatal

Stroke
- Numbness, confusion, visual disturbance, loss of balance or co-ordination, severe headache - FAST

Presentation of under anticoagulation

Treatment of under anticoagulation

- Increase dose of warfarin if patient presents with sub-therapeutic INR and monitor
- In high risk patients, bridge anticoagulation with LMWH until INR reaches therapeutic range
- Monitor patients with erratic INR control closely
- Educate the patient about symptoms and dangers of sub-therapeutic INRs

Anticoagulant therapy: information for community pharmacists

Patient counselling

- Indication for warfarin therapy
- Target INR
- Duration of treatment
- Consider medical history and other medication
- Be prepared to tailor the consultation to suit the patient

Counselling points

- What is warfarin and how does it work?
- How much warfarin will I need and how long will I need it?
- What is the INR?
### Counselling points

- Do I have to take it every day?
- What if I miss a dose?
- Why do I need my blood monitored?
- What are the signs of too much warfarin?
- Does warfarin have any side effects?

### Counselling points

- Interactions with other medicines
- What about my current medication?
- What can I eat?
- Can I drink alcohol?
- Visiting the dentist
- Pregnancy (if appropriate)

### Yellow oral anticoagulant therapy pack

- New pack – became available in 2009
- Issued to patients Summer ’09
- Available from the BSO (previously CSA)
  - Separate information booklet
  - Therapy record book
  - Anticoagulant alert card

### Anticoagulation in pregnancy

**Pregnancy and oral anticoagulants**

- Warfarin, acenocoumarol and phenindione are teratogenic
  - First trimester – foetal warfarin syndrome
  - Second and third trimesters - congenital malformations
  - Problems can be avoided if the patient stops taking warfarin before the sixth week of pregnancy

- Dabigatran and Rivaroxaban – manufacturer recommends avoid in pregnancy

### Women who require anticoagulation during pregnancy

1. Women who are already taking warfarin for an existing condition and become pregnant
2. Women who develop a VTE during pregnancy
3. Women who have had a VTE or who have antiphospholipid syndrome

### Delivery and commencing warfarin post-delivery

- Labour induced around 38 weeks
- Enoxaparin given day before induction and is recommenced once the baby has been delivered
- If warfarin is to be commenced, it may be started on the day of delivery
  - Enoxaparin should be continued until the INR is therapeutic, and in the case of a DVT / PE for at least five days
- Daily INR monitoring is required until the INR is in therapeutic range
- Maintaining INR within therapeutic range is particularly difficult in post-partum patients
Enoxaparin may be prescribed:
- For seven days following a Caesarian Section
- For four weeks following hip fracture surgery
- As bridging therapy when a high-risk patient has a low INR or is undergoing elective surgery