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

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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

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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

Drug	Effect on INR	Mechanism of Action	Management
Alcohol	Chronic alcoholics decrease INR Binge drinkers increase INR	Stimulates hepatic enzymes Warfarin not eliminated, INR increased	Advise patients about safe levels of alcohol. Assess alcoholics if warfarin appropriate. Monitor closely.
Amiodarone	Increase INR	Inhibits cytochrome concerned with metabolism of s-enantiomer, elimination reduced, anticoagulant effects prolonged.	Reduce dose by one third to one half. Monitor weekly. Effects persist for 6 –16 weeks after stopping amiodarone.
Aspirin	Increase INR for doses 2 – 4g daily	Pharmacodynamic potentiation so low dose increases risk of bleeding	Advise patients to avoid aspirin containing products.

Drug interactions with warfarin

Drug	Effects on INR	Mechanism of Action	Management
Antibiotics - Chloramphenicol Metronidazole Sulphonamides	Increase INR	Not understood – may be due to liver enzyme inhibiton	Monitor closely.
Cephalosporins Tetracyclines	Increase INR	Mechanism is not clear - have been a number of reported incidents of increased INR	Monitor closely. Can cause bleeding & hypothrombinaemia.
Macrolides	Increase INR	Inhibits liver enzymes	Monitor closely, particularly in patients who clear warfarin slowly.
Quinolones [reports of interaction with ciprofloxacin, norfloxacin and levofloxacin]	Increase INR Unpredictable	Inhibits liver enzymes	Watch out for patients on prophylactic doses - effect not necessarily seen immediately.

Drug interactions with warfarin

Drug	Effect on INR	Mechanism of Action	Management
Trimethoprim	May increase INR	May inhibit the metabolism of warfarin	Monitor closely
Antidepressants - SSRIs	May increase INR	Pharmacodynamic interaction – increased risk of bleeding	Be aware of risk of bleeding if used concomitantly
Antidepressants - Tricyclics	Increase or decrease INR	Not understood. May inhibit metabolism or slow GI motility	Monitor closely when commence and stopped
Carbamazepine	Decrease INR	Warfarin metabolism increased. Elimination increased.	Warfarin dose may need doubled is patient stabilised. Monitor weekly initially.
Carbimazole	Decrease INR	Decrease in metabolism of clotting factors	Warfarin dose may need increased

Drug interactions with warfarin

Drugs	Effect on INR	Mechanism of Action	Mangement
Corticosteroids	Increase or decrease INR	Mechanism not clear	Monitor closely, dose reduction may be required.
Disulfriam	Increase INR	Leads to increase warfarin activity possibly due to disulfiram affecting thrombin formation	Monitor closely, watch alcoholics as start and stop therapy and alcohol.
Fibrates	Increase INR	Not well understood	Dose may need to be reduced by one third to one half.
Imidazole anti-fungals	Increase INR	Effect on liver enzymes	Monitor closely. Avoid oral/vaginal preparations if possible.

Drug interactions with warfarin

Drug	Effect on INR	Mechanism of Action	Management
Levothyroxine	Increase INR	Increase in metabolism of clotting factors	Warfarin dose reduced and closely monitored.
PPIs– esomeprazole, omeprazole and pantoprazole	Increase INR	Effect on liver enzymes	Monitor closely.
Statins	Increase INR	Effects CYP2C9 enzyme system	Monitor closely start of treatment, changes and increase in dose.
Tamoxifen	Increase INR	Warfarin & tamoxifen compete for same metabolising systems	Patients may need dose of warfarin halved.
Tramadol	Increase INR	Unknown	Closely monitor, may be required for patients who need a strong pain relief

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

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

Herbal remedy and vitamin interactions with warfarin

Herbal Remedy/Vitamin	Effect	Mechanism Of Action
Evening Primrose Oil	Increased risk of bleeding	Potential antiplatelet effect, may increase risk of bruising and bleeding.
Fenugreek	Increased risk of bleeding	Potential antiplatelet effect, may increase risk of bleeding.
Feverfew	Increased risk of bleeding	May increase risk of bleeding, used to treat pain and arthritis
Flaxseed Oil	Increased risk of bleeding	May decrease platelet aggregation and increase bleeding.
Garlic	Increased risk of bleeding	Has antiplatelet effects.
Ginkgo Biloba	Increased risk of bleeding	In vitro evidence suggests inhibits platelet aggregation.
Ginger	Increased risk of bleeding	Inhibits platelet aggregation.
Ginseng	Increase INR	Contains coumarin
Glucosamine	Increase INR	Mechanism unclear.

Herbal remedy and vitamin interactions with warfarin

Herbal Remedy/Vitamin	Effect	Mechanism Of Action
Multivitamin supplements	Decrease INR	Use cautiously in patients taking warfarin. Many contain Vitamin K. Many contain ingredients that affect warfarin metabolism eg. Ginseng, bilberry, Vitamin E.
Red Clover	Increase INR	Contains coumarin-like chemicals. May increase risk of bleeding.
St John's Wort	Decrease INR	Might induce the enzyme involved in warfarin metabolism.
Vitamin E	Increased risk of bleeding	Inhibits platelet aggregation and antagonises the effects of clotting factors. Effects are dose dependent and clinically significant with >400 units/ day.

Drugs that can increase the risk of VTE

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

- **Stop**
- **Start**
- **Dose change**

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Initiating warfarin therapy

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 phytomenadione (vitamin K) 5-10mg slow intavenous injection
- Give Prothrombin Complex Concentrate, e.g. Octaplex® or Beriplex® 30-50 units/kg

Minor bleeding:

- Stop warfarin
- Urgent INR
- Give phytomenadione (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 phytomenadione (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 phytomenadione (vitamin K) orally. If given, check INR in 24 hours

Treatment of over anticoagulation (3)

Bleeding with therapeutic or sub-therapuetic 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

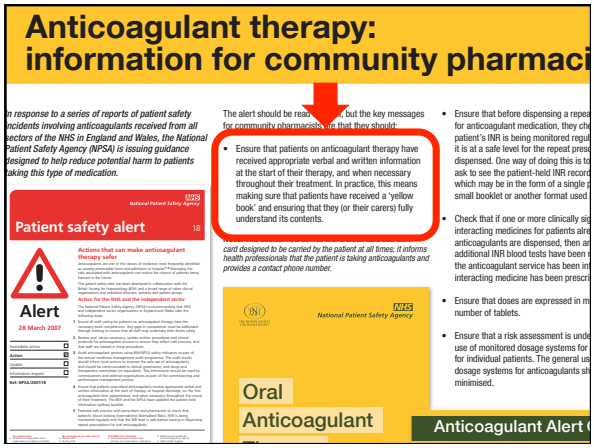
- Increased risk of further VTE, especially if patient has had a DVT/PE in past four weeks
- In patients with a mechanical heart valve, increased risk of a clot forming around valve and stroke
- In patients with atrial fibrillation, increased risk of stroke

Presentation of under anticoagulation

- 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

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



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Patient counselling

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 in practice

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**