Antiplaetelets and Anticoagulants

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Clinical update

• Introduction
• NUH anticoagulation service
• Antiplatelets
• Anticoagulants – warfarin, LMWH
• New anticoagulants
Introduction

• Anticoagulants consistently associated with serious adverse incidents in primary and secondary care (at least 600 between 1990-2002)

• Warfarin and NSAID’s among most frequent drug related reason for hospital admissions

• Due to this – BCSH/ACCP guidelines and NPSA alerts
NUH anticoagulation service

- Fully merged service across both sites dosing ~6800 patients
- Morning clinics (20-100+ patients) at QMC site Mon-Fri with capillary sampling
- GP remote dosing in pm (300-800+ samples) – Most Nottingham GP’s do not dose patients
- Monday early morning clinics
- Self testing patients
- Dosing for **SAFE** discharge on both sites – cut off times due to GP work in pm
- Helpline – 9194413
- PGD’s for warfarin, enoxaparin, vitamin k
- Out patient DVT service run with NEMS
- KPI for waiting times, discharges etc
Antiplatelets

- Arterial thrombi platelet rich so use antiplatelets
- Agents disrupt platelet activation via inhibition of agonists and adhesion/aggregation
- Aspirin – irreversibly inhibits COX-1 and block formation of platelet agonist thromboxane – effect last platelet lifetime (~10/7)
Antiplatelets

• Dipyridamole increases platelet aggregation inhibitor cAMP
• Thienopyridine drugs (clopidogrel and prasugrel) reduce platelet activation by non-competitively and irreversibly blocking the binding of ADP to P2Y$_{12}$ receptors on platelet membrane
Antiplatelets

• Clopidogrel is transformed by CYP450 enzymes to active metabolite which results in variability in effect
• Prasugrel more potent inhibitor and less affected by CYP450 variation
• Ticagrelor is direct reversible P2Y$_{12}$ antagonist and does not require hepatic activation
Antiplatelets uses

- Not used in primary prevention of cardiovascular events
- **MI/unstable angina** – aspirin long term and P2Y$_{12}$ blocker for 12 months (STEMI at least 4 weeks dual therapy but PCI preferred treatment), if aspirin C/I monotherapy with P2Y$_{12}$ blocker
- **PCI** – bare metal stents aspirin long term clopidogrel for at least 28 days – drug eluting stents aspirin long term clopidogrel for at least 12 months, if aspirin C/I monotherapy with P2Y$_{12}$ blocker
- **Stable angina/CAD** – aspirin long term, if aspirin C/I monotherapy with P2Y$_{12}$ blocker
Antiplatelets uses

- **Ischaemic stroke (not AF related) --**
  - long term clopidogrel
  - if clopidogrel plus PPI not tolerated
    - dipyridamole and aspirin alternative
  - if clopidogrel and dipyridamole not tolerated or C/I use aspirin alone
  - If clopidogrel and aspirin not tolerated or C/I use dipyridamole
Antiplatelet uses

- **Peripheral arterial disease and multivascular disease** – clopidogrel long term
- **TIA** - dipyridamole and aspirin long term – if aspirin not tolerated or C/I dipyridamole alone
Antiplatets and anticoagulants

- Therapy can be combined e.g. aspirin and warfarin for AF in pts with ACS
- 5-10% of pts with a stent have an indication for anticoagulation
- Triple therapy in some pts – usually used for shortest possible time then to dual therapy
- If pts have stable CAD and on warfarin usually no antiplatelet therapy necessary
Counselling points

- Reason for therapy
- Missed doses
- Side effects
- Peri operative issues
- Duration of therapy
Anticoagulants

- The cost of blood clots in the UK:
- DVT leads to 66,000 hospitalisations each year
- 15,000 deaths due to PE each year
- VTE costs the NHS £8781 per 100 patients
- The cost of each stroke patient admitted to hospital is approx £2,000
- The major burden of stroke is chronic disability, it accounts for around 6% of total NHS and social services expenditure - £2.3 billion per year
Warfarin

• Competitively antagonises the effect of vitamin K which is essential for the synthesis of clotting factors II, VII, IX and X (and the natural anticoagulants protein C and S).
• The clotting factor levels are reduced at rates proportional to their half-lives
• Monitored by the prothrombin time (INR), this is prolonged by deficiencies of factors V, VII, X, II and low fibrinogen, it reflects alterations in the extrinsic and common pathways
• Alternatives phenindione and acenocoumarol
Relationship Between INR and Efficacy/Safety

- **Low-intensity treatment:**
  - Efficacy rapidly diminishes below INR 2.0
  - No efficacy below INR 1.5

- **High-intensity treatment:**
  - Safety compromised above INR 4 (risk of bleeds increases significantly at INR>5)
Relative Contraindications to Warfarin Therapy

• Pregnancy (teratogenic use LMWH)
• Situations where the risk of hemorrhage is greater than the potential clinical benefits of therapy
  – Uncontrolled alcohol/drug abuse
  – Unsupervised dementia/psychosis
Warfarin: Major Adverse Effect—Hemorrhage

- Factors that may influence bleeding risk:
  - Intensity of anticoagulation
  - Concomitant clinical disorders
  - Concomitant use of other medications
  - Quality of management
## Warfarin: Current Indications/Intensity

<table>
<thead>
<tr>
<th>Indication</th>
<th>INR range</th>
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<tbody>
<tr>
<td>Prophylaxis of venous thrombosis (high-risk surgery)</td>
<td>2-3</td>
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<tr>
<td>Treatment of venous thrombosis</td>
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<tr>
<td>Treatment of PE</td>
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<td>Prevention of systemic embolism (arterial)</td>
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<td>Tissue heart valves</td>
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<td>AMI (to prevent systemic embolism)</td>
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<tr>
<td>Valvular heart disease</td>
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<td>Atrial fibrillation</td>
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<td>Bileaflet mechanical valve in aortic position</td>
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<tr>
<td>Mechanical prosthetic valves (high risk)</td>
<td>2.5–3.5</td>
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<tr>
<td>Certain patients with thrombosis and the antiphospholipid syndrome</td>
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<tr>
<td>Recurrent thrombosis and older prosthetic valves</td>
<td>3-4</td>
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Reversal of anticoagulants

• Warfarin use vitamin K and concentrated clotting factors if needed (octaplex or rVIIa)
• UFH reverse with protamine
• LMWH can be partially reversed with protamine
Duration of therapy and thrombophilia screening

- 3 months – DVT below knee, provoked DVT/PE
- 3 months – above knee DVT unprovoked, PE unprovoked (but follow up with resp and ?long term)
- Long term – heart valves, recurrent VTE, inherited clotting disorders, AF
- NUH follow up unprovoked events if <50, VTE at unusual sites and if strong family history
Drug interactions with warfarin

- These can broadly be divided into 2 mechanisms – pharmacokinetic and pharmacodynamic
- PHARMACOKINETIC interactions affect the processes by which drugs are: absorbed, distributed, metabolised and excreted (does not usually effect warfarin)
- PHARMACODYNAMIC interactions occur when the effects of one drug are changed by the presence of another drug at its site of action
- Can be additive e.g. antihypertensives
- Can be antagonistic e.g. warfarin and vitamin K
Absorption interactions with warfarin

- Can effect rate or total amount of absorption
- Colestyramine binds to warfarin and reduces its absorption
- May also reduce vitamin K absorption
- Need to separate dosages by at least 2 hours
- Sucralfate may also bind to and reduce warfarin absorption
Distribution interactions with warfarin

• Warfarin very highly plasma protein bound

• Interaction usually due to displacement of warfarin from protein binding sites in plasma

• Increases the amount of free warfarin which is then exposed to metabolism

• Effect usually transient and not thought to play a major role in interactions
Metabolism interactions with warfarin

- Most drugs are altered to make them more water soluble and thus more easily excreted.
- This mostly occurs in the liver by enzymes known as cytochrome P450 system.
- Interactions between drugs can result in:
  1. Increased metabolism (via enzyme induction).
  2. Decreased metabolism (via enzyme inhibition).
Cytochrome (CYP) P450 and warfarin (1)

• There are many subtypes of cytochrome enzymes
• Warfarin is a mixture of 2 isomers – R and S
• S-warfarin is the more potent (by 4 fold) anticoagulant and is metabolised by CYP2C9
• R-warfarin is metabolised by CYP1A2, CYP2C19 and CYP3A4
CYP450 and warfarin (2)

- Can possibly predict warfarin interactions from knowing which other drugs affect the same cytochrome enzymes.
- Patients may show considerable variation in their CYP450 ability and response to inhibitors or inducers (depends on dose of inducer/inhibitor and warfarin, genetics, age and hepatic disease).
- Accurate prediction of interactions can be difficult and problems usually arise when drugs are added or withdrawn to patients stabilised on warfarin.
Enzyme induction interactions (1)

- These drugs increase metabolism of warfarin by inducing the synthesis of new liver enzymes and thus lowering INR.
- Initial effect within first 2 days, maximal effect after ~ 1 week (may take several weeks to fully develop) – onset depends on half life of drug (e.g. rifampicin onset more rapid than phenobarbitone).
- Dissipation of effect gradual – again depends on half life of inducer and decay of enzymatic activity.
Enzyme induction interactions (2)

- May need to raise warfarin dose while patient taking inducer

- Examples include: alcohol (chronic), barbiturates, carbamazepine, griseofulvin, nevirapine, phenytoin, rifampicin (potent inducer), tobacco smoke
Enzyme inhibition interactions (1)

- These drugs reduce warfarin metabolism by inhibiting liver enzymes and increasing INR
- Initial effect rapid (within 1-3 days)
- Dissipation of effect more rapid than induction
- May need to reduce warfarin dose whilst patient taking inhibitor drug
Enzyme inhibition interactions (2)

- Numerous drugs act as inhibitors and may raise INR
- Inhibitors of S-warfarin include: amiodarone, cimetidine, co-trimoxazole, disulfiram (may chelate metal ions necessary for production of active thrombin), fluvoxamine, metronidazole, phenylbutazone, zafirlukast
- Inhibitors of R-warfarin include: clarithromycin, ciprofloxacin, danazol, erythromycin, fluconazole, fluoxetine, itraconazole, ketoconazole, miconazole, norfloxacin, omeprazole, zileuton
Enzyme inhibition interactions (3)

• Other CYP 450 inhibitors that can affect warfarin include: allopurinol, azapropazone, dextropropoxyphene, fibrates (can also increase affinity of the anticoagulant for its receptor) and propafenone
Other mechanisms (1)

- Tamoxifen may compete with warfarin for metabolism by CYP system – can raise INR
- Thyroid/Antithyroid drugs – hypothyroid catabolism of clotting factors low and if started on thyroid replacement will need less warfarin. Hyperthyroid increased catabolism and if started on antithyroid drug need more warfarin
Other mechanisms (2)

• High dose corticosteroids may increase the coaguability of the blood

• Oral contraceptives may increase plasma levels of factor X and fibrinogen and reduce antithrombin III levels
Unknown mechanisms

- Flutamide, anabolic steroids and paracetamol (higher dose and prolonged use) may increase INR by largely unknown mechanisms.

- Cytotoxic drugs may decrease INR (azathioprine) or increase INR (fluorouracil) again by largely unknown mechanisms.
Warfarin interactions with herbal medicines

- Perception of being ‘safe’ but still potential for interaction with warfarin
- Possibly similar mechanisms as for conventional medicines, but information on products limited
- **Reported** and **theoretical** interactions
- Difficult to predict outcome as levels of active ingredients vary between herbal preparations for same product
Reported interactions (1)

- Liver enzyme induction – St. Johns Wort, avocado (also may impair warfarin absorption)
- Liver enzyme inhibition – cranberry juice, lycium, grapefruit juice
- Anti-platelet actions – danshen (plus antithrombin III action and reduced elimination of warfarin), panax ginseng, garlic, gingko biloba, boldo
- Contains coumarin derivatives – dong quai (plus inhibits platelet activation), PC-SPES, fenugreek, sweet woodruff, tonka,
Reported interactions (2)

- Increased vitamin K content – green vegetables etc
- Vitamin K like action – co-enzyme Q10
- Increased vitamin K synthesis and absorption – Natto
- Unknown mechanism but increased INR – devil’s claw, glucosamine, papain, mango fruit
Theoretical interactions (1)

- Antiplatelet – arnica, clove (eugenol), cod liver oil (DHA and EPA) and other fish oils, dandelion root, feverfew, flaxseed oils, tumeric
- Contains coumarin derivatives – alfalfa, anise, capsicum, chamomile, ginseng (Siberian), horse chestnut, horseradish, liquorice root, nettle, parsley, rue
- Liver enzyme inhibitors – echinacea, ipriflavone, milk thistle
Theoretical interactions (2)

• Contains salicylates – black haw, German sarsaparilla, meadowsweet, poplar, willow bark

• Miscellaneous – chondroitin (anticoagulant or antithrombotic) and evening primrose oil (anticoagulant)
Which drugs are common ‘culprits’?

• In practice we usually encounter issues commonly with:
  • Amiodarone
  • Rifampicin (very potent inducer)
  • Antibiotics/antifungals
  • Miconazole
• However interactions are complex and unpredictable
Heparins

- UFH is a polysaccharide mixture and binds to antithrombin III which inactivates thrombin (factor II) and factor Xa
- Monitor by using APTT ratio (1.5-2.5) this screens the INTRINSIC pathway and shows any abnormality of factors II, V, VIII, IX, X, XI and XII
- LMWH largely only inactivate factor Xa, have a longer half-life and a more predictable response, so no routine monitoring required (except in pregnancy, high or low body weight)
- Fondaparinux synthetic Xa inhibitor
Heparins

- NUH use enoxaparin for VTE prophylaxis, VTE treatment, ACS treatment
- Also used off license for thrombus prevention in AF, sub therapeutic INR’s in patients with mechanical heart valves, long term VTE treatment in patients unable to tolerate oral anticoagulants and VTE treatment in pregnancy
- Fondaparinux synthetic and used if patients refuse porcine products or heparin allergy
Conversion of heparin to warfarin

• May begin concomitantly with heparin therapy
• Heparin should be continued for a minimum of four to five days
  – Time to peak antithrombotic effect of warfarin is delayed 96 hours (despite INR)
• When INR reaches desired therapeutic range, discontinue heparin (after a minimum of four to five days)
Management of Warfarin During Invasive Procedures

- For subtherapeutic or normal INR: Hold warfarin for 3–5 days pre-procedure.
- Prophylactic enoxaparin (20-40mg daily) or UFH (5000u BD-TDS) if severe renal impairment: hold warfarin 3–5 days pre-procedure and begin LMWH/UFH therapy 1–2 days pre-procedure.
- Treatment dose enoxaparin (1.5mg/kg daily or 1mg/kg BD if MHV) or UFH infusion (if severe renal impairment or high risk of bleeds): timings as above.
- Enoxaparin dose reduced in renal impairment (1mg/kg daily).
- Restart heparin or warfarin post-op when considered safe to do so.
Effective Patient Education

• Teach basic concepts of safe, effective anticoagulation
• Discuss importance of regular INR monitoring
• Tablet strength and supply
• Counsel on use of other medications, alcohol, diet, exercise, smoking, long journeys, pregnancy, compression hosiery for DVT
• Develop creative strategies for improving compliance
Effective patient education

- NUH use DVD to show patients on initial clinic visit
- Patient help line, who to contact, alert card and PIL
- Counseling checklist to enhance consistent information
- Regular communication audit
- NPSA alert data required to be collected on this area
Questions?