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## Diagnosis of DVT and Effective Anticoagulation - Main Session (Workshop options scheduled)

Saturday, 17 August 2013 Start 9:30am Duration: 20mins Plenary

# Venous Thrombo-embolism and Effective Anticoagulation

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# Topics

- Risk assessment for DVT
- D-Dimer assays
- Role of warfarin and new oral anticoagulants
- Duration of anticoagulation
- Pregnancy
- Cancer-associated thrombosis

# Background

- VTE is 5th commonest cause of death in NZ
  - Annual incidence 160 per 100,000 for DVT
  - 20 per 100,000 for symptomatic non-fatal PE
  - 50 per 100,000 for fatal autopsy detected PE
- Objective diagnosis and prompt treatment are essential in this common, complex and costly problem
- There is an explosion of data in the past few years but is it time to say farewell to warfarin?

# RISK ASSESSMENT FOR VTE

# Risk assessment for VTE

| Clinical Feature | Score |
|---|---|
| Active cancer (within 6/12) | 1 |
| Paralysis or recent leg plaster | 1 |
| Recent immobility for > 3 days or major surgery within 4 weeks | 1 |
| Localised tenderness along vein | 1 |
| Entire leg swollen | 1 |
| Calf swelling by more than 3 cm | 1 |
| Pitting oedema | 1 |
| Collateral superficial veins | 1 |
| Alternative diagnosis as likely or more likely than DVT | -2 |

# Risk assessment for VTE

- Pretest probability of DVT
  - High probability = 3 or greater
  - Moderate probability = 1 or 2
  - Low probability = 0 or less

- Up to 90% of patients referred for ultrasonography with suspected DVT of the leg do not have one

# D-DIMER ASSAYS

# D-Dimer assays

- Plasma levels increase on average 8-fold in VTE
- Levels fall in parallel with duration of symptoms and introduction of anticoagulant therapy in healthy population
- Levels also increased in:
  - Infection/inflammation
  - Cancer
  - Surgery
  - Trauma, extensive burns or bruises
  - Ischaemic heart disease, stroke, peripheral artery disease
  - Ruptured aortic aneurysm or aortic dissection
  - Pregnancy

# D-Dimer assays

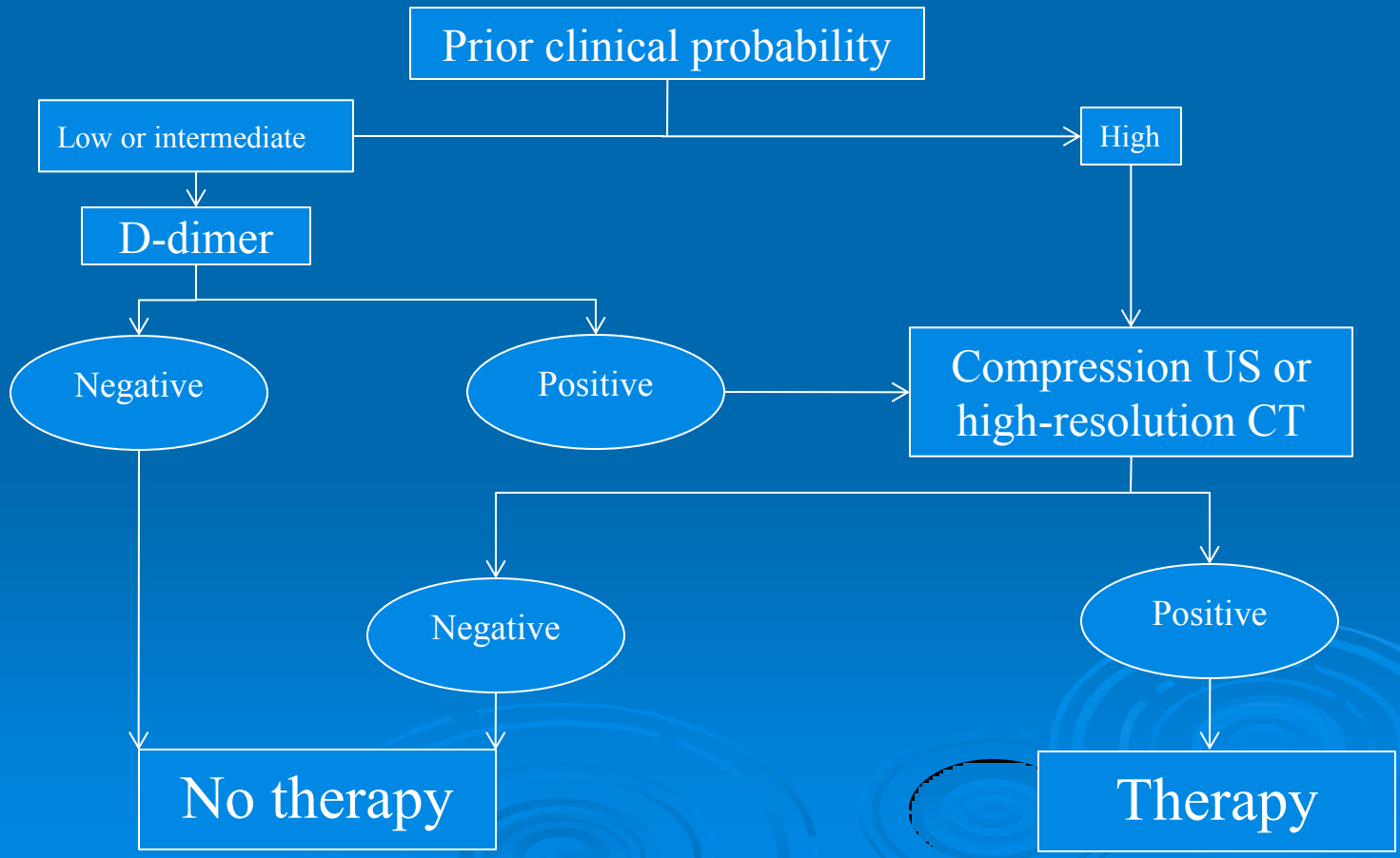
- SimpliRed® test
  - Designed for whole blood point-of-care testing
  - Result in < 5minutes
  - Inter-observer variability
  - Sensitivity 83% for DVT and 87% for PE
  - Enough to rule out VTE but only in presence of a **LOW** clinical probability

# D-Dimer assays

- Caveats in special populations
  - Elderly
    - Significant decrease of specificity and therefore clinical usefulness with ↑ age
    - Rule out PE in 2/3 pts aged < 40, but 5% aged >80
    - Age adjusted range in some labs
  - Pregnancy
    - Levels increase as pregnancy progresses
  - Pts with small thrombus burden
    - Lower in distal DVT
  - Pts with prolonged duration of symptoms
  - Pts already on anticoagulant treatment

# D-Dimer assays

- Place of D-Dimer in diagnostic algorithm



# ROLE OF WARFARIN AND NEW ORAL ANTICOAGULANTS (NOAC)

# Role of warfarin and NOAC

- Tens of millions of patients worldwide are on short- or long-term anticoagulant therapy
- Benefits of ↓ thromboembolism come at a cost of ↑ bleeding
- When considering replacing warfarin with a NOAC consider
  - Efficacy
  - Safety
  - Predictable fixed dosing without need to monitor
  - Long-term adherence (pt. unable or unwilling to continue drug)
- Each anticoagulant varies in effects on routine and specialty coagulation assays

# Role of warfarin and NOAC

| Assay | UFH | LMWH | Warfarin | Dabigatran (thrombin inhibitor) | Rivaroxaban or apixaban (Xa inhibitors) |
|---|---|---|---|---|---|
| APTT | ↑↑ | No effect or ↑ | ↑ | ↑↑ | ↑ |
| PT/INR | Little or no effect | No effect | ↑↑ | ↑ | ↑↑ |
| Thrombin TCT | ↑↑↑ | ↑ | No effect | ↑↑↑ | No effect |
| | | | | | |
| Anti Thrombin III | ↓ | No effect | No effect | No effect or ↑ | ↑ or No effect |
| Protein C activity | Falsely high | No effect | ↓ | ↑ or No effect | ↑ or No effect |
| Protein S activity | ↑↓ or N | No effect | ↓ | ↑↓ or N | ↑↓ or N |
| Lupus anticoagulant | False | No effect | False | False | False |

# Role of warfarin and NOAC

- In general
  - PT, APTT and routine TCT are not ideal assays to measure new agents because they tend to be either too sensitive or too insensitive or fail to show appropriate dose response
  - Pharmaceutical companies working on new assays but not available yet (e.g. Ecarin-clotting time)
  - Note < 10% of requested tests give clinical details of which oral anticoagulant taken!
  - No reversal antidotes in event of a major bleed

# Role of warfarin and NOAC

- Characteristics of new oral anticoagulants compared with warfarin

| Feature | Warfarin | New agents |
|---|---|---|
| Onset | Slow | Rapid |
| Dosing | Variable | Fixed |
| Food effect | Yes | No |
| Interactions | Many | Few |
| Monitoring | Yes | No |
| Offset | Long | Shorter |
| Reversal | Prothrombinex, vitamin K or FFP | Nonreversible with conventional agents |

# Role of warfarin and NOAC

- Characteristics of new oral anticoagulants compared with warfarin
  - Warfarin indirect on multiple targets, onset several days; no renal excretion
  - Rivaroxaban and apixaban oral bioavailability > 50%, rapid onset in 1-4 hours; 25-33% active drug excreted in urine
  - Dabigatran prodrug requiring metabolic activation, rapid onset 1-2 hours; 80% active drug excreted in urine
  - Potential for drug accumulation in pts with severe renal impairment (creat clearance <30 mL/Min)

# Role of warfarin and NOAC

- Characteristics of new oral anticoagulants compared with warfarin
  - Noninferior to warfarin for efficacy
  - ↓ intracranial bleeding than warfarin
  - Trend for ↓ mortality compared with warfarin
  - No hepatic toxicity
- Differentiating between new agents
  - Small ↑ risk of MI with dabigatran compared with warfarin
  - ↑ GI bleeding with dabigatran and rivaroxaban than warfarin
  - Only dabigatran (150mg bd) assoc. with ↓ risk of ischaemic stroke than warfarin
  - Only apixaban assoc. with both ↓ risk of stroke and major bleeding than warfarin

# Role of warfarin and NOAC

- Choice of anticoagulant based on patient characteristics

| Characteristic | Drug choice | Rationale |
|---|---|---|
| Mechanical valve or valvular AF | Warfarin | New agents not studied |
| Liver abnormal + ↑ INR | Warfarin | New agents require hepatic metabolism |
| Poor compliance | Warfarin or nothing | Missed doses greater problem with short-acting agents |
| Stable on warfarin | Warfarin | Consider switching at pt request |
| CrCl < 30 mL/min | Warfarin | Pts excluded from trials of NOAC |
| CrCl 30-50 mL/min | Rivaroxaban or apixaban | Less affected by impaired renal func |
| Dyspepsia or upper GI symptoms | Rivaroxaban or apixaban | Dyspepsia in 10% given dabigatran |
| Recent GI bleed | Apixaban or warfarin | NOT dabigatran or rivaroxaban |
| Recent ischaemic stroke on warfarin | Dabigatran | Assoc. with lower ischaemic stroke |
| Recent acute coronary syndrome | Rivaroxaban or apixaban | Small ↑ MI with dabigatran |
| Request for once daily dose | Rivaroxaban | Only NOAC once daily |

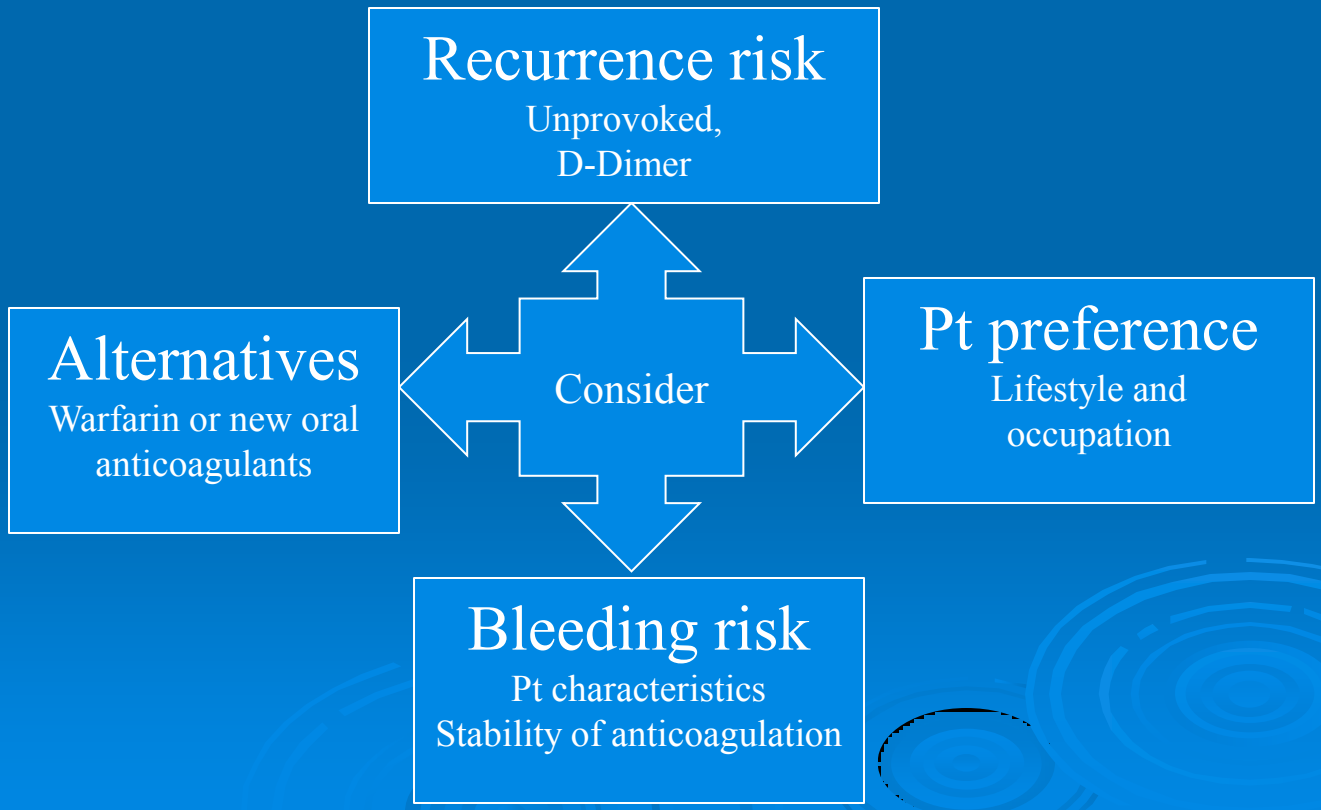
# DURATION OF ANTICOAGULATION

# Duration of anticoagulation

| Duration | Circumstances of VTE | Recommended duration of therapy |
|---|---|---|
| Limited duration | 1st VTE provoked by transient risk factor | 3 months |
| | Surgery | |
| | Trauma | |
| | Immobilisation >3 days | |
| | Isolated distal DVT of leg or DVT of upper extremity | |
| | Combined OCP | |
| | Unprovoked VTE | 3-6 months± personal evaluation |
| | Pregnancy or postpartum | Until 6 weeks post-partum for minimum 3 months |
| Extended duration | First VTE provoked by persistent risk factor | Extended duration or until 6 months after assumed cure of cancer |
| | Cancer | |
| | Recurrent VTE | Extended duration |

# Duration of anticoagulation

- After cessation of therapy, unprovoked VTE assoc. with annual recurrence rate 10% in first 2 years then 3% in subsequent years
- Considerations in extending therapy beyond 6 months in first unprovoked VTE



# THROMBOSIS IN PREGNANCY

# Thrombosis in Pregnancy

- Major cause of direct maternal mortality causing 1.2 to 4.7 deaths per 100,000 pregnancies; many assoc. with failure to obtain objective diagnosis (? unfounded concerns of radiation exposure for fetus)
- RR of antenatal VTE 7 to10-fold higher in preg. than non-preg. women of same age due to changes in coagulation and venous systems assoc. with pregnancy
- Absolute risk low 1 in 1000 pregnancies
  - Antepartum 5-12 per 10,000
  - Postpartum 3-7 per 10,000
- Puerperium time of greatest risk; RR 15 to 35-fold
- Approx. 80% of events occur in first 3 weeks after delivery

# Thrombosis in Pregnancy

| Risk factor for DVT | Adjusted Odds Ratio |
|---|---|
| Previous VTE | 24.8 |
| Immobility | 7.7 |
| - if combined with BMI≥ 25 | 62 |
| BMI > 30 | 5.3 |
| Smoking | 2.7 |
| Weight gain > 21kg (vs 7-21kg) | 1.6 |
| Parity > 1 | 1.5 |
| Age > 35 years | 1.3 |
| Pre-eclampsia | 3.1 |
| Pre-eclampsia with fetal growth restriction | 5.8 |
| Assisted reproductive techniques | 4.3 |
| Twin pregnancy | 2.6 |
| Antepartum haemorrhage | 2.3 |
| Post-partum haemorrhage | 4.1 |
| Caesarean section | 3.6 |
| Medical condition (e.g.. SLE, Heart disease, infection) | 2.0 – 8.7 |
| Blood transfusion | 7.6 |

# Thrombosis in Pregnancy

- Compression duplex ultrasound of entire proximal venous system considered optimal first-line diagnostic test for DVT
- If apparently normal with significant symptoms and signs consider repeat US on day 3 and 7
- If iliac vein thrombosis suspected (back pain and swelling of entire limb) MR venography or contrast venography should be considered
- D-Dimer levels will be outside normal range at term and post-term in most normal pregnancies (also reports of false negatives in pregnancy)
- May manifest with unusual presentations such as buttock, groin, flank or abdominal pain; most events left-sided

# Thrombosis in Pregnancy

- Prefer V/Q lung scan over CT-PA
  - High negative predictive value
  - Most pregnant women will not have comorbid pulmonary pathology
  - Substantially lower radiation dose to breast tissue

- Well below recommended radiation exposure to fetus of 5cGy for entire pregnancy
  - Full V/Q scan 0.58 cGy to fetus
  - CT PA 0.066 to fetus
  - Low dose perfusion (omit ventilation scan for negative perfusion scan) <0.012 cGy to fetus

# Thrombosis in Pregnancy

- Management of VTE in pregnancy
  - Vitamin K antagonists cross placenta; warfarin can be used post-partum as no significant excretion in breast milk
    - limited data on New Oral Anticoagulants (may cross placenta as relatively small molecules)
  - Heparin including LMWH remains treatment of choice in pregnancy (does not cross placenta or is present in breast milk in appreciable amounts)
  - LMWH more effective, lower risk of bleeding, and assoc. with lower mortality than UFH for initial treatment of DVT and equivalent in initial treatment of PE; substantially lower risk of HIT, haemorrhage and osteoporosis

# Thrombosis in Pregnancy

- Management of VTE in pregnancy
  - Consider BD enoxaparin (1mg/kg twice daily) initially then once daily 1.5mg/kg
  - Leg elevation
  - Graduated elastic compression stockings; help to prevent post-thrombotic syndrome ↓ by 50% if started within 2 weeks and worn for 2 years
  - IVC filters rarely necessary
  - Dose same as despite weight gain; LMWH does not cross placenta so weight of feto-placental unit not relevant
  - Continue for at least 6 weeks postpartum and for a minimum total duration of 3 months

# CANCER-RELATED THROMBOSIS

# Cancer-related thrombosis

- Prevalence of undiagnosed cancer in unprovoked VTE was 6.1% at baseline and 10% at 12 months (SOMIT study 2004)
- How should a patient be investigated for cancer with first unprovoked VTE?
  - Offer all patients  over age 40 diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:
  - a physical examination (guided by the patient's full history) **and**
  - a chest X-ray **and**
  - blood tests (full blood count, serum calcium and liver function tests) **and**
  - Urinalysis

  (NICE Guidance UK 2012)

# Cancer-related thrombosis

- Use therapeutic anticoagulation (extended duration LMWH) for all incl. incidental PE, DVT and acute symptomatic visceral vein thrombi
- Predictors of cancer-associated thrombosis
  - Site of primary cancer

    (stomach, pancreas >> lung, lymphoma, gynae, bladder, testes)
  - Platelet count ≥ 300 x $10^9$/l
  - Total WCC >11 x $10^9$/l
  - Hb < 10 x $10^9$/l
  - D-Dimer elevation
  - High CRP
  - High levels of Tissue Factor or soluble P-selectin levels

# Cancer-related thrombosis

- Thromboprophylaxis currently recommended for cancer inpatients without contraindications (ASCO)
  - Benefit from longer duration of prophylaxis for up to 1 month post surgery
- LMWH is the recommended treatment for cancer-assoc. VTE
  - More efficacious than warfarin
  - Reduces risk of symptomatic recurrent VTE by 52%
  - Recurrence on treatment escalate dose by 20-25%
- Use of new oral anticoagulants for the treatment of cancer –associated VTE is not supported by published studies

# Pearls of Wisdom!

- Don’t start on the pathway if you don’t think it’s a DVT!
- D Dimer is only useful if it’s negative
- A good safe, reliable, readily reversible NOAC is the final frontier
- It’s all good until you need to reverse it in a hurry!
- Smartphone app: Management of Dabigatran

Disclosure of interest: NONE