Venous Thromboprophylaxis

Feeling the squeeze?

Nepean WTET summary 5/1/21

Background and Rationale

- Venous thromboembolism (VTE) -to include deep vein thrombosis (DVT) and pulmonary embolism (PE)- is a recognised complication associated with critical illness (virchow's triad prevalent – endothelial injury, altered blood flow and hypercoagulability). Pharmacological prophylaxis may decrease the incidence by approx. 50%, however despite this DVT incidence still remains high at 5-20%
- VTE is often poorly tolerated amongst the critically ill and the burden of morbidity (to include need for therapeutic anticoagulation!) and mortality, need to be weighed against the perceived risks of harm of administering prophylactic measures

Advantages and Disadvantages

- UFH vs LMWH
    - Heparin; higher HITTS risk, more osteopenia/perosis, multiple injections, protein bound
    - LMWH; dose alterations in renal failure (excl. dalteparin), less 'reversible', longer half-life
    - Both; dosing in obesity, absorption in low cardiac output states
- Mechanical VTE prophylaxis
    - Less effective in isolation than pharmacological prophylaxis
    - Can cause skin breaks, ulcers, blisters and necrosis may occur. Contraindicated in severe peripheral vascular disease and lower limb ischaemia. Cost of intermittent Pneumatic Compression (IPC) not insignificant
    - Sizing and position (can impeded flow!) of graded compression stockings important
    - Thigh-length may be superior (CLOTS 2) to below knee compression stockings (CVA)
    - IPCs are likely superior to compression stockings in reducing DVT

Key studies

- **Protect 2011 NEJM**
    - MC (67) RCT; superiority trial of dalteparin vs heparin VTE prophylaxis in critically ill (=/>18y/o, =/>45kg, expected to be in ICU =/>3d) excluded trauma, neurosx, orthopaedic, or indication for therapeutic anticoagulation. Randomised to dalteparin 5000 IU daily vs UFH 5000 IU heparin BD. Stratified to center, admission type (medical vs surgical). Ceased/changed if major bleeding, platelet count <50 000/cm^3 or fall to <50% baseline platelet count, or HITTs suspected. N=3746 (90% ventilated, 76% medical, 45% vasopressor)
    - Primary outcome; incidence of new-onset proximal leg DVT =/>3d after randomisation (screening compression ultrasonography); 5.1% vs 5.8% (HR 0.92, 95% CI 0.68-1.23, P=0.57)
    - But less PE (1.3% vs 2.3%, HR 0.52, 95% CI 0.30-0.88, P=0.01) and HITTs (HR 0.27, 95% CI 0.08-0.98, P=0.046). No difference in major bleeding (5.5% vs 5.6%, P=0.98) or death in hospital (HR 0.92, P=0.21)

- **CLOTS 3 JAMA 2013**
    - MC (94) RCT; <3d admission with acute stroke (excl. subarachnoid haemorrhage), immobile (unable to mobilise to the bathroom without assistance). Minimisation algorhythm for stroke onset (0-2d vs =/>2d), leg weakness (able to raise both off bed, and use of thrombolytic agent /anticoagulation. Randomised to +/- IPC (with thigh-length sleeves) for 30d or until second US performed if after 30d (planned US day 7-10 and day 25-30). N= 2876
    - Primary outcome; symptomatic DVT or asymptomatic proximal (femoral/popliteal) DVT on imaging within 30d; 8.5% (IPC) vs 12.1% (no IPC), OR 0.65, 95% CI 0.51-0.84, P=0.001 after adjustment for baseline variables; ARR 3.6%
    - More skin breaks with IPC
- **PREVENT 2019 NEJM**
    - MC (20) RCT; <48h admission to ICU and expected to stay =/>72h, with no contraindication to pharmacological thromboprophylaxis with either LMWH or UFH. Randomised to +/- IPC (minimum 18h/d) stratified based on site and type of heparin. Recommended use of multi-chamber IPC with thigh-length sleeves where possible (but single chamber and knee-length sleeves permitted). In the control arm, IPC only allowed when interruption of pharmacological prophylaxis. Graduated compression stockings not permitted in either arm. Sonographers imaged proximal lower limbs <48h from randomisation and then twice weekly (or on clinical suspicion). N=2003
    - Primary outcome; new proximal DVT beyond 3rd calendar day from randomisation until ICU discharge, death, attainment of full mobility or d28; 3.9% (IPC) vs 4.2% (control), RR 0.93, 95% CI 0.60-1.44, P=0.74
    - No significant differences in secondary outcomes e.g. PE 0.8% vs 1.0%, VTE (PE or any lower limb DVT) 10.4% vs 9.4%, lower limb skin injury / ischaemia or risk of death
    - Underpowered as incidence of primary outcome in control group lower than expected

- *Meta-analysis (Alhazzani, CCM, 2013) of seven trials (N=7226) of medical-surgical ICU patients UFH and LMWH with each other or no anticoagulant prophylaxis found that UFH/LMWH both reduce incidence of DVT (P<0.0001) and PE (P=0.04). LMWH reduced both symptomatic and asymptomatic PE more than UFH but there was no difference in reduction in symptomatic/asymptomatic DVT, major bleeding (P=0.83) or mortality between the two*

Summary (my practice)

- I consider a patient's individual risk of VTE (both acquisition and relative risk of harm against treatment burdens) and balance supportive therapies e.g. avoiding intravascular hypovolaemia, prolonged immobility, femoral CVC's, against other competing medical priorities
- I review VTE prophylaxis daily. If pharmacological prophylaxis absolutely contraindicated (e.g. active major bleeding, severe thrombocytopenia) or is being administered but unclear absorption (low cardiac output states) with no contraindication for mechanical prophylaxis, I will ensure IPC devices are in situ (and are being used >18h/d)
- The risk and associated harm of VTE is significant, whereas the risk of major bleeding attributable to low-dose LMWH (and UFH) is often disproportionally feared. Many of our patients that appear on conventional clotting studies to be coagulopathic may also concomitantly be hypercoaguable (e.g. liver failure) and active consideration of VTE strategies need to be made
- Where pharmacological prophylaxis is appropriate and being reliably administered, there is no benefit of concomitant mechanical VTE devices and this may be associated with unnecessary reduction in mobility, more risk skin tears and increased financial costs. I preferentially chose LMWH over and above UFH due to its superiority in reducing PE, lower risk of osteopenia, HITTS and benefits of single daily injection. Similarly where absorption is uncertain, aXa assays (unlike APTT for UFH) may provide assistance in confirming absorption as well as dosing in renal failure (if dalteparin not available). aXa may assist dosing in the extremes of weight (unvalidated)