PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM
Supporting Information

This guideline has been prepared with reference to the following:

NICE. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. 2019. NICE. London

https://www.nice.org.uk/guidance/ng89

Afshari A, Ageno W, Ahmed A et al. European Guidelines on perioperative venous thromboembolism prophylaxis: Executive summary. Eur J Anaesthesiol. 2018;35:77-83

https://journals.lww.com/ejanaesthesiology/Fulltext/2018/02000/European_guidelines_on_perioperative_venous.13.aspx

Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e195S-226S

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278052/

Dalteparin 5000 units (subcutaneous) every 24 hr until mobile or discharged, reduces the incidence of venous thromboembolism (VTE) in patients with no increased risk of bleeding?
The PREVENT trial (Leizorovicz, 2004) randomised 3706 acutely ill medical patients to receive either subcutaneous dalteparin 5000 IU or placebo daily for 14 days. Participants were then followed up for 90 days. The incidence of venous thromboembolism was reduced from 4.96% (73 of 1473 patients) in the placebo group to 2.77% (42 of 1518 patients) in the dalteparin group, representing an absolute risk reduction of 2.19% or a relative risk reduction of 45% (RR 0.55; 95% CI 0.38-0.80; P = 0.0015). This observed benefit was maintained at 90 days. Major bleeding was rare, being recorded in 9 patients in the dalteparin group (0.49%), vs 3 patients in the placebo group (0.16%).
The CLOT trial (Lee, 2003) was an open-label study in 672 cancer patients who had already suffered an episode of thromboembolism. Half the patients received dalteparin (200 IU/kg subcutaneously once daily for 5-7 days) followed by a coumarin derivative for 6 months (sufficient to maintain an INR of 2.5). The other half received dalteparin alone (200 IU/kg daily for 1 month, followed by 150 IU/kg daily for 5 months). During the 6-month study period, 27 of 336 patients (8%) in the dalteparin group had recurrent thromboembolism, vs 53 of 336 patients (15%) in the oral anticoagulant group (hazard ratio 0.48; P = 0.002).

Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-53
http://www.nejm.org/doi/full/10.1056/NEJMoa025313#t=articleTop

Leizorovicz A, Cohen AT, Turpie AG, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004;110:874-9
http://circ.ahajournals.org/content/110/7/874.long

Evidence Level: I

Dalteparin 5000 units is necessary in this setting, whereas 2500 units is sufficient for surgical patients peri-operatively?
A meta-analysis of 59 studies in surgical patients (Mismetti, 2001) included 8 studies of LMWH vs placebo or no treatment (5520 patients) and 51 studies of LMWH vs UFH (48624 patients). One of the findings was that doses of LMWH </= 3400 units did not significantly reduce the incidence of VTE compared to UFH, but were associated with a significantly reduced risk of bleeding, particularly major haemorrhage (RR 0.76 (0.63-0.92); p = 0.005). Doses > 3400 units significantly reduced VTE compared with UFH, but at the cost of a significant increase in bleeding, again particularly major haemorrhage (RR 1.53 (1.07-2.19); P = 0.02). The authors concluded that the optimal dose regimen in general surgery patients needed further investigation.
The PREVENT trial (Leizorovicz, 2004) found a very low incidence of bleeding in medical patients receiving dalteparin 5000 units, so the necessity for lower doses of LMWH in order to prevent major haemorrhage appears to be lacking in this group of patients.

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Leizorovicz A, Cohen AT, Turpie AG, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004;110:874-9
http://circ.ahajournals.org/content/110/7/874.long

Mismeti P, Laporte S, Darmon JY, et al. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. Br J Surg 2001;88:913-30

Evidence Level: I

Thromboembolism deterrent (TED) stockings are effective if dalteparin is contraindicated?
A Cochrane systematic review of 19 trials in 1681 patients (Sachdeva, 2015) confirmed that GCS reduce the risk of DVT in hospitalised surgical patients. It also demonstrated that GCS may reduce the risk of developing DVT in the thighs (proximal DVT) and PE in such patients, though these results were based on a much smaller number of participants. The incidence of adverse effects and complications associated with wearing GCS was poorly reported in the included studies. Limited evidence was available for hospitalised medical patients, with only one study suggesting the effectiveness of GCS in preventing DVT in such patients.
TED stockings may be used as an adjunct to dalteparin, as well being suitable for those patients with contraindications to treatment with heparin (Turpie, 2006).
A guideline from the American College of Physicians (Qaseem, 2011) recommends against the use of mechanical prophylaxis with graduated compression stockings for prevention of venous thromboembolism, citing a lack of statistically significant reduction in mortality and an increase in lower-extremity skin damage.

Sachdeva A, Dalton M, Amaragiri S et al. Graduated compression stockings for prevention of deep vein thrombosis. Cochrane Database Syst Rev. 2015. Art. No.: CD001484
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001484.pub3/full

Qaseem A, Chou R, Humphrey LL, et al. Venous thromboembolism prophylaxis in hospitalized patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2011;155:625-32
http://annals.org/article.aspx?articleid=1033137

Turpie AG, Leizorovicz A. Prevention of venous thromboembolism in medically ill patients: a clinical update. Postgrad Med J 2006;82:806-9
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2653926/pdf/806.pdf

Evidence Level: I

The risk of thrombocytopenia can be ignored if prophylaxis continues for longer than 21 days?
Heparin-induced thrombocytopenia (HIT) typically occurs about a week after the start of heparin therapy, but can begin rapidly in patients who have received heparin within the previous 100 days. A study in 243 patients (Warkentin, 2001) found that 170 (70%) showed a fall in the platelet count (signalling the onset of HIT) within 5 to 8 days of beginning treatment. In the remaining 73 patients (30%), onset was rapid (median 10.5 hours after the start of treatment) and all of these patients had been treated with heparin within the previous 100 days.

Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. N Engl J Med 2001;344:1286-92

Evidence Level: II

Addendum:
The findings of the EXCLAIM (Extended Clinical prophylaxis in Acutely Ill Medical patients) study were presented at the XXIst International Society on Thrombosis and Haemostasis Congress in Geneva, July 2007. These showed a 44% RR reduction in VTE events when treatment with enoxaparin was extended form 10 days to 5 weeks. There was, however, no difference in all-cause mortality between extended enoxaparin vs placebo at 6 months (10.1% vs 8.9%; p=0.18).

Low Molecular Weight Heparin (LMWH) should not be administered within 12 hr of inserting or withdrawing a spinal/epidural catheter, lumbar puncture or following deep peripheral nerve block?
This advice is based upon expert opinion, in the absence of research evidence (Vandermeulen, 2010).

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Vandermeulen, E. Regional anaesthesia and anticoagulation. Best Pract Res Clin Anaesthesiol 2010; 24:121–31

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