Optimal dosing for thromboprophylaxis in medical inpatients

Clinical question
What is the optimal dosing regimen for thromboprophylaxis in hospitalized medical patients?

Bottom line
Until a direct comparison study is performed, the best information available suggests that although 3-times-daily dosing of 5000 units unfractionated heparin (UH) is more effective then twice-daily dosing (approximately 1 fewer pulmonary embolism (PE) and 2 fewer deep vein thromboses (DVTs) per 1000 patient days), it is associated with more major bleeds (1 per 2500 patient days). Remember that both regimens are better than doing nothing for high-risk hospitalized medical patients. (LOE = 1a-)

Reference
King CS, Holley AB, Jackson JL, Shorr AF, Moores LK. Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: a meta-analysis. Chest 2007;131:507-516.

Study Design
Meta-analysis (randomized controlled trials)

Funding
Unknown/not stated

Setting
Inpatient (any location)

Synopsis
Guidelines now recommend thromboprophylaxis with low-dose UH or low-molecular-weight heparin (LMWH) in acutely ill medical inpatients, especially those with heart failure, respiratory disease, who are confined to bed, or who have a previous history of DVT or PE. Some studies have used 5000 units UH subcutaneously given 2 times per day, while others have given the same dose 3 times daily; the 2 different dosing frequencies have never been directly compared. The authors of this meta-analysis carefully searched the literature for all studies of UH prophylaxis with adequate verification of DVT or PE and performed in a nonsurgical population. They identified a total of 447 articles, of which 435 were excluded, mostly because they had studied a surgical or postoperative population. The mean ages of the enrolled patients in the remaining 12 studies ranged from 58 years to 75 years. Nine of the studies had between 38 patients and 223 patients; the remaining 3 studies had 482, 726 and 5776 patients, respectively. Most of the patients in these studies were at moderate- to high-risk for DVT or PE. There were a total of 1664 patients receiving 3-times-daily dosing and 6314 receiving twice-daily dosing in the 12 studies.The authors found no significant difference between the groups regarding the rate of DVT (5.4 for twice daily vs 3.0 for 3 times daily per 1000 patient-days; P = .42), but a trend toward fewer PEs in the 3-times-daily dosing group (1.5 vs 0.5 per 1000 patient-days; P = .09). Bleeding complications were more common in the 3 times per day group (0.73 vs 0.33 per 1000 patient-days; P < .001; number needed to treat to harm = 250). The largest study, accounting for more than 90% of patients receiving twice-daily dosing, had no placebo group, did not clearly describe randomization, was not blinded, and used autopsy to confirm the diagnoses of DVT and PE. It therefore reported much lower rates of these outcomes than the other studies. When this study is excluded, the difference between twice daily and 3 times daily groups regarding the number of venous thromboembolic events increased and became statistically significant, but the differences in bleeding rates lost statistical significance.

Guidelines for the clinical diagnosis of VTE (AAFP, ACP)

Clinical question
What are effective strategies in diagnosing venous thromboembolic events in primary care?

Bottom line
The main points of these guidelines to the diagnosis of venous thromboembolic events (VTE) are:1. Begin by using validated clinical prediction rules, like the Wells prediction rule, to estimate the clinical likelihood of VTE.2. In patients with a low clinical likelihood of VTE, a negative result from a high-sensitivity D-dimer test confirms that the patient is unlikely to have a VTE.3. Perform an ultrasound of the lower extremities in patients with intermediate to high clinical likelihood of VTE.4. Patients with intermediate or high clinical likelihood of pulmonary embolism require diagnostic imaging studies. (LOE = 1a)

Reference
Qaseem A, Snow V, Barry P, et al, for the Joint American Academy of Family Physicians/American College of Physicians Panel on Deep Venous Thrombosis/Pulmonary Embolism. Current diagnosis of venous thromboembolism in primary care: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. Ann Fam Med 2007;5:57-62.

Study Design
Practice guideline

Funding
Foundation

Setting
Various (guideline)

Synopsis
This clinical practice guideline was derived from a well-done systematic review of the literature* performed by the Agency for Healthcare Research and Quality Evidence-Based Practice Centers. The guideline is aimed at any clinician who diagnoses VTE; there is an accompanying guideline on managing VTE.** The guideline answers questions about the role of clinical prediction rules, D-dimer tests, ultrasounds, and computed axial tomography (CT) in the diagnosis of VTE. The authors found 19 studies using clinical prediction rules, 17 of which used the Wells prediction rule. These studies support the use of prediction rules. With the combination of a negative D-dimer result and a negative clinical prediction rule in low-risk patients, the probability of VTE is quite low. The authors found 4 studies evaluating D-dimer testing without the concomitant use of a clinical prediction rule. These studies support the theory that a negative result from a highly sensitive D-dimer test can exclude VTE in low-risk patients. The evidence-based practice center review found ultrasound to be very sensitive (89%-96%) and specific (94%-99%) in diagnosing symptomatic proximal vein lower extremity thromboses. It is less sensitive in asymptomatic thromboses (47%-62%). The studies of CT were of variable quality and the results were less consistent. Because of this, further imaging is likely needed in patients who have a high pretest probability of pulmonary embolism and a negative CT scan result.*Segal JB, et al. Ann Fam Med 2007;5:63-73.** Snow V, et al. Ann Fam Med 2007;5:74-80

Guidelines for managing VTE (AAFP, ACP)

Clinical question
What are the effective approaches to managing patients with venous thromboembolic events?

Bottom line
Both unfractionated heparin or low-molecular-weight heparin (LMWH) are appropriate for the initial treatment of pulmonary embolism, however these guidelines suggest starting with LMWH whenever possible. Patients with deep vein thrombosis, and possibly pulmonary embolism, can be managed safely and cost-effectively as outpatients under the right circumstances. Use compression stockings for at least 1 year to prevent post-thrombotic syndrome. Maintain anticoagulation for 3 months to 6 months in patients with first-time venous thromboembolic events (VTE) or those with VTE due to transient risk factors. Patients with recurrent VTE should be treated for more than 12 months. LMWH and vitamin K antagonists have comparable effectiveness for the long-term treatment of VTE and may be preferable for patients with cancer. (LOE = 1a)

Reference
Snow V, Qaseem A, Barry P, et al, for the Joint American College of Physicians/American Academy of Family Physicians Panel on Deep Venous Thrombosis/Pulmonary Embolism. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Fam Med 2007;5:74-80.

Study Design
Practice guideline

Funding
Foundation

Setting
Various (guideline)

Synopsis
This guideline was based on a systematic review performed by the Agency for Healthcare Research and Quality Evidence-Based Practice Centers. The guideline is aimed at any clinician caring for patients with VTE. There is an accompanying guideline on diagnosing VTE. The recommendations were derived largely from high-quality randomized controlled trials. The authors found 16 systematic reviews of clinical trials comparing LMWH and unfractionated heparin. No studies demonstrated unfractionated heparin to be more effective than LMWH, and patients treated with LMWH had fewer bleeding complications. Nine of these reviews reported that patients treated with LMWH had a lower mortality rate during the 3 months to 6 months after treatment than those treated with unfractionated heparin. The authors also found consistent evidence (from randomized controlled trials and cohort studies) that outpatient treatment of VTE with LMWH is cost-saving and at least as safe as inpatient treatment among highly selected patients. These studies used very well-developed educational and home care infrastructures as the foundation for managing these patients. The authors found 2 randomized controlled trials of compression stockings started within 1 month of diagnosis. Both trials found that the compression stockings reduced the incidence and severity of post-thrombotic syndrome. They found 11 observational studies of VTE in pregnancy and concluded that the evidence was insufficient to make any recommendations. Numerous trials have evaluated the duration and intensity of treatment. For patients with VTE due to transient risk factors (eg, recent immobilization, surgery, and so forth), treatment with warfarin (Coumadin) should last 3 months to 6 months with a target international normalized ratio of 2 to 3. Patients with a second VTE should be treated for at least 1 year. The authors found insufficient data to make recommendations on the use of vena cava filters and catheter-directed thrombolysis.

Antioxidants may increase mortality

Clinical question
Do antioxidant supplements reduce all-cause mortality for adults?

Bottom line
Current evidence suggests that regular supplementation with the antioxidants beta carotene, vitamin A, and vitamin E increases mortality risk in adults. This report found no evidence of benefit or harm from supplementation with vitamin C and selenium. (LOE = 1a-)

Reference
Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention. Systematic review and meta-analysis. JAMA 2007;297:842-857.

Study Design
Meta-analysis (randomized controlled trials)

Funding
Government

Allocation
Concealed

Setting
Various (meta-analysis)

Synopsis
These investigators analyzed the effects of antioxidant supplements (beta carotene, vitamins A, C, and E, and selenium) on all-cause mortality. They performed a thorough search of multiple databases including the Cochrane Registry, Science Citation Index, MEDLINE, and relevant references for randomized controlled trials evaluating these supplements, either singly or in combination. Two authors independently reviewed individual trials for quality. Disagreements were resolved through consensus discussion with a third individual. Assignment of individual trial quality scores occurred using standard methods. Overall methodological quality of the individual trials was good. From an initial list of 1201 references reporting approximately 815 individual trials, 68 met study inclusion criteria (n = 232,606). The mean age of participants was 62 years (18 years - 103 years); follow-up occurred for a mean of 3.3 years (1 month - 14 years). When all the trials were combined, there was no significant effect of antioxidant supplements on mortality. An analysis of outcomes from only high-quality trials showed a significantly increased risk of mortality with beta carotene, vitamin A, and vitamin E, either singularly or combined. Selenium and vitamin C had no significant effect on overall mortality. Results of the individual trials did not meet standard criteria for heterogeneity (meaning that the findings from individual trials were generally consistent). No formal discussion of publication bias was reported. The majority of studies were funded by commercial sources (thus preferring not to publish negative trials), so it is likely that these summary results underestimate the true increased risks.