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Articles selected and commented on by:
Richard Beasley and Irene Braithwaite
Medical Research Institute of New Zealand
Pulmonary embolism and deep vein thrombosis.

**Authors:** Goldhaber SZ, Bounameaux H.


**Comments:** This excellent review focuses on the optimal diagnostic strategy and management for acute pulmonary embolism and deep vein thrombosis.

**Bottom line:** A must read for physicians responsible for the care of patients with pulmonary embolism and deep vein thrombosis.

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Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial.

**Authors:** Aujesky D et al.


**Comments:** One of the crucial clinical issues in the initial assessment and management of patients with DVT or PE is how to identify those patients who can be safely treated as an outpatient. This manuscript reports the findings from a randomised controlled trial which compared outpatient (discharged within 24 hours of randomisation) versus initial inpatient treatment of patients with PE at a low risk of death (PESI risk class 1 or 2). There were no differences in symptomatic recurrent VTE within 30 days or major bleeding within 14 days, but a higher rate of major bleeding at 90 days with outpatient care (1.8% vs 0%). Compared with initial inpatient care, patients in the outpatient group had a 3.4-day reduction in mean length of hospital stay but a 2.6-day longer duration of treatment with initial low molecular weight heparin. Depending on the criteria used, around one in four patients presenting with PE would be eligible for outpatient care.

**Bottom line:** In selected low risk patients with PE, outpatient care can be safely and effectively used in place of inpatient care.
Selective D-dimer testing for diagnosis of a first suspected episode of deep vein thrombosis: a randomized trial.

Authors: Linkins L-A et al.
URL: http://annals.org/article.aspx?articleid=1556362
Comments: The major limitation of D-dimer testing is that it is sensitive but not specific for diagnosing VTE. One logical approach to improve the trade-off between D-dimer sensitivity and specificity is to vary the threshold distinguishing a negative from a positive test depending on the patient’s clinical probability of having a DVT or PE. The rationale behind this novel approach is that as the prevalence of DVT is low in patients with low clinical pre-test probability, the use of a higher less sensitive threshold might exclude DVT in more patients without an unacceptable increase in the number of missed diagnoses. In this trial of patients with a first suspected episode of DVT, the selective D-dimer test strategy was a D-dimer test for outpatients with a low or moderate clinical probability (DVT excluded at <1000 µg/L for low clinical probability and <500 µg/L for moderate clinical probability), and venous ultrasound without D-dimer testing for high clinical probability and inpatients. This strategy was compared with uniform testing, based on D-dimer testing for all participants (DVT excluded at D-dimer levels <500 µg/L). The incidence of symptomatic VTE at 3 months was 0.5% in both study groups with a reduction in D-dimer and ultrasound testing with the selective test regime.

Bottom line: A selective D-dimer testing strategy seems to be as safe and more efficient than having everyone undergo D-dimer testing when diagnosing a first episode of suspected DVT.

Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts.

Authors: Douma RA et al.
URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2847688/
Comments: The use of D-dimer testing represents a major clinical advance in the assessment of patients with suspected VTE. A D-dimer concentration below the conventional cut-off point of...
500 µg/L combined with a low or intermediate clinical probability can safely rule out a diagnosis in about 30% of patients with suspected PE. One major limitation is the low specificity in older patients due to the increase in D-dimer concentrations with age. For example, the test can rule out PE in 60% of patients aged <40 years, but only 5% aged >80 years. This study validates the use of a new D-dimer cut-off value, defined as patient’s age x 10 µg/L in patients aged >50 years. This age-adjusted D-dimer cut-off point combined with clinical probability greatly increased the proportion of older patients in whom PE could be safely excluded.

**Bottom line:** For patients aged >50, the age-adjusted D-dimer cut point of patient’s age x 10 µg/L, can be used when combined with clinical probability, to exclude PE in clinical practice.

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**Management consensus guidance for the use of rivaroxaban – an oral, direct factor Xa inhibitor.**

**Authors:** Turpie AGG et al.


**URL:** [http://www.schattauer.de/en/magazine/subject-areas/journals-a-z/thrombosis-and-haemostasis/contents/archive/issue/1599/manuscript/18242.html](http://www.schattauer.de/en/magazine/subject-areas/journals-a-z/thrombosis-and-haemostasis/contents/archive/issue/1599/manuscript/18242.html)

**Comments:** It is always difficult becoming familiar with the use of new medications, obtaining the knowledge and experience to ensure their effective and safe use in clinical practice. Currently this applies to the use of the direct factor Xa inhibitors such as rivaroxaban which has been shown to have comparable efficacy and safety to standard care with warfarin (and bridging low molecular weight heparin use). This article provides practical guidelines for the use of rivaroxaban based on the clinical trial data, feedback on its use in clinical practice, and the authors’ experience with its use.

**Bottom line:** An important reference document which provides guidance for the use of rivaroxaban in clinical practice.
**Effectiveness and safety of novel oral anticoagulants compared with vitamin K-antagonists in the treatment of acute symptomatic venous thromboembolism – a systematic review and meta-analysis.**

**Authors:** van der Hulle T et al.


**Comments:** This systematic review and meta-analysis provides the current evidence regarding the efficacy and safety of the new direct oral anticoagulants (NOAC’s) compared with vitamin K antagonists (VKA). There are five studies included with one of the direct thrombin inhibitor dabigatran, and four of the factor Xa inhibitors rivaroxaban (2), apixaban (1) and edoxaban (1). The relative risk (RR) for recurrent VTE, fatal PE and overall mortality for NOAC’s versus VKA were 0.88 (95% CI 0.74 to 1.05), 1.02 (95% CI 0.39 to 5.96) and 0.97 (95% CI 0.83 to 1.14) respectively. The RR of major bleeding was 0.60 (95% CI 0.41 to 0.88) with the NNT with NOAC’s instead of VKA to prevent one episode of major bleeding of 149. There were no significant differences between individual NOAC’s compared with rivaroxaban. The main limitation with this meta-analysis was that the results could not be generalised to all patients with VTE since specific populations including the elderly, patients with cancer, renal insufficiency and patients with rare VTE sites (e.g. mesenteric thrombosis, cerebral vein thrombosis) and morbid obesity are under-represented or excluded.

**Bottom line:** NOAC’s have comparable efficacy and are associated with a significantly lower risk of bleeding in the treatment of acute VTE, although the number to treat to prevent one major bleeding case was relatively high. The use of NOAC’s can now be recommended in the treatment of acute VTE and prescribers need to be familiar with their use in clinical practice.
Thrombolytic therapy for submassive pulmonary embolus? PRO viewpoint.

Authors: Howard LS.  
Reference: Thorax 2013; doi:10.1136/thoraxjn-2013-203413  
URL: http://thorax.bmj.com/content/early/2013/04/25/thoraxjn-2013-203413.long

AND

Thrombolysis for acute submassive pulmonary embolism: CON viewpoint.

Authors: Simpson AJ.  
Reference: Thorax 2013; doi:10.1136/thoraxjn-2013-204193  
URL: http://thorax.bmj.com/content/early/2013/09/17/thoraxjn-2013-204193.long

Comments: One of the important considerations in the management of submassive PE is the balance of the benefit versus risk with thrombolysis. In this PRO/CON viewpoint debate the cases for and against the use of thrombolysis are made. The related paper by Sanchez et al in the European Heart Journal (2008; 29: 1569-77) highlights the importance of RV dysfunction assessed by CT or echocardiography and cardiac biomarkers as predictors of risk of mortality in patients with haemodynamically stable PE. The recent publication of the MOPETT trial (Sharifi M et al. Am J Cardiol 2013; 111: 273-7) is also relevant to these considerations, suggesting that ‘low dose’ thrombolysis with tPA plus standard anticoagulation is safe and effective in the treatment of moderate PE, significantly reducing the risk of death plus recurrent PE (1.6%) compared with standard anticoagulation (10%).

Bottom line: While recognising the clinical uncertainty, the balance of evidence probably favours the use of thrombolytic therapy for submassive pulmonary emboli in patients who can be predicted to be at markedly increased risk of mortality based on CT, echocardiography or cardiac biomarkers, with consideration of the use of the ‘low dose’ tPA regime.
Aspirin for preventing the recurrence of venous thromboembolism.

Authors: Becattini C et al.

Comments: The risk of recurrent VTE is particularly high amongst patients with unprovoked PE, about 20% of whom have a recurrence within 2 years after treatment with VKA has been discontinued. Although extending treatment with these agents reduces the risk of recurrence it is associated with an increased risk of bleeding. One option is to use low dose aspirin which has been associated with risk reduction in the primary prevention of VTE of 20 to 50%. This RCT has extended the use of aspirin from primary to secondary prevention. Aspirin in a dose of 100mg daily reduced the risk of recurrence by about 40% when given to patients with unprovoked VTE who had discontinued anticoagulant treatment, with no apparent increase in the risk of major bleeding.

Bottom line: Low dose aspirin represents an option for the long term treatment of patients with idiopathic VTE after completion of treatment with oral anticoagulant therapy.
**Oral rivaroxaban for symptomatic venous thromboembolism.**

**Authors:** The EINSTEIN investigators.


**AND**

**Extended use of dabigatran, warfarin, or placebo in venous thromboembolism.**

**Authors:** Schulman S et al.


**AND**

**Apixaban for extended treatment of venous thromboembolism.**

**Authors:** Agnelli G et al.


**Comments:** The efficacy and safety of oral thrombin inhibitor dabigatran and the oral factor Xa inhibitors rivaroxaban and apixaban has now been examined for the extended treatment of VTE. These three studies provide evidence that these agents reduce the risk of recurrent VTE by at least 80%, with variable effects on bleeding risk.

**Bottom line:** Both oral thrombin inhibitors and factor Xa inhibitors represent therapeutic options for patients with VTE who have completed 3 to 12 months of initial anticoagulant therapy with VKA’s.
Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials.

Authors: Boutitie F et al.
URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3100759/
Comments: The optimal duration of anticoagulant treatment after a VTE episode remains uncertain despite many trials that have compared different lengths of treatment. The conundrum is that the case fatality rate for recurrent VTE decreases with time whereas the risk of major bleeding increases with age. In this linked meta-analysis of individual participant data there was no benefit of continuing to treat for more than 3 months if the intention was to stop eventually. This main finding is also consistent with the previous BMJ study (Campbell et al. BMJ 2007; 334: 674-80) and associated editorial (Eikelboom et al. BMJ 2007; 334: 645).

Bottom line: If the risk of recurrent VTE is not high enough to justify indefinite anticoagulation, then treatment can be stopped after 3 months in most patients. At that stage a range of therapeutic options to reduce the risk of recurrent VTE needs to be considered including but not limited to preventive measures (e.g. stockings, intermittent pneumatic compression devices, low molecular weight heparin, novel oral anticoagulant agents) during periods of risk (e.g. surgery, travel), avoidance of known provoking factors (oral contraceptive therapy, hormone replacement therapy) and long term treatment with aspirin, or statins which have been shown to be effective in primary prevention.

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