

# APSR Respiratory Research Review

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## Welcome to the latest edition of APSR Respiratory Research Review.

This research review discusses several articles on venous thromboembolism (VTE) disease including: How good are we at preventing VTE? What is the prognosis of an acute PE event as well as the prognosis three years post event? What is the incidence and importance of heparin-induced thrombocytopenia? Is minor leg trauma a risk factor for PE? Does the combination of selective serotonin reuptake inhibitors and coumarins increase the risk of bleeding? How great is the risk of adverse events when warfarin therapy is interrupted for five days to allow for the induction of a medical procedure?

We hope you enjoy the latest edition and welcome your comments and feedback.

Kind regards,

**Dr Lutz Beckert**

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## Risk of venous thromboembolism in the acute hospital care setting

**Authors:** Cohen AT et al

**Summary:** The ENDORSE cross-sectional survey assessed the prevalence of risk for venous thromboembolism (VTE) among patients in acute hospital care settings in 32 countries, and investigated the proportion who received effective prophylaxis. A total of 30,827 surgical and 37,356 medical patients were enrolled. Among these, 51.8% (95% CI 51.4 to 52.2) were judged to be at risk of VTE according to the 2004 American College of Chest Physicians (ACCP) consensus guidelines, with notable differences in prevalences among the countries ranging from 35.6% to 72.6%. Surgical patients accounted for a greater proportion of at-risk patients with 64.4% (95% CI 63.8 to 64.9) judged to be at risk, while 41.5% (41.0 to 42.0) of medical patients were at risk. ACCP-recommended VTE prophylaxis was provided for 58.5% (95% CI 57.8 to 59.2) of at-risk surgical patients and 39.5% (38.7 to 40.3) of at-risk medical patients. The differences in the provision of recommended VTE prophylaxis were extremely variable among countries, ranging from 0.2% to 92.1% for at-risk surgical patients and 3.1% to 70.4% for at-risk medical patients.

**Comment:** British, French and American authors report on almost 70,000 patients in 358 hospitals across 32 countries. This study and its accompanying editorial indicated that pharmacological prophylaxis reduced the risk of PE by 75% in surgical patients and 57% in medical patients. Currently, pharmacological prophylaxis is only used in 58.5% of surgical and 39.5% of at-risk medical patients. The take home message: "VTE is a major public health issue: it is an easily preventable disease with a substantial risk of morbidity and mortality in patients hospitalised for acute medical and surgical illnesses. Recommended VTE prophylaxis is underused worldwide."

<http://www.ncbi.nlm.nih.gov/pubmed/18242412?dopt=Abstract>

**Reference:** *Lancet* 2008; 371(9610):387-397



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## Risk of venous thrombosis associated with minor injuries

**Authors:** Karlijn J et al

**Summary:** The link between minor injuries and the risk of venous thrombosis was investigated in 2,471 case patients with a first lower-limb deep vein thrombosis (DVT) or pulmonary embolism (PE) and 3,534 controls. Among the study population, 154 (4.4%) had experienced a minor injury in the preceding 3 months. The adjusted OR for venous thrombosis following a minor injury was 3.1 (95% CI 2.5 to 3.8), but the association was strongest for the first 4 weeks following injury, and no longer apparent after 10 weeks. Moreover, the association was stronger for leg injuries (adjusted OR 5.1; 95% CI 3.9 to 6.7) than for other areas of the body. The investigators note that the minor injuries may be a major contributor to venous thromboses due to their relatively high frequency.

**Comment:** This group from Leiden is investigating the hypothesis that injuries not requiring a cast, surgery or prolonged bed rest may also be a risk factor for developing DVT. They found that upper limb injuries do not predispose to VTE, whereas lower limb injuries, such as ruptured ligaments or muscles, sprains and contusions, were strongly associated with DVT. The authors postulated that this may be due to an increased prothrombotic state, partial immobilisation or venous obstruction through oedema. We will be awaiting confirmatory studies with interest.

<http://archinte.ama-assn.org/cgi/content/short/168/1/21>

**Reference:** *Arch Intern Med* 2008; 168(1):21-26

## Prognostic value of right/left ventricular end-diastolic diameter ratio in acute PE

**Authors:** Frémont B et al

**Summary:** The value of echocardiographic right/left ventricular end-diastolic diameter (RV/LV) ratio for predicting mortality in patients with acute pulmonary embolism (PE) was assessed in this retrospective study of 950 patients in whom relevant registry data were available. The hospital mortality rate for these patients was 3.3%. An RV/LV ratio of  $\geq 0.9$  was found to predict hospital mortality with 72% sensitivity and 58% specificity, and a multivariate analysis identified this measure as an independent predictor of hospital mortality (OR 2.66;  $p=0.01$ ). Other independent predictors of hospital mortality included systolic BP  $< 90$  mm Hg (OR 10.73;  $p < 0.0001$ ) and history of left heart failure (8.99;  $p < 0.0001$ ).

**Comment:** This prospective French study adds to our understanding of risk stratifying patients with PE, who have hospital mortality rates ranging from 5% to 30%. The authors describe a simple echocardiographic estimate of right to left ventricular ratio. An increased ratio was associated with increased mortality. As the accompanying editorial points out, factors such as low systolic BP, right heart strain seen on ECG, increased troponin levels and echocardiographic or CT estimates of right heart enlargement, may allow for risk stratification and hopefully tailored management.

<http://dx.doi.org/10.1378/chest.07-1231>

**Reference:** *Chest* 2008; 133:358-362

## Bleeding risk with concomitant coumarins and selective serotonin reuptake inhibitors

**Authors:** Schalekamp T et al

**Summary:** The impact of combining selective serotonin reuptake inhibitor (SSRI) and coumarin therapies on bleeding risk was investigated in this case-control study. Data from 1,848 cases of hospitalisation for abnormal major bleeding among Dutch patients receiving acenocoumarol or phenprocoumon and 5,818 matched nonhospitalised control patients with similar coumarin exposure were included. SSRI use was associated with a significantly increased risk of hospitalisation due to non-GI bleeding (OR 1.7; 95% CI 1.1 to 2.5), but not for GI bleeding (0.8; 0.4 to 1.5). In comparison, NSAID use was associated with a similar increase in risk for non-GI bleeding (OR 1.7; 95% CI 1.3 to 2.2) and a higher risk of GI bleeding (4.6; 3.3 to 6.5).

**Comment:** This Dutch group identified patients admitted for bleeding while on coumarins. They used a pharmaceutical database to match up to four controls to each index patient. Patients on coumarins and NSAIDs had an increased risk of GI and non-GI bleeding. Patients on SSRIs had no increased risk of GI bleeding but an increased risk of non-GI bleeding. Patients taking amitriptyline had no increased risk of bleeding. The authors believe that the increased risk of bleeding with SSRIs may be attributed to the depletion of platelets by serotonin.

<http://archinte.ama-assn.org/cgi/content/abstract/168/2/180>

**Reference:** *Arch Intern Med* 2008; 168(2):180-185

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## Outcomes following deep vein thrombosis and pulmonary embolism

**Authors:** Spencer FA et al

**Summary:** To assess community-based clinical characteristics and outcomes associated with pulmonary embolism (PE) and deep vein thrombosis (DVT), the medical records of patients with diagnoses of possible venous thromboembolism (VTE) in a New England community were analysed. During 3 years of follow-up, patients who had initially presented with PE (n = 549) or isolated DVT (1,142) had similar incidences for subsequent PE (5.9% versus 5.1%), overall VTE (15.0% versus 17.9%) and major bleeding (15.6% versus 12.4%). The 30-day mortality rate for patients initially diagnosed with PE was significantly greater than for patients diagnosed with DVT (13.0% versus 5.4% p=0.01), and the difference persisted for the 3-year mortality rate (35.3% versus 29.6%; p=0.01). The occurrence of a major bleeding complication was an important predictor of 3-year mortality (HR 1.36; 95% CI 1.07 to 1.73). The investigators concluded that efforts are needed to improve the identification of patients at risk of VTE sequelae, and to develop better community-based long-term anticoagulation strategies.

**Comment:** This real life study of patient survival after VTE serves as a reminder of the seriousness of this illness. Approximately 1 in 4 patients with clinically recognised VTE die within the first year of diagnosis. Patients presenting with PE have 35% three-year mortality, with some of the deaths attributed to an underlying illness precipitating PE, some due to recurrence of PE and many due to haemorrhagic complications (15% incidence of major bleeding). The authors conclude that there is considerable room for improvement in the treatment of these high-risk patients.

<http://archinte.ama-assn.org/cgi/content/abstract/168/4/425>

**Reference:** *Arch Intern Med* 2008; 168(4):425-430

## Incidence and impact of thrombocytopenia with prolonged heparin therapy

**Authors:** Gustavo BF et al

**Summary:** Data from 2,420 US patients (mean age 65.2 years) who were receiving unfractionated or low-molecular-weight heparin were analysed in this study to describe features of heparin-associated thrombocytopenia. The incidence of thrombocytopenia was 36.4% (95% CI 34.5 to 38.3). Death occurred in 5.1% of these patients, compared with 1.6% of patients without thrombocytopenia (OR 3.4; 95% CI 2.1 to 5.6; p<0.001). The strongest independent predictor of death was a platelet count reduction of >70%, while platelet count reductions of 50–70%, worse Killip class, thromboembolic complications, advanced age and longer duration of heparin therapy were other independent predictors. MI and CHF also occurred in more patients who developed thrombocytopenia than those who didn't (ORs 2.1%; 95% CI 1.5 to 2.8; p<0.001, and 1.3; 1.1 to 1.6; p=0.01, respectively). Thrombocytopenia remained an independent predictor of haemorrhagic and thrombotic events after adjustment for important covariates.

**Comment:** This American group reports on the outcomes of the CATCH (Complications after thrombocytopenia caused by heparin) study. Although most patients in the study received heparin for DVT prophylaxis, most complications were seen in patients with renal dysfunction or MI, or after coronary intervention. The overall incidence of thrombocytopenia was 36% for low-molecular-weight heparin and 53% for unfractionated heparin, with the median time to onset occurring after 55 hours. The authors were perturbed by the delay of diagnosis (2 days), low consultation rate and nonadherence to published guidelines. The take home message: "when prescribing powerful drugs be aware of and manage adverse events."

<http://archinte.ama-assn.org/cgi/content/abstract/168/1/94>

**Reference:** *Arch Intern Med* 2008; 168(1):94-102

## Thromboembolism risk with short interruptions of warfarin therapy

**Authors:** Garcia DA et al

**Summary:** The impact of temporarily withholding warfarin therapy for invasive surgical procedures was investigated in a cohort of 1,024 patients (mean age 71.9 years). The duration that warfarin was withheld varied, but was ≤5 days in 80% of the cohort. The risk of postprocedure thromboembolism occurring was low with only 7 patients (0.7%; 95% CI 0.3 to 1.4) experiencing this complication, none of whom received periprocedural bridging anticoagulation therapy. Six patients (0.6%; 95% CI 0.2 to 1.3) experienced a major bleeding event within 30 days, while another 17 (1.7%; 1.0 to 2.6) experienced a clinically significant nonmajor bleeding event. Periprocedural anticoagulation therapy was received by 14 of the 23 patients who experienced a major or nonmajor bleeding event. The investigators note that for patients who require interruption of warfarin therapy while undergoing an invasive surgical procedure, no matter how minor, the risk of clinically significant bleeding should be weighed against the thromboembolic risk before bridging anticoagulant therapy is administered.

**Comment:** This prospective study addresses a critical gap in our knowledge of the best advice to give patients on anticoagulation medication who require a medical procedure that involves interruption of their warfarin therapy. It draws data from 101 hospital sites and 102,732 patients, and identifies 1,584 episodes of warfarin therapy interruption. This paper is worth reading in full as it contains a lot of practical information. The bottom line: when interrupting warfarin therapy for 5 days, 0.7% of patients will experience VTE and 0.6% will experience a major bleed within 30 days.

<http://archinte.ama-assn.org/cgi/content/abstract/168/1/63>

**Reference:** *Arch Intern Med* 2008; 168(1):63-69

*Independent commentary by  
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## Risk of lung cancer with cannabis smoking

**Authors:** Aldington S et al

**Summary:** The risk of lung cancer associated with cannabis smoking among young New Zealand adults (age  $\leq 55$  years) was investigated in this case-control study. A total of 79 cases of lung cancer and 324 randomly selected controls were included. After adjustment for confounding factors, including cigarette smoking, the risk of lung cancer increased by 8% (95% CI 2 to 15) for each joint-year of cannabis smoking. The increased risk for cigarette smoking after adjusting for confounding factors, including cannabis smoking, was 7% (95% CI 5 to 9) for each pack-year. After adjusting for confounding factors, including cigarette smoking, the highest tertile of cannabis smoking was associated with increased lung cancer risk (relative risk 5.7; 95% CI 1.5 to 21.6).

**Comment:** This New Zealand study researched the impact of cannabis smoking on the risk of developing lung cancer at a young age ( $< 55$  years). The study is a little underpowered, but found that in the highest level of cannabis use ( $> 10.5$  joint-years) there is an increased risk of lung cancer (RR 5.7) after correcting for cigarette smoking. The accompanying editorial summarised the impact of cannabis smoking and suggests that we ask our patients: "Do you smoke tobacco and/or cannabis?" The bottom line: smoking one cannabis joint per day is almost equivalent to smoking one packet of cigarettes per day.

<http://erj.ersjournals.com/cgi/content/abstract/31/2/280>

**Reference:** *Eur Respir J* 2008; **31:280-286**

**Disclaimer:** This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

## Bullous lung disease associated with cannabis smoking

**Authors:** Hii SW et al

**Summary:** Details of a case series of 8 male and 2 female cannabis smokers with a mean age of 41 years who developed bullous lung disease were described in this paper. Each of these patients admitted regular, chronic marijuana smoking for  $> 1$  year, and had presented with dyspnoea, pneumothorax or a chest infection. Emphysematous bullae were identified on high-resolution CT scans in all 10 patients. These bullae were asymmetrical, varied in size and were localised in the upper and mid pulmonary zones. They also occurred in the setting of normal chest x-rays and/or normal lung function in 4 and 5 of the patients, respectively.

**Comment:** This group from Melbourne reports on a series of 10 patients presenting with bullous emphysema, shortness of breath, pulmonary abscesses, respiratory failure and pneumothoraces. The authors came to the conclusion that patients who smoke marijuana on a regular basis had lung damage approximately 20 years earlier than those using tobacco alone. Although they used very different methods to the New Zealand investigators, they came to the same conclusion that marijuana smoke is significantly more damaging to the lungs than tobacco smoke.

<http://www.blackwell-synergy.com/doi/abs/10.1111/j.1440-1843.2007.01186.x>

**Reference:** *Respirology* 2008; **13(1):122-127**

## Lung clearance index as a marker of structural lung abnormalities in cystic fibrosis

**Authors:** Gustafsson PM et al

**Summary:** The respective agreements between both lung clearance index (LCI) and spirometric parameters with structural lung disease were examined in 44 paediatric patients with cystic fibrosis (CF; mean age 12 years), to assess the sensitivity and validity of LCI as a marker of structural lung abnormalities. LCI detected abnormal lung structure with 85–94% sensitivity, while the sensitivities of FEV<sub>1</sub> and FEF<sub>75</sub> were 19–26% and 62–75%, respectively. The specificities were 43–65% for LCI, and 89–100% and 75–88% for FEV<sub>1</sub> and FEF<sub>75</sub>, respectively. The correlation between LCI and high-resolution CT scores was greater for LCI (Rs = +0.85) than for FEV<sub>1</sub> (–0.62) or FEF<sub>75</sub> (–0.66). It was concluded that LCI was more sensitive than FEV<sub>1</sub> and FEF<sub>75</sub> for detecting abnormal lung structure, and it may also be even more sensitive than high-resolution CT scans for detecting lung involvement in CF.

**Comment:** The combination of high performance computers, an increased understanding of respiratory physiology and a new analyser brings a re-appreciation of the LCI through multi-breath washout techniques. These methods are advantageous as they can be performed at tidal breathing and are therefore suitable for children. Using high-resolution CT as the reference standard, the authors have elegantly shown the superiority of LCI using sulphur hexafluoride compared with standard spirometry. Thorax published two papers, accompanied by two editorials, which are likely to point towards a new area of respiratory physiology over the next decade.

<http://thorax.bmj.com/cgi/content/abstract/63/2/129>

**Reference:** *Thorax* 2008; **63:129-134**

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