# Respiratory Research Review

### Making Education Easy

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#### Abbreviations used in this issue

6MWD = 6-minute walk distance BNP = brain natriuretic peptide CTEPH = chronic thromboembolic pulmonary hypertension CTPA = computed tomography of pulmonary angiogram DVT = deep vein thrombosis ERA = endothelin receptor antagonist HR = hazard ratio ICU = intensive care unit LMWH = low-molecular-weight heparin PAH/PH = pulmonary (arterial) hypertension PDE = phosphodiesterase PE = pulmonary embolism QOL = quality of life RCT = randomised controlled trial VTE = venous thromboembolism

## Welcome to this issue of Respiratory Research Review.

The terrorist attack in Christchurch has left us heartbroken. We would like to acknowledge the fantastic civil response and the humanity of our leadership in response to this tragedy, as well as the humility, compassion and courage of the Muslim community. Thank you for all your expressions of aroha. We hope you enjoy this month's review.

In this issue, we will highlight one or two articles of general interest, point out great illustrations, and will identify our favourite publication. The three sections covered will be articles of universal interest, an update on PAH (pulmonary arterial hypertension) and research highlights around VTE (venous thromboembolism).

You will have seen the recent N Engl J Med <u>publication</u> on the effect of shift changes on fatigue. While writing the review, discussion about the working conditions of Resident Medical Officers (RMOs) are ongoing. Two articles may assist in keeping a focus on patient care. An international group of researchers has published a <u>systematic literature review</u>, including data of almost 43,000 physicians with a mean age of 38 years, finding strong correlations between physician burnout, patient safety, low professionalism and reduced patient satisfaction. Also, in <u>JAMA</u> is a reminder on the increased diagnostic accuracy when working as a small collective rather than as individual physicians.

Short of time and need a quick update on the 'Advances in the Diagnosis and Treatment of Venous Thromboembolism' over the last 5 years? This <u>update</u> by the Canadian Group, with Philip Wells as the senior author, delivers both a brief reading time and an international evidence base, and it covers the clinical topics from clinical decision rules, D-dimer testing, imaging and a flow diagram to inform on the length of treatment. Our colleagues from Melbourne give an <u>Australasian perspective</u> on the same evidence, and also include the complete table comparing warfarin, dabigatran, rivaroxaban and apixaban in their 'Update on diagnosis and anticoagulant therapy for venous thromboembolism'.

Eur Respir J is running a series updating our understanding of PH following the world symposium in Nice in March 2018. Nazzareno Galiè, Vallerie McLaughlin, Lewis Rubin, Gérald Simonneau edit the series and give an <u>overview</u> on the topic covered. They include updates on the genetic background, the role of provocation like exercise or fluid loading, the controversial updated haemodynamic definition and classification of PH with a mean pulmonary arterial pressure  $\geq$ 20mm Hg and pulmonary vascular resistance of  $\geq$ 3 Wood units, stratification in the management and updates on the rapidly immerging field of CTEPH (chronic thromboembolic pulmonary hypertension). Three quick articles touch on CTEPH, each only a few cases long: i) 'Elevated pulmonary pressure – get with the right group: a teachable moment' (JAMA Intern Med); ii) determinants of the diagnostic delay identifying CTEPH, which leads to an increased risk of death (<u>Eur Respir J</u>); and iii) a recommendation from a colleague, a review on the post-PE syndrome: 'a new concept for chronic complications of pulmonary embolism' (<u>Blood Rev</u>).

If you only have time to read one article, make it the <u>editorial</u> in Lancet Respir Med on 'Pulmonary hypertension: the unaddressed global health burden'. The authors cover the initial epidemics associated with aminorex and then fenfluramine. PH can be found in about 20% of older patients and has increased all-cause mortality. My favourite diagram shows that in resource-rich countries, the cause is either idiopathic (3%), secondary to COPD or secondary to heart disease. In resource-poor countries, the top eight aetiologies include schistosomiasis, high altitude, HIV infection, rheumatic heart disease and haematological disorders.

We always appreciate your comments and suggestions, so please keep sending them.

Kind regards Professor Lutz Beckert

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#### Independent commentary by Professor Lutz Beckert.

Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board. FOR FULL BIO CLICK HERE



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### Symptom severity and its effect on health-related quality of life over time in patients with pulmonary hypertension

#### Authors: Yorke J et al.

Summary: This prospective longitudinal study reported health-related QOL and symptomatology of PH and factors influencing its evolution for a cohort of 185 patients from specialist centres in the UK; 126 patients had 18 months of follow-up data. Significant impairment was apparent at baseline for health-related QOL, anxiety, depression, dyspnoea and severe fatigue, with no significant changes over 18 months except for a significant reduction in Hospital Anxiety and Depression Scale - Anxiety score (p=0.04). Health-related QOL was significantly predicted by depression and dyspnoea (respective p values 0.002 and 0.03). Associations were also seen between oxygen use and both reduced health-related QOL and increased symptom severity.

Comment: One of the articles in the series mentioned in the introduction updating our understanding of PH following the world symposium in Nice in March 2018 also covers 'The importance of patient perspectives in pulmonary hypertension' (Eur Respir J). With current treatments, patients with PAH can now expect survival of around 7 years. These English researchers highlight that this comes with a considerable burden of symptoms, in particular, dyspnoea, fatigue, anxiety, depression and poor sleep quality. Bottom line: even though our PAH guidelines are mostly silent about addressing QOL, this evidence suggests that we can maintain and improve QOL in patients with PH.

Reference: BMJ Open Respir Res 2018;5:e000263 Abstract



## Choice of initial oral therapy for pulmonary arterial hypertension: age and long-term survival

#### Authors: Heresi GA et al.

Summary: Patient characteristics at baseline for predicting response to ERAs (endothelin receptor antagonists; n=91) or PDE-5 inhibitors (n=146) were reported for a retrospective cohort of patients with PAH. Over median follow-up of 1304 days, the respective mortality rates for ERA and PDE-5 inhibitor recipients were 52.7% and 48.6%, with no significant between-group difference after adjustments. A significant interaction was detected between treatment exposure and age, with significantly lower mortality among younger ERA versus PDE-5 inhibitor recipients and better survival among older PDE-5 inhibitor versus ERA recipients.

Comment: This article, published as a letter, and the accompanying editorial address daily clinical questions. These North American authors performed a multivariant analysis of data from the Cleveland Clinic. Key findings were that in patients younger than 45 years of age, survival and symptom control were improved through treatment with ERAs. However, for patients above the age of 65 years, survival was increased with the use of a PDE-5 inhibitor and appeared slightly worse with an ERA. Bottom line: no difference in survival was seen in patients initially treated with ERAs or PDE-5 inhibitors. ERAs were associated with decreased mortality in younger patients and initial PDE-5 inhibitors in older patients.

Reference: Am J Respir Crit Care Med 2018;198:1090-3 Abstract

## Features and outcomes of methamphetamine-associated pulmonary arterial hypertension

#### Authors: Zamanian RT et al.

Summary: Clinical presentation, histopathology and outcomes were compared between cohorts of 90 patients with (meth) amphetamine-associated PAH and 97 with idiopathic PAH in this prospective study. Patients with (meth)amphetamineassociated PAH were less likely to be female, but their ages, BMIs and 6MWDs were similar to those of patients with idiopathic PAH. Compared with the idiopathic PAH group, the (meth)amphetamine-associated PAH group had more advanced heart failure symptoms, significantly higher right atrial pressure (12.7 vs. 9.8mm Hg [p=0.001]) and a lower stroke volume index (22.2 vs. 25.5 mL/m<sup>2</sup> [p=0.01]). Patients with (meth)amphetamine-associated PAH had respective 2.5-, 5- and 10-year event-free survival rates of 64.2%, 47.2% and 25%, and were at significantly greater risk of clinical worsening or death compared with their counterparts with idiopathic PAH (HR 2.04 [95% CI 1.28, 3.25]). Data from California showed that hospitalised (meth)amphetamine users had a 2.6-fold increased likelihood of receiving a diagnosis of PAH.

Comment: As outlined in the Lancet Respir Med editorial on 'Pulmonary hypertension: the unaddressed global health burden', the diet pills aminorex and fenfluramine have caused PAH epidemics. Since the late 1990s, methamphetamine use has emerged, with an estimated up to 50 million users. The Stanford authors estimated that the risk of being hospitalised for PAH is approximately 2.5-times higher for amphetamine users. Although the PAH pressures, walking distance and BNP levels were similar, the prognosis was far worse in methamphetamine-associated PAH. In their accompanying editorial, Gérald Simonneau and Marc Humbert give us their bottom line: methamphetamine use is associated with severe and progressive PAH and should be upgraded to be a definite risk factor for PAH.

Reference: Am J Respir Crit Care Med 2018;197:788-800 Abstract

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References: 1. Feldman G.J et al. Adv Ther 2017; 34:doi 10.1007/s12325-017-0626-4. Anoro<sup>®</sup> Ellipta<sup>®</sup> (umeclidinium bromide/vilanterol trifenatate inhaler 62.5/25mcg per inhalation) is a fully funded Prescription Medicine for the regular treatment of COPD - Special Authority Critera apply. Anoro<sup>®</sup> has risks and benefits. GlaxoSmithKline NZ Ltd Auckland. Spiolto<sup>®</sup> is a registered trademark of Boehringer Ingelheim TAPS DA1852JS/18JU/UCV/0009/18 ΙΝΝΌνινλ

### **Respiratory** Research Review



## Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH)

#### Authors: Sadushi-Kolici R et al.

Summary: Patients with CTEPH that was nonoperable or with persistent or recurrent PH after pulmonary endarterectomy were randomised to receive continuous subcutaneous treprostinil at target doses of ~30 ng/kg/min (high-dose; n=53) or ~3 ng/kg/min (low-dose; n=52) at week 12 in this phase 3 trial. Compared with the low-dose group, high-dose treprostinil was associated with a significantly greater improvement from baseline in marginal mean 6MWD by week 24 (44.98 vs. 4.29m [p=0.0016]). In the high-dose group, there were twelve serious adverse events affecting ten participants, and in the low-dose group, there were 16 serious adverse events affecting nine participants. Pain and other reactions at infusion sites constituted most of the treatment-related adverse events reported in both groups.

Comment: CTEPH is a treatable cause of PH, with the preferred treatment being the surgical removal of the chronic thromboembolic lesions via an endarterectomy. However, patients need to have clots proximal enough to be surgically removable and be fit enough for this major operation. The second-line treatment is medical treatment and so far, we have reasonable evidence for the use of riociguat, bosentan and iloprost. In this study, the European authors report the use of subcutaneous treprostinil in about 100 patients with CTEPH. Bottom line: treatment with treprostinil was safe, improved exercise capacity, and added a treatment option for patients with CTEPH.

Reference: Lancet Respir Med 2019;7:239-48 Abstract

## Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients

#### Authors: Delcroix M et al.

Summary: These researchers investigated the prognostic value of the ERS/ESC PH risk stratification strategy in 561 medically treated registry patients with CTEPH, among whom 231 had follow-up data for a median of 7 months; study patients had not undergone pulmonary endarterectomy, had data on  $\geq 3$  of six variables, namely WHO functional class, 6MWD, BNP level, right atrial pressure, cardiac index and mixed venous oxygen saturation, and were classified into low-, intermediate- and high-risk groups. The estimated 1- and 5-year survival estimates at baseline differed significantly for the low-risk (98.6% vs. 88.3%), intermediate-risk (94.9% vs. 61.8%) and high-risk (75.5% vs. 32.9%) groups (p<0.0001 for all), whereas follow-up data revealed that the 1-year survival rates were 100%, 92% and 69%, respectively. An association was seen between the number of low-risk noninvasive criteria and survival.

Comment: In Respiratory Research Review issue 146, we explored the ERS/ESC validation of the risk stratification tools, the simplest being the three French criteria (WHO functional class I or II, BNP level <50 ng/L, 6MWD >440m). The authors used the 561 patients from the European COMPERA database with a diagnosis of CTEPH. The authors were able to report similar risk prediction criteria at the time of CTEPH diagnosis as for the original idiopathic PAH cohort, with survival rates of 92%, 75% and 60% at 1, 3 and 5 years, respectively. Bottom line: in patients with CTEPH, the current abbreviated ERS/ESC risk score is applicable.

#### Reference: Eur Respir J 2018;52:1800248 Abstract

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### Adjunctive intermittent pneumatic compression for venous thromboprophylaxis

Authors: Arabi YM et al., for the Saudi Critical Care Trials Group

Summary: Patients aged ≥14 years who had been admitted to an ICU <48 hours prior were randomised to receive unfractionated heparin or LMWH thromboprophylaxis with (n=991) or without (n=1012) intermittent pneumatic compression for a median of 22 hours each day for a median of 7 days. There was no significant difference between the pneumatic compression and control arms for incident proximal lower-limb DVT after day 3 out to day 28, ICU discharge, death or attainment of full mobility (primary outcome; 3.9% vs. 4.2% [p=0.74]), PE or any lower-limb DVT (10.4% vs. 9.4%) or the 90-day all-cause mortality rate (26.1% vs. 26.7%).

Comment: This RCT was coordinated by the Saudi Critical Care Trials Groups and funded by King Abdulaziz City for Science and Technology and King Abdullah International Medical Research Center. The authors work off the premise that a DVT develops in 5-20% of critically ill patients despite pharmacological prophylaxis. Their RCT of 2000 patients reported that all patients were pharmacologically prophylaxed mainly with LMWH and unfractionated heparin, and half receiving additional intermittent pneumatic compression. Bottom line: critically ill patients receiving pharmacological DVT prophylaxis do not benefit from further intermittent pneumatic compression.

Reference: N Engl J Med; Published online Feb 18, 2019







## Rates of overtreatment and treatment-related adverse effects among patients with subsegmental pulmonary embolism



#### Authors: Raslan IA et al.

Summary: These researchers conducted a retrospective review of 223 CTPA scans classified as proximal, lobar, segmental or subsegmental PE to determine how often clinicians opted for clinical surveillance over therapeutic anticoagulation for the 79 scans classified as subsegmental. Of the 71 scans of presumed isolated subsegmental PE, 87% were systemically anticoagulated, compared with 94% of more proximal emboli. The main determinants for the nine patients with subsegmental PE who did not receive anticoagulation were bleeding at diagnosis or poor prognosis. Adverse events were commonly recorded for both groups. The 3-month ED presentation or readmission rate for VTE-unrelated reasons was 42% among patients anticoagulated for isolated subsegmental PE, and 34% had decreased haemoglobin levels of  $\geq 2$  g/dL. None of the ten deaths were VTE-related.

**Comment:** This scientific letter and invited <u>commentary</u> by Lisa Moores, with the title 'Less is more', is my 'article of choice' for this issue: 'Are we overtreating isolated subsegmental pulmonary embolism? First do no harm'. A group of authors from McGill University, Quebec, review their database of CTPA scans performed. Of their 223 patients with a positive CTPA scan, 79 (36%) had only subsegmental PE. Lisa Moores reviews that the coefficient of variation for these subsegmental PE is low at 0.38. Of the 62 patients who were systemically anticoagulated, 21 (34%) had decreased haemoglobin levels of 2 g/dL or greater and 10 died. Whilst there has never been an RCT, <u>observational studies</u> suggest that the recurrence rate of VTE in untreated VTE is 0%; however, 7% of treated patients have clinically important bleeding. Lisa Moores gives us the **bottom line: given the clinical equipoise, patients with subsegmental PE should at minimum have a discussion regarding the advantages and disadvantages of anticoagulation treatment.** 

Reference: JAMA Intern Med 2018;178:1272–4 Abstract

## Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer

Authors: Khorana AA et al., for the CASSINI Investigators

**Summary:** Ambulatory patients with cancer and a Khorana score  $\geq 2$  out of 6 for VTE risk but without DVT were randomised to receive rivaroxaban 10 mg/day (n=420) or placebo (n=421) for  $\leq 180$  days, and were screened every 8 weeks. The 180-day rate of the composite primary endpoint of objectively confirmed proximal DVT in a lower limb, PE, symptomatic DVT in an upper limb, distal DVT in a lower limb or death from VTE did not differ significantly between the rivaroxaban and placebo arms (6.0% vs. 8.8%; HR 0.66 [95% CI 0.40, 1.09]), but it was significantly lower among rivaroxaban recipients in a prespecified intervention period analysis (2.6% vs. 6.4%; 0.40 [0.20, 0.80]). The major bleeding rate did not differ significantly between rivaroxaban and placebo recipients (2.0% vs. 1.0%; HR 1.96 [95% CI 0.59, 6.49]).

**Comment:** Rivaroxaban is funded in NZ for the treatment of atrial fibrillation and VTE (Intern Med J). The next two trials explore outpatient VTE prophylaxis in high-risk patients with cancer. As Giancarlo Agnelli in his accompanying <u>editorial</u> points out, we know from trials using LMWH that ambulatory patients with metastatic or locally advanced cancers have an approximately 50% lower risk of VTE. This trial randomised patients to rivaroxaban 10mg daily or placebo and found a decrease in the rate of VTE, which wasn't statistically significant; there was no increase in the rate of bleeding. **Bottom line: rivaroxaban reduced the VTE-related events; however, it didn't quite reach statistical significance.** 

Reference: N Engl J Med 2019;380:720–8 Abstract



## Apixaban to prevent venous thromboembolism in patients with cancer

Authors: Carrier M et al., for the AVERT Investigators

Summary: Ambulatory patients starting chemotherapy for cancer who had a Khorana score ≥2 were randomised to receive thromboprophylaxis with apixaban 2.5mg (n=288) or placebo (n=275) twice daily in this trial. Compared with placebo, apixaban was associated with a significantly lower 180-day VTE occurrence rate (4.2% vs. 10.2%; HR 0.41 [95% Cl 0.26, 0.65]). In a modified intent-to-treat analysis, apixaban recipients had a significantly higher major bleeding rate (3.5% vs. 1.8%; HR 2.00 [95% Cl 1.01, 3.95]); the major bleeding rate on treatment was also higher, but statistical significance was not reached (2.1% vs. 1.1%; 1.89 [0.39, 9.24]).

**Comment:** This study also randomised high-risk patients with cancer for treatment with a direct factor-Xa oral anticoagulant, apixaban, to reduce the risk of VTE-related events. The results of this study are neatly summarised in a 2-minute QuickTake <u>video</u> (Apixaban for venous thromboembolism in cancer) and also the accompanying <u>editorial</u> by Giancarlo Agnelli. Apixaban is currently neither licensed nor funded for the primary prophylaxis of VTE in patients with cancer. The data are supportive, even so apixaban was associated with a statistically significant increase in major bleeding. **Bottom line: apixaban resulted in reduced VTE complications in patients with cancer, and only a minor increase in bleeding complications.** 

Reference: N Engl J Med 2019;380:711–9 Abstract

## Inhaled tranexamic acid for hemoptysis treatment

Authors: Wand 0 et al.

**Summary:** Patients hospitalised with haemoptysis of various aetiologies were randomised to receive nebulised tranexamic acid 500mg (n=25) or normal saline (n=22) three times daily in this trial. Compared with saline, tranexamic acid was associated with a significant reduction in expectorated blood volume starting from hospital day 2, a greater rate of haemoptysis resolution within 5 days of admission (96% vs. 50% [p<0.0005]), a shorter mean length of stay in hospital (5.7 vs. 7.8 days [p=0.046]) and fewer participants needing invasive procedures to control their bleeding (0% vs. 18.2% [p=0.041]). There were no adverse effects in either group and the 1-year recurrence rate was significantly reduced in the tranexamic acid group (p=0.009).

**Comment:** Tranexamic acid is a lysine analogue that inhibits the activation of plasminogen and blocks the action of plasmin on fibrin. It has proven antifibrinolytic activity and is used to reduce surgical blood loss, uterine bleeding and traumatic haemorrhage. In this investigator-initiated trial, about 50 patients with haemoptysis received 500mg of tranexamic acid or placebo via nebulisation three times a day. The background illnesses were malignancy, bronchiectasis, infection, COPD and no known cause. **Bottom line: patients receiving nebulised tranexamic acid had a quicker resolution of haemoptysis, less blood loss and no need for interventional procedures.** 

Reference: Chest 2018;154:1379–84 Abstract

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