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# Respiratory Research Review™

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## In this issue:



**Abbreviations used in this issue**

**BMPR-2** = bone morphogenic protein type 2 receptor
**LMWH** = low-molecular-weight heparin
**NT-proBNP** = NT terminal of probrain natriuretic peptide
**OR** = odds ratio
**P(A)H** = pulmonary (arterial) hypertension
**PE** = pulmonary embolism
**PERT** = Pulmonary Embolism Response Team
**RCT** = randomised controlled trial
**TGF** = transforming growth factor
**VTE** = venous thromboembolism

## Welcome to this issue of Respiratory Research Review on the topics of VTE (venous thromboembolism) and PAH (pulmonary arterial hypertension).

After a multitude of papers reporting on compliance with thromboprophylaxis and lack thereof, we are starting off with the N Engl J Med article by colleagues from Leiden in the Netherlands who report a lack of effect following knee arthroscopy. We go on to review great research on a prediction score to identify patients with VTE who are at risk of bleeding on anticoagulation therapy and review a risk score to predict *post partum* VTE. Finally, we reflect on a European approach to using NT-proBNP level measurements to stratify patients for outpatient treatment and a North American approach of a multidisciplinary PERT (Pulmonary Embolism Response Team) in cases of suspected PE (pulmonary embolism). The interested reader will also enjoy the French cross-sectional evaluation on the pathophysiology of dyspnoea in acute PE; a function of vascular consequences and sensory-affective domains associated with age, depression and breathing variability. Personally, and probably because I also trained during the 1980s, I most enjoyed the editorial by Donald Yealy from Pittsburgh on managing and embracing one's fears after diagnosing a PE.

Our understanding of PAH is improving, which will eventually lead to treatments beyond our current vasodilator therapies. Clinically, one of the greatest challenges is to identify the few patients with idiopathic PAH among the many patients with raised pulmonary arterial pressure secondary to heart disease and respiratory disease. Margaret Redfield from the Mayo Clinic published a case-based clinical review on 'Heart Failure with Preserved Ejection Fraction', which occurs in about 50% of patients with heart failure. Others have previously reviewed PH secondary to respiratory disease, another illness with a significant disease burden, which is difficult to manage. We highlight some primary research on the effect of selective TGF (transforming growth factor)-β ligands to attenuate PAH, the role of *BMPR2* mutations on vascular changes in PAH and the ability of exercise to predict outcomes in patients with systemic sclerosis. We end this review with two articles reflecting on the status quo of our current therapy – a meta-analysis of the efficacy and safety of single and combined PAH-specific therapy and a *post hoc* analysis of the AMBITION data, suggesting that upfront combination therapy with endothelium antagonists and phosphodiesterase inhibitors may provide a survival benefit compared with subsequential therapy.

We hope you enjoy the selection and are looking forward to feedback and comments.

Kind regards

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## Thromboprophylaxis after knee arthroscopy and lower-leg casting

**Authors**: van Adrichem RA et al., for the POT-KAST and POT-CAST Group

**Summary**: The POT-KAST (evaluable n=1451) and POT-CAST (evaluable n=1435) were parallel open-label trials that randomised patients undergoing knee arthroscopy (POT-KAST) or who required casting of the lower leg (POT-CAST) to receive or not receive anticoagulation prophylaxis with LMWH (low-molecular-weight heparin) for 8 days after knee arthroscopy or during the full period of immobilisation due to casting. There was no significant difference between the LMWH and control arms for the 3-month VTE rate in the respective POT-KAST and POT-CAST trials (0.7% vs. 0.4%; relative risk 1.6 [95% CI 0.4, 6.8] and 1.4% vs. 1.8%; 0.8 [0.3, 1.7]). Bleeding events had occurred in 0.1% of each group in POT-KAST and in none of the POT-CAST participants at 3 months. The most common adverse event was infection in both trials.

**Comment**: Several departments in Leiden, The Netherlands, including orthopaedics and thrombosis and haemostasis, with support from clinical epidemiology, medical statistics and bioinformatics collaborated to perform two parallel, pragmatic, multicentre RCTs to evaluate the efficacy of LMWH in patients following knee arthroscopy to prevent VTE. As Stephen Moll in the accompanying editorial reminds us, the evidence for VTE prophylaxis following knee arthroscopy is low and the 2012 American College of Chest Physicians didn't recommend prophylaxis in patients who don't have a history of previous VTE. **Bottom line: LMWH is not effective in preventing symptomatic VTE after knee arthroscopy.**

***Reference: N Engl J Med 2017;376(6):515–25***
Abstract

## Prediction of bleeding events in patients with venous thromboembolism on stable anticoagulation treatment

**Authors**: Klok FA et al.

**Summary**: These researchers used pooled *post hoc* analysis data from the RE-COVER studies, which compared dabigatran and standard treatment in 5107 patients with VTE, to derive a score for predicting bleeding during stable dabigatran. The resultant VTE-BLEED model included six variables and had a C statistic of 0.72 (95% CI 0.67, 0.76). In the derivation cohort, the low-risk group had a bleeding incidence of 2.8% while those in the high-risk group had an incidence of 12.6% (OR 5.0 [95% CI 3.5, 7.1]). The score was found to accurately predict the primary endpoint of major bleeding after day 30 in patients receiving dabigatran and also in those receiving warfarin (respective C statistics 0.75 [95% CI 0.61, 0.89] and 0.78 [0.68, 0.86]).

**Comment**: Offering any treatment is always a weighing up of the potential beneficial effects versus the natural history versus unwanted effects of treatment. One of the most concerning adverse effects of anticoagulation is bleeding. Here a group of European researchers used data from the dabigatran efficacy studies to identify patients at risk of bleeding. The group presents a new risk score based on six objective clinical variables: active cancer, male with uncontrolled hypertension, anaemia, history of bleeding, renal dysfunction and age older than 60 years. **Bottom line: this VTE-BLEED score identifies the quarter of patients who have a 6-fold higher bleeding risk.**

***Reference: Eur Respir J 2016;48(5):1369–76***
Abstract

## Development and validation of risk prediction model for venous thromboembolism in postpartum women

**Authors**: Sultan AA et al.

**Summary**: These researchers used data from England and Sweden for pregnant women with *post partum* follow-up to develop and validate a model for predicting VTE risk during the first 6 weeks after delivery. There were 433,353 and 662,387 deliveries in the respective English and Swedish cohorts, for which VTE occurred at absolute rates of 7.2 and 7.9 per 10,000 deliveries, respectively. The strongest predictors of VTE in the final multivariable model were emergency caesarean delivery, stillbirth, varicose veins, pre-eclampsia/eclampsia, *post partum* infection and comorbidities. The model had C statistic values of >0.70 in both cohorts, and calibration of observed and predicted risks was excellent. More VTE events were identified using this model than predicted by the existing English (sensitivity 68% vs. 63%) and Swedish (30% vs. 21%) guidelines at similar thresholds.

**Comment**: Considering the prothrombotic side effects of oral contraceptives is important; however, pregnancy also increases the risk of thrombosis. In the UK, VTE is one of the leading causes of maternal death and 50% of the VTE-related maternal deaths occur in the *post partum* period. In a collaboration between the UK and Sweden, the researchers use data from more than 1 million deliveries to derive and validate a new prediction model based on clinical variables available at the point of childbirth. **Bottom line: the authors present a freely available risk prediction calculator that can be integrated into a designated website or a general practice/ hospital computer system.**

***Reference: BMJ 2016;355:i6253***
Abstract



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## Efficacy and safety of outpatient treatment based on the Hestia clinical decision rule with or without N-terminal pro-brain natriuretic peptide testing in patients with acute pulmonary embolism

**Authors**: den Exter PL et al., for the Vesta Study Investigators

**Summary**: Outpatients with PE and none of the Hestia criteria were either discharged directly (n=275) or subjected to additional NT-proBNP level testing (n=275) in this noninferiority RCT. In the additional NT-proBNP level testing arm, 12% had an NT-proBNP level >500 ng/L and were admitted, and the remainder had lower levels and were discharged. None of the admitted patients with an elevated NT-proBNP level and none of those with a *post hoc*-determined elevated NT-proBNP level from the direct discharge group experienced a primary endpoint event (30-day PE- or bleeding-related mortality, cardiopulmonary resuscitation or intensive care unit admission). There was also no significant difference between the entire direct discharge group versus the entire additional NT-proBNP testing group for the primary endpoint event rate (1.1% vs. 0% [p=0.25]) or for the 3-month VTE recurrence rate (1.1% vs. 0.73% [p=0.65]).

**Comment**: PE is a common and potentially fatal disease, and treatment is often initialised in hospital. Evidence for treating PE as an outpatient isn't that solid, but even so, two risk prediction scores are validated: the PESI (Pulmonary Embolism Severity Index) and the Hestia clinical decision rule. In this prospective study in 17 Dutch hospitals, the authors used NT-proBNP level in addition to clinical criteria to identify patients who could be treated at home. Donald Yealy from Pittsburgh wrote a most reflective editorial on embracing and managing our fears after diagnosing PE. **Bottom line: use of clinical criteria alone was sufficient to identify patients at low risk.**

***Reference: Am J Respir Crit Care Med 2016;194(8):998–1006***
Abstract

## A multidisciplinary pulmonary embolism response team: initial 30-month experience with a novel approach to delivery of care to patients with submassive and massive pulmonary embolism

**Authors**: Kabrhel C et al.

**Summary**: This research prospectively evaluated the performance of a rapid-response PERT (Pulmonary Embolism Response Team) that included specialists in cardiovascular medicine/surgery, emergency medicine, haematology, pulmonary/critical care and radiology. There were 394 distinct PERT activations over a 30-month period, 80% of which were for confirmed PE, and 46% and 26% of which were for submassive and massive confirmed PEs, respectively. Every 6 months, PERT activations increased by 16%. Systemic or catheter-directed thrombolysis was used for 11% of PE cases managed by the PERT, and 69% were treated with anticoagulation alone. Haemorrhagic complications were rare, particularly among patients treated with catheter-directed thrombolysis. The 30-day all-cause mortality rate among patients with confirmed PE was 12%.

**Comment**: This is the report from the Massachusetts General Hospital PERT. PE occurs in about 1–2 per 1000 adults per year, is frequently fatal, and our treatment paradigm hasn't changed over the last 50 years despite new technology and treatments becoming available. This report summarised the patients seen, team activation, patient characteristics, PE severity, treatment offered and short- as well as long-term outcomes. The interested reader will find the website of the national PERT consortium, encompassing representatives from more than 35 centres, inspiring. **Bottom line: PERT may become the new standard of care for patients with PE.**

***Reference: Chest 2016;150(2):384–93***
Abstract





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## A selective transforming growth factor-β ligand trap attenuates pulmonary hypertension

**Authors**: Yung L-M et al.

**Summary**: Using signalling studies of cultured human pulmonary artery smooth muscle cells, these researchers investigated the impact of soluble TGFBR2-Fc (TGF-β type 2 receptor extracellular domain expressed as an immunoglobulin-Fc fusion protein), as a selective TGF-β1/3 ligand trap, in experimental models of PH in monocrotaline-treated Sprague-Dawley rats, SU5416/hypoxia-treated Sprague-Dawley rats and SU5416/hypoxia-treated C57BL/6 mice; TGFBR2-Fc inhibits TGF-β1 and TGF-β3, but not TGF-β2, signalling. *In vivo* TGFBR2-Fc treatment resulted in attenuation of Smad2 phosphorylation and normalisation of plasminogen activator inhibitor-1 expression, and also mitigated PH and pulmonary vascular remodelling in the three murine models. Right ventricular systolic pressures, right ventricular function and survival were also improved in monocrotaline-treated and SU5416/hypoxia-treated rats with established PH. No evidence of cardiac structural or valvular abnormalities emerged on treatment with TGFBR2-Fc.

**Comment**: BMPR-2 (bone morphogenic protein type 2 receptor) is a member of the TGF-β family. Enhanced signalling leads to smooth muscle hypertrophy, perivascular fibrosis, extracellular remodelling and PAH. However, general TGF-β blockers have been associated with cardiovascular and other toxicities. This Harvard group is presenting elegantly executed studies creating selective TGF-β1 and TGF-β3 blockades, sparing the TGF-β2 ligand. These TGF-β1/3 ligands reduced pulmonary vascular remodelling and PAH in three animal models. The editorial explains the **bottom line: ligand traps are entering the clinical arena and may provide new therapeutic avenues to treat PAH.**

***Reference: Am J Respir Crit Care Med 2016;194(9):1140–51***
Abstract



**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 with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or considering future collaborations.

## *BMPR2* mutation status influences bronchial vascular changes in pulmonary arterial hypertension

**Authors**: Ghigna M-R et al.

**Summary**: A systematic analysis and morphometry were performed on clinical and lung histology data obtained from 44 patients with PAH to ascertain the histological profile of *BMPR2* mutation carriers. The lungs of patients with PAH who carried *BMPR2* mutations exhibited increased bronchial artery hypertrophy/dilatation, bronchial angiogenesis and muscular remodelling of septal veins. Patients with increased bronchial artery remodelling and bronchial microvessel density were more likely to experience severe haemoptysis, regardless of mutation status, but those carrying a *BMPR2* mutation more often had a history of haemoptysis >50mL. Compared with noncarriers, a greater proportion of *BMPR2* mutation carriers had singular large fibrovascular lesions (43.5% vs. 9.5%), which appeared to be closely related to the systemic lung vasculature.

**Comment**: About 70% of patients with idiopathic and 10–40% of patients with sporadic PAH have mutations in the *BMPR2* gene. This French group is exploring whether they can correlate anatomical differences to BMPR-2 receptor status in 44 of their patients who have had a lung transplant. Using a number of elegant anatomical techniques, the researchers describe the phenotype. *BMPR2* mutation carriers are more prone to haemoptysis, which in itself is related to bronchial arterial remodelling, angiogenesis and increased pulmonary venous remodelling. **Bottom line: patients with PAH and *BMPR2* mutation display a distinct clinical profile.**

***Reference: Eur Respir J 2016;48(6):1668–81***
Abstract

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## Exercise pulmonary haemodynamics predict outcome in patients with systemic sclerosis

**Authors**: Stamm A et al.

**Summary**: The prognostic value of exercise haemodynamics measured during right heart catheterisation was evaluated in patients with systemic sclerosis who had been referred for evaluation of PH. The participants were tested at rest and during maximal supine incremental cycle exercise, and grouped into the following three groups: i) resting precapillary PH (mean pulmonary artery pressure ≥25mm Hg and pulmonary artery wedge pressure <15mm Hg; n=17); ii) exercise-induced PH (mean pulmonary artery pressure ≥30mm Hg and mean pulmonary artery pressure/cardiac output >3mm Hg/L/min at maximal exercise; n=28); and iii) no PH (n=27). Median follow-up was 33 months. Compared with the group without PH, the resting precapillary PH and exercise-induced PH groups had significantly shorter estimated respective mean transplant-free survival durations (4.4 and 5.2, respectively, vs. 9.5 years [p<0.05]). A Cox regression analysis revealed that predictors of transplant-free survival were exercise-induced increase in mean pulmonary artery pressure (hazard ratio 1.097 [95% CI 1.002, 1.200]) and the coefficient of pulmonary vascular distensibility alpha (0.100 [0.012, 0.871]), but not resting haemodynamics.

**Comment**: Exercise-induced PAH has been abandoned as a diagnostic criterion due to insufficient data and a lack of agreement in the literature. Still it is likely that exercise-induced PAH is a precursor to progressive PAH and it may assist in identifying and treating patients early. This group from Zurich provides a significant contribution to the literature by providing data on more than 70 patients with scleroderma with median follow-up of almost 3 years. **Bottom line: exercise-induced PAH is associated with a reduced survival similar to that of patients with resting PAH.**

***Reference: Eur Respir J 2016;48(6):1658–67***
Abstract

## Efficacy and safety of pulmonary arterial hypertension-specific therapy in pulmonary arterial hypertension

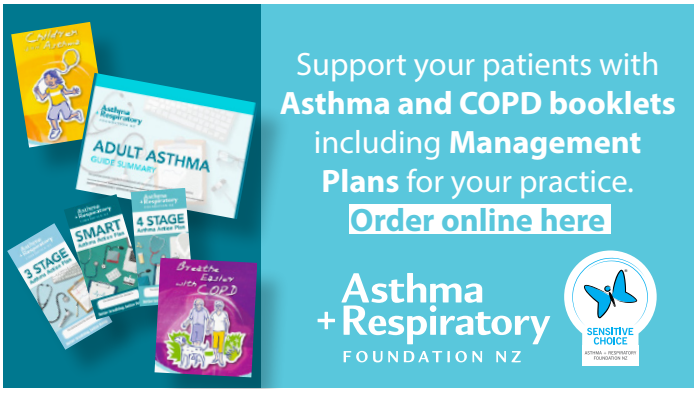
**Authors**: Liu H-L et al.

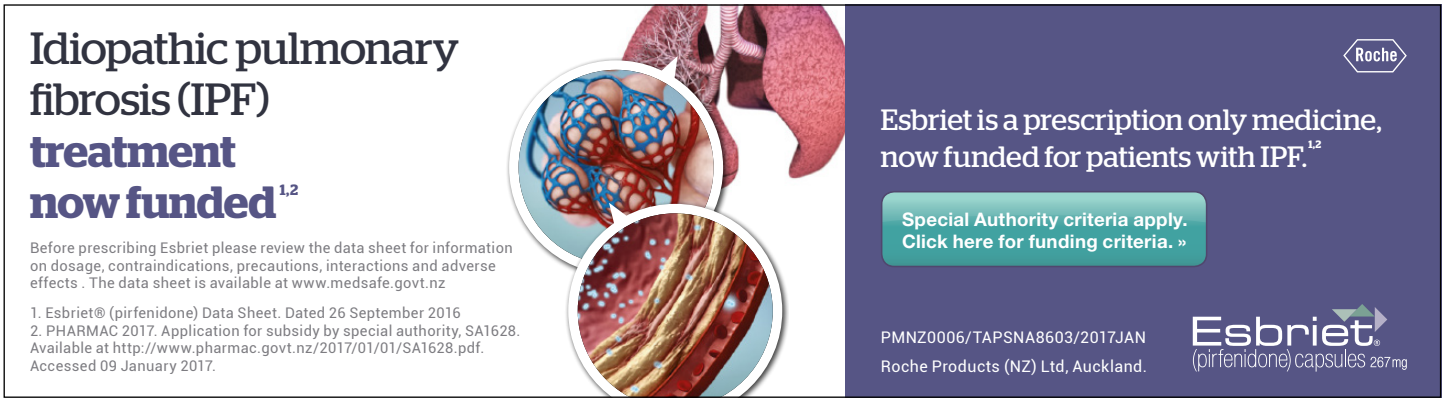
**Summary**: This was a meta-analysis of 35 RCTs (n=6702) evaluating any PAH-specific monotherapy versus placebo/conventional therapy. Compared with placebo/conventional therapy, monotherapy was associated with significant effects on mortality (OR 0.50 [95% CI 0.33, 0.76]), New York Heart Association/WHO functional class (2.48 [1.51, 4.07]), 6-minute walk test distance (mean difference 31.10m [p<0.00001]), and haemodynamic status based on mean pulmonary artery pressure, pulmonary vascular resistance, cardiac index and withdrawals due to adverse effects. Compared with combination therapy, monotherapy was associated with significant effects on 6-minute walk test distance (mean difference 19.96m [p<0.00001]), functional class (OR 1.65 [95% CI 1.20, 2.28]), haemodynamic status and withdrawals due to adverse effects (2.01 [1.54, 2.61]), but not mortality (0.98 [0.57, 1.68]).

**Comment**: This group from China presents an astute analysis on the effect of monotherapy and combination therapy in the management of PAH. They make the observation that improvement due to adding any second agent to background PAH-specific therapy does not lead to the same magnitude of improvement as would occur if the agent had been started as monotherapy. They provide an important meta-analysis for all agents currently used. **Their bottom line: PAH-specific monotherapy improves mortality, exercise capacity, functional class and haemodynamic status; combination therapy improves it further at smaller magnitudes without an effect on mortality and with a higher incidence of adverse effects.**

***Reference: Chest 2016;150(2):353–65***
Abstract



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# Initial combination therapy with ambrisentan and tadalafil and mortality in patients with pulmonary arterial hypertension

**Authors**: Hoeper MM et al.

**Summary**: This was a secondary analysis of the AMBITION trial, which randomised treatment-naive patients with PAH to receive ambrisentan plus tadalafil (evaluable n=302) or each agent as monotherapy (combined n=303). This analysis focussed on mortality events from randomisation to study end, including participants who discontinued their assigned treatment. The 7-day postrandomisation mortality rate was 1% in the combination group versus 4% in both monotherapy groups combined (hazard ratio 0.21 [95% CI 0.06, 0.73]), and the respective end-of-study mortality rates were 10% and 14% (0.67 [0.42, 1.08]).

**Comment**: The AMBITION study demonstrated that upfront combination therapy with an endothelial antagonist and phosphodiesterase inhibitor showed a significant reduction in reaching the composite primary endpoint, mainly because of the reduction of hospital admissions. The primary endpoint of death only occurred in 25 (4%) of the 605 participants, although the total number of deaths was 70 (12%). This group performed a *post hoc* analysis of the AMBITION data suggesting a survival advantage of upfront combination therapy. Paul Hassoun in his editorial gives the **bottom line: upfront combination therapy may improve survival; however, this needs to be assessed by prospective studies.**

***Reference: Lancet Respir Med 2016;4(11):894–901***
Abstract



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