Pulmonary hypertension

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ABSTRACT In 2015, more than 800 papers were published in the field of pulmonary hypertension. A Clinical Year in Review article cannot possibly incorporate all this work and needs to be selective. The recently published European guidelines for the diagnosis and treatment of pulmonary hypertension contain an inclusive summary of all published clinical studies conducted until very recently. Here, we provide an overview of papers published after the finalisation of the guideline. In addition, we summarise recent advances in pulmonary vasculature science. The selection we made from the enormous amount of published work undoubtedly reflects our personal views and may not include all papers with a significant impact in the near or more distant future. The focus of this paper is on the diagnosis of pulmonary arterial hypertension, understanding the success of combination therapy on the right ventricle and scientific breakthroughs.

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The review summarises advances in pulmonary hypertension since the publication of the recent ESC/ERS guidelines http://ow.ly/WUwoe

The global picture of pulmonary arterial hypertension

Table 1 summarises the recent classification of pulmonary hypertension [1, 2]. Based on data from the large European and North American registries, the most common types of pulmonary arterial hypertension (PAH) are idiopathic PAH and PAH associated with connective tissue disease. Less is known of the epidemiology of PAH in other parts of the world. Using the data from a large reference centre in Brazil, ALVES et al. [3] showed that schistosomiasis is among the top three of causes of PAH in that country. These global epidemiological data emphasise the importance of accounting for such differences in future clinical trials.

Pulmonary veno-occlusive disease

An important change from the previous classification is that significant progress has been made in the field of pulmonary veno-occlusive disease (PVOD). Several causes of PVOD have been identified in recent years, including genetics, drugs and radiation therapy. The finding of the EIF2AK4 (eukaryotic translation initiation factor 2α kinase 4) mutation in familial PVOD and pulmonary capillary haemangiomatosis (PCH) might boost further research [4, 5]. By the discovery of this gene, it is possible to confirm the diagnosis of PVOD or PCH by demonstrating the presence of the mutation instead of a histological diagnosis [5]. Of interest is the recent study by PERROS et al. [6] showing not only that mitomycin is a risk factor for the development of PVOD, but also that mitomycin induces pulmonary vascular disease in rats that resembles the pathological features of PVOD. This finding not only offers a representative animal model to study the disease but also sheds new light on the possible role of alkylating chemotherapy on the development of pulmonary hypertension [7]. New associations between drugs and disease were not only made in PVOD; in PAH, a possible relationship between a drug and the disease also was found. A recent...
paper by Savale et al. [8] showed a possible relationship between interferon and the development of pulmonary hypertension. As indicated by those authors, a prospective case–control study is necessary to establish a definitive link between interferon exposure and PAH.

### Novel insights into treatment strategy in PAH

In 2015, an impressive number of clinical trials in PAH and chronic thromboembolic pulmonary hypertension (CTEPH) was published. We aim to give an overview of these clinical trials in table 2.

Although a significant number of drugs is currently approved for the treatment of PAH, relatively little is known about the optimal strategy for combining treatments. The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) researchers investigated the effect of initial combination therapy with ambrisentan and tadalafil [13]. In this event-driven, double-blind study, patients were randomly assigned to receive initial combination therapy or monotherapy. The primary end-point in this study was time to the first event of clinical failure. The study showed that in comparison to monotherapy, initial combination treatment resulted in a significantly lower risk of clinical failure. The main reason in this study for clinical failure was hospitalisation for worsening PAH. Since the symptoms of PAH are related to right ventricular function,
| First author [ref.] | Therapy | Diagnosis | Patients n | Study design | Follow-up | Primary end-point(s) | Conclusion |
|----------------------|---------|-----------|------------|--------------|-----------|----------------------|------------|
| CHEN [9]             | Pulmonary artery denervation | WHO group 1, 2 and 4 | 66 | Phase II, non-randomised, open-label study | 1 year | Haemodynamic, functional and clinical response | PADN procedure was associated with favourable 1-year outcomes |
| KHAN [10]            | Ranolazine 1000 mg twice daily | PAH | 11 | Phase I | 3 months | Safety and tolerability | No major adverse events |
| RUITER [11]          | Intravenous iron | Iron-deficient iPAH | 15 | Open-label intervention study | 12 weeks | Change in 6MWD | No significant increase in 6MWD |
| HASSOUN [12]         | Tadalafil 40 mg and ambrisentan 10 mg | SSc-PAH | 24 | Open-label, prospective clinical trial | 36 weeks | Changes in PVR and RV mass | Significant decrease in PVR and RV mass |
| GALIE [13]           | Tadalafil 40 mg and/or ambrisentan 10 mg | PAH NYHA II–III | 500 | Randomised, double-blind, phase 3–4 study | 24 weeks | First event of clinical failure | HR for event of clinical failure was significantly reduced in combination therapy group compared to mono therapy groups |
| EHLKEN [14]          | Low-dose exercise training 4–7 days per week | PAH, CTEPH | 87 | Randomised controlled trial | 15 weeks | Change in peak \( V'\)O_2 per kg | Peak \( V'\)O_2 per kg increased after low-dose exercise training |
| FROST [15]           | Imatinib | PAH | 78 | Open-label extension study | Up to 204 weeks | Long-term safety and tolerability | SAEs and safety concerns preclude the use of imatinib in the treatment of PAH |
| GRANTON [16]         | Endothelial NO synthase gene-enhanced progenitor cell therapy | PAH refractory to PAH therapy | 7 | Phase I, dose-escalating trial | 6 months | Tolerability | Delivery of endothelial progenitor cells overexpressing endothelial NO synthase was tolerated haemodynamically in patients with PAH |
| MCLAUGHLIN [17]      | Addition of bosentan/placebo to sildenafil | PAH patients on sildenafil therapy | 334 | Double-blind, event-driven trial | Mean \( \pm \)SD 39.7±22.6 months | Time to morbidity/mortality event | No significant effect of addition of bosentan to sildenafil on time to morbidity/mortality was observed |
| SPEICH [18]          | Imatinib | PAH | 15 | Open-label, observational study | Median 37 months | Efficacy and tolerability | Long-term treatment with imatinib may improve functional class and quality of life The occurrence of 5% SDH per patient-year is concerning |
| PROVENCHER [19]      | Thermostable epoprostenol sodium versus epoprostenol sodium | PAH | 16 | Multicentre, open-label, single-arm study | 4 weeks | HRQoL, ease of administration and change in dose from baseline | No significant improvement in HRQoL was measured Subjects preferred the thermostable product The products had similar safety and efficacy profiles |

Continued
| First author | Therapy | Diagnosis | Patients n | Study design | Follow-up | Primary end-point(s) | Conclusion |
|-------------|---------|-----------|------------|--------------|-----------|---------------------|------------|
| GALIE [20]  | Riociguat and sildenafil | PAH patients on sildenafil therapy | 17 | Blinded, randomised controlled and extension study | 12 weeks, thereafter extension | Change in supine SBP and safety | No difference in SBP was observed. Potentially unfavourable safety signals with sildenafil plus riociguat were observed. |
| RUBIN [21]  | Riociguat | PAH | 396 | Open-label extension study | Mean 95 weeks | Safety, tolerability and efficacy (6MWD, WHO functional class) | Long-term riociguat was well tolerated in patients with PAH. Data support sustained efficacy on 6MWD and WHO functional class. |
| SIMONNEAU [22] | Riociguat | CTEPH or persistent PH after PEA | 237 | Open label extension study | Mean 83 weeks | Safety, tolerability and efficacy (6MWD, WHO functional class) | Long-term riociguat was well tolerated in patients with CTEPH. Data support sustained efficacy on 6MWD and WHO functional class. |
| CHIN [23]  | Treprostinil sodium | PAH | 206 | Open-label extension study | Up to 24 months | 6MWD | Long-term therapy with inhaled treprostinil demonstrated persistent benefit for PAH patients who remained on therapy for up to 24 months. |
| SITBON [24] | Selexipag versus placebo | PAH | 1156 | Blinded, randomised controlled trial | Median 63.7 weeks (placebo), 70.7 weeks (selexipag) | Time-to-event, composite of death or a complication related to PAH | The risk for the primary composite end-point was significantly lower among patients on selexipag compared to patients on placebo. |

WHO: World Health Organisation; iPAH: idiopathic pulmonary arterial hypertension; SSc-PAH: systemic sclerosis-associated pulmonary arterial hypertension; NYHA: New York Heart Association functional class; PH: pulmonary hypertension; PEA: pulmonary endarterectomy; 6MWD: 6-min walk distance; PVR: pulmonary vascular resistance; RV: right ventricular; $V'_{O_2}$: oxygen uptake; HRQoL: health-related quality of life; SBP: systolic blood pressure; PADN: pulmonary artery denervation; HR: hazard ratio; SAE: serious adverse event; SDH: subdural haematoma.
the question arises of why initial combination treatment seems to save the right ventricle better than
monotherapy. Although this study was not designed to provide insight on this, the 67% drop in N-terminal
pro-brain natriuretic peptide (NT-proBNP), a marker of right ventricular wall tension [25], in the combination
arm was significantly greater than in the monotherapy arms. Although this is speculative, this may indicate that
combination treatment was able to lower right wall tension effectively. Earlier studies showed that when
treatment lowers NT-proBNP by at least 40%, survival is excellent [26]. The importance of lowering right
ventricular wall stress was also demonstrated in a study by Van de Veerdonk et al. [27], where an increase in
right ventricular end-diastolic and end-systolic volume together with a decrease in right ventricular ejection
fraction preceded progressive disease in seemingly stable pulmonary hypertension patients. Why does the right
ventricle dilate in one PAH patient and not in the other? Although this question cannot be answered yet, it
became clear from another recent study that the contractile reserve of the right ventricle in advanced stages
of PAH is absent [28]. For this reason dilatation might be the only option for the right ventricle to preserve
stroke volume.

Another important study on new (combination) treatment in PAH is the Prostacyclin Receptor Agonist in
Pulmonary Arterial Hypertension (GRIPHON) study. In this large, multicentre trial, 1156 PAH patients
were randomised 1:1 to placebo or selexipag, which is an oral selective IP prostacyclin receptor agonist [24].
Patients on selexipag had a significantly reduced risk of the composite end-point of death or PAH-related
complication. However, a beneficial effect of selexipag on survival rate was not observed.

Although positive results of combination therapy in PAH were provided in the GRIPHON and AMBITION
trial [13, 24], superiority of sildenafil and bosentan to sildenafil monotherapy was not significant in the
COMPASS-2 (Effects of Combination of Bosentan and Sildenafil versus Sildenafil Monotherapy on
Morbidity and Mortality in Symptomatic Patients with Pulmonary Arterial Hypertension) trial [17].

Pulmonary hypertension due to left heart disease

One of the diagnostic challenges in clinical practice is the distinction between pulmonary hypertension
secondary to heart failure with preserved ejection fraction and PAH. The importance of this distinction
remains relevant, as Hoendermis et al. [29] recently showed. In their study, treatment with sildenafil did
not reduce pulmonary artery pressures and did not improve other invasive haemodynamic or clinical
parameters in a well characterised cohort of patients with heart failure and preserved ejection fraction and
predominantly isolated post-capillary pulmonary hypertension. The demonstration of a wedge pressure
and/or left ventricular end-diastolic pressure >15 mmHg is considered proof that left heart failure is the
primary cause of pulmonary hypertension. Obviously, an invasive approach is required to make the
distinction. The question is whether a noninvasively assessed risk score can help to discriminate between
PAH and pulmonary hypertension secondary to left heart failure. Simple noninvasive parameters such as
signs of left ventricular hypertrophy on ECG, assessment of left atrial size on echocardiography and
medical history can help to discriminate between left heart disease-related pulmonary hypertension and
PAH [30]. The finding that left atrial size is a strong discriminator is in line with an earlier study [31].

Pulmonary hypertension secondary to pulmonary disease

It is well known that the presence of pulmonary hypertension in different types of lung disease is strongly
associated with poor outcome. Whether or not the pulmonary hypertension is also a cause of death in
those patients is unknown. It is known that, when present, pulmonary hypertension progresses slowly in
chronic obstructive pulmonary disease (COPD) [32]. Much less is known about the natural cause of
pulmonary hypertension in idiopathic pulmonary fibrosis (IPF), because most studies are limited by their
focus on advanced lung disease. Recently, Raghur et al. [33] filled this gap using right heart catheterisation
data from 488 subjects enrolled in a placebo-controlled study of ambrisentan in IPF with mild–moderate
lung volume restriction. As in COPD, it was shown that severe pulmonary hypertension is rare in IPF and
that pulmonary artery pressure remains stable over a 1-year period in the majority of IPF patients. An
earlier report from the same study showed that treatment with ambrisentan is not effective in these
patients and is even associated with shorter time to disease progression [34]. In a later placebo-controlled
trial by Cort et al. [35], patients with IPF and pulmonary hypertension were randomised to bosentan or
placebo. At a 16-week follow-up, no difference was found between the placebo and treatment group in
pulmonary haemodynamics, symptoms and functional capacity in patients with idiopathic interstitial
pneumonia and pulmonary hypertension. A subgroup analysis could not reveal patient characteristics
associated with a beneficial effect of bosentan.

Whether or not pulmonary hypertension treatment changes exercise performance in lung disease is a
matter of ongoing debate. While phosphodiesterase (PDE)5 inhibition may decrease mean pulmonary
artery pressure and increase cardiac output in COPD [36], this does not translate into an increased
exercise capacity [37]. Blanco et al. [38] showed, in a randomised controlled trial, that sildenafil did not
increase exercise capacity in COPD patients enrolled in a pulmonary rehabilitation programme. More recently, Goude et al. [39] investigated, in a randomised, double-blind, parallel-group, placebo-controlled trial, whether tadalafil could improve exercise performance or quality of life in a group of 120 COPD patients. In line with previous studies, PDE5 inhibition did not result in an improvement in exercise capacity or quality of life despite effective pulmonary vasodilation. Taken together, these studies show that although mild pulmonary hypertension is common in lung disease, pulmonary vasodilatory treatment does not improve exercise performance. It remains to be determined whether in the small subgroup of patients with severe pulmonary hypertension and a circulatory impairment of exercise capacity, vasodilator treatment could still be effective [40].

**Chronic thromboembolic pulmonary hypertension**

The pathogenesis of CTEPH is still poorly understood. Although the disease was considered pre-capillary, pathological studies revealed that, in humans and experimental CTEPH, the disease is also partly due to post-capillary remodelling [41]. The same study also revealed the presence of bronchial arterial to pulmonary venous shunting in CTEPH. Further studies are needed to assess the functional importance of this finding clinically. Although the treatment of choice in CTEPH is surgery, not all patients can be considered operable due to peripheral obstructive lesions and/or comorbidities. In recent years, two alternative treatment options for these inoperable patients have become available: medical (riociguat) [42] and balloon pulmonary angioplasty [43, 44].

In 2015, the CHEST-2 study was published with long-term results of riociguat in inoperable CTEPH. Long-term riociguat had a favourable benefit–risk profile and showed sustained benefits in exercise and functional capacity for up to 1 year [22]. Single-centre experience with the results of balloon pulmonary angioplasty for inoperable CTEPH is promising. In a recent study, Fuku et al. [45] showed a marked improvement in right ventricular end-diastolic and end-systolic volume index together with marked improvements in functional capacity in 20 inoperable CTEPH patients treated by balloon pulmonary angioplasty. The changes were similar as previously observed after pulmonary endarterectomy [46].

**Novel insights**

Recent excellent reviews have described the progress made in the field of the pathobiology of PAH and potential novel treatment targets in PAH [47, 48]. Many years’ research has revealed the involvement of inflammatory factors, growth factors, abnormalities in calcium signalling, disturbances in the bone morphogenic protein (BMP) receptor type II/transforming growth factor-β axis, neurohumoral dysregulation, dysregulated angiogenesis, metabolic disturbances in the pulmonary vasculature, mitochondrial dysregulation, disturbances in the extracellular matrix and abnormal levels of vasoactive mediators. What is unknown for most of these factors is whether the observed disturbances are causes or consequences of the disease. Answering this question in upcoming years is important since not all treatment targets can be tested in clinical trials given the low number of patients. In addition, side-effects of the potential novel drugs need to be taken into account before a proper decision can be made of which drug to choose. This was also illustrated by the publication of the long-term (up to 204 weeks) safety and efficacy of imatinib in an open-label extension study. Although imatinib treatment resulted in improved haemodynamics and exercise capacity in a controlled trial (IMPRES (Imatinib in Pulmonary Arterial Hypertension)), long-term follow-up showed serious adverse events leading to a high discontinuation rate. Based on these findings, the authors concluded that the risks of the drug outweigh any possible improvements in haemodynamics and walk distance [15].

A starting point for our understanding of the disease and development of novel treatment is the loss of function mutations in the BMP receptor type II (BMPR2) gene in heritable PAH. Reduced BMPR2 expression is even observed in patients without a mutation [49]. Restoration of BMPR2 signalling thus might be of benefit in PAH patients. Spiekeroog et al. [50] identified in an earlier study that low-dose FK506 (tacrolimus) can act as a potent BMPR2 activator that reverses experimental PAH. Based on these findings, the same group recently reported the outcome of the first three patients treated with FK506 [51]. Further studies are required to show the safety and efficacy of FK506 in PAH. Another approach to targeting the loss of BMPR2 is the use of BMP ligands that selectively target this signalling pathway. A recent paper identified BMP9 as such a promising ligand. In a set of experiments, the group showed the promise of direct enhancement of endothelial BMP signalling by BMPR9 as a new therapeutic strategy for PAH [52]. A better understanding of genetics may also improve understanding of the susceptibility to hypoxia-induced pulmonary hypertension. Variations in the vasoconstrictive response to a low-oxygen environment between individuals and between animal species are still poorly understood. Zhao et al. [53], used a comparative genomics approach to exploit this variation in the rat and identified the gene Slc39a12, encoding the zinc transporter ZIP12, as a major regulator of hypoxia-induced pulmonary vascular remodelling. In a set of elegant experiments, it was demonstrated that genetic disruption of ZIP12 expression attenuates the development of pulmonary hypertension in rats housed in a hypoxic atmosphere.
This insight into the fundamental role of a zinc transporter in the development of hypoxia-related pulmonary hypertension might have therapeutic consequences in the near future. The zinc transporter ZIP12 regulates the pulmonary vascular response to chronic hypoxia.

In conclusion, while significant progress has been made in recent years in our understanding of pulmonary hypertension and in treating patients with this condition, significant gaps in our knowledge remain. Key research questions have been and continue to be: can we identify new treatments that are categorically different from vasodilators? Do we need to treat all patients with upfront dual or even triple combination therapy, or is a stepwise strategy noninferior (and associated with fewer side-effects and lower cost)? How do we prevent deterioration in right ventricular function in patients who are seemingly stable on maintenance therapy? How do we treat pulmonary hypertension in chronic heart and parenchymal lung disease? Can we repair pulmonary vascular remodelling in all types of pulmonary hypertension?

Survival in PAH has improved to the point that the disease is becoming more and more of a chronic condition that is not imminently life threatening in the majority of patients. Notwithstanding this positive result of a tremendous research effort in the past three decades, PAH remains associated with significant morbidity and mortality, and a significant reduction in quality of life. A continued collaborative research effort in the next decade could lead to significant further progress and perhaps even a cure of the disease.

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