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

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TABLE 1 Updated classification of pulmonary hypertension (PH)

1 Pulmonary arterial hypertension
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 *BMPR2* mutation
  - 1.2.2 *ALK1*, *ENG*, *SMAD9*, *CAV1* and *KCNK3* mutation
  - 1.2.3 Unknown
- 1.3 Drug and toxin induced
- 1.4 Associated with
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart diseases
  - 1.4.5 Schistosomiasis

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
- 1′.1 Idiopathic
- 1′.2 Heritable
  - 1′.2.1 *EIF2AK4* mutation
  - 1′.2.2 Other mutations
- 1′.3 Drug, toxin and radiation induced
- 1′.4 Associated with
  - 1′.4.1 Connective tissue disease
  - 1′.4.2 HIV infection

1″ Persistent PH of the newborn

2 PH due to left heart disease
- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3 PH due to lung diseases and/or hypoxia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases

4 Chronic thromboembolic PH

5 PH with unclear multifactorial mechanisms
- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders and splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis and lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease and thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure and segmental PH

BMPR: bone morphogenic protein receptor type II; ALK1: activin receptor-like kinase 1; ENG: endoglin; CAV1: caveolin-1; KCNK3: potassium channel, two pore domain subfamily K, member 3; EIF2AK4: eukaryotic translation initiation factor 2α kinase 4. Reproduced and modified from [1].

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,

TABLE 2 Overview of clinical trials in pulmonary arterial hypertension (PAH) and chronic thromboembolic hypertension (CTEPH) in 2015

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
Galiè [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±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

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TABLE 2 Continued

First author [ref.]	Therapy	Diagnosis	Patients n	Study design	Follow-up	Primary end-point(s)	Conclusion
Galiè [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, RAGHU *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 CORTE *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

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increase exercise capacity in COPD patients enrolled in a pulmonary rehabilitation programme. More recently, Goudie *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, Fukui *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, neurohumoural 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 BMRP2 signalling thus might be of benefit in PAH patients. Spiekerkoeter *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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