Supplement 1 · December 2020

EMJ

European Edition

+ ESC CONGRESS 2020

Looking PHorward to Improving Long-Term Outcomes in Pulmonary Arterial Hypertension

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The Lung, at the Heart of Pulmonary Arterial Hypertension

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Looking PHorward to Improving Long-Term Outcomes in Pulmonary Arterial Hypertension

This symposium took place on 29th August 2020, as part of the European Society of Cardiology (ESC) Congress 2020

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Disclosure: Dr Howard has received speaker fees and honoraria for advisory boards and steering committees from Actelion. Dr Lang has received speaker fees and honoraria for advisory boards and steering committees from Actelion, AOP Orphan, Ferrer, and Medtronic. Dr Escribano has served on the board or advisory committee for Acceleron, Actelion/Johnson & Johnson, Bayer/Merck, and GlaxoSmithKline; has received speaker fees from Actelion/Johnson & Johnson, Bayer/Merck, Ferrer, and GlaxoSmithKline; and has received research support from Actelion/Johnson & Johnson and Bayer/Merck. Prof Rosenkranz has received honoraria for lectures and/or consulting fees from Abbott, Actelion, Arena, Bayer, Ferrer, GlaxoSmithKline, MSD, Novartis, Pfizer, and United Therapeutics. Prof Galiè has served on the advisory board and received speaker fees from Actelion, Janssen, Pfizer, and Ferrer.

Acknowledgements: Medical writing assistance was provided by Jenny Lloyd, Compass Medical Communications, Ltd., UK.

Disclaimer: The views and opinions expressed are those of the speakers and not necessarily those of Janssen.

Support: This content was funded by Janssen.

Citation: EMJ. 2020;5[Suppl 1]:2-9.

Meeting Summary

In this interactive symposium and question and answer session at the European Society of Cardiology (ESC) Congress 2020, co-chair Dr Howard gave an overview of pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH). He highlighted the need for early intervention while right ventricular (RV) function is preserved. Dr Escribano addressed the challenges faced in the diagnosis of the different forms of PH, particularly the difficulties in distinguishing patients with PAH from those with PH due to left heart disease (LHD). She detailed a three-step pragmatic approach for their differential diagnosis: 1) identification of a specific PH-LHD phenotype; 2) definition of a pretest probability of PH-LHD; and 3) haemodynamic assessment. Prof Rosenkranz highlighted the implication of right heart remodelling on long-term outcomes, as well as the treatment strategies to improve RV function; regular RV imaging (echocardiography, cardiac MRI [cMRI]) and haemodynamic assessments are recommended. Further, early diagnosis of PAH and prompt initiation of treatment to maintain or improve RV function are important for patient outcomes.

Prof Galiè presented a risk management-based approach to treatment decisions and outlined the critical importance of improving long-term outcomes in PAH through timely treatment choices. He highlighted key messages from several studies that have shown beneficial effects of PAH-specific treatments (e.g., double combination therapy with macitentan and a phosphodiesterase-5 inhibitor [PDE-5i] or triple combination therapy with selexipag, a PDE-5i, and an endothelin receptor antagonist [ERA]) on morbidity/mortality events in PAH. He emphasised that choosing the right treatments is key to achieving the best long-term outcomes in PAH. In her closing remarks, co-chair Dr Lang underlined that current treatment regimens are based on appropriate risk assessments that need to be repeated every 3–6 months, and that nowadays, we have learned to combine medications upfront and that "more is better."

Introduction

Doctor Luke Howard

PH encompasses a heterogeneous group of conditions, including PAH (Group 1), PH due to LHD (Group 2), PH due to lung diseases and/or hypoxia (Group 3), PH due to pulmonary artery obstructions (Group 4), and unclear/multifactorial mechanisms (Group 5).[1,2] Patients, particularly those with LHD, can present with multiple comorbidities,[3] which complicate assessment and treatment. Patients can also have characteristics of more than one group, which can be challenging. For example, there may be a continuum from typical idiopathic PAH (IPAH) (Group 1), through atypical IPAH, to PH due to heart failure with preserved ejection fraction (HFpEF) (Group 2), on which patients have a declining precapillary component, an increasing risk factor profile, and may have declining efficacy and increasing side effects of targeted PAH therapy.[4]

Intervention early in the course of PH, while a patient has preserved RV function, is likely beneficial as a patient's condition can decline precipitously in later stages.[5] Regular assessment of RV function can be used to assess treatment response and identify patients whose condition is deteriorating.[6] Regular risk assessment allows for early intervention and prompt treatment intensification, resulting in improved functional capacity and prognosis, and a decreased risk of progressive remodelling and right heart failure.[7]

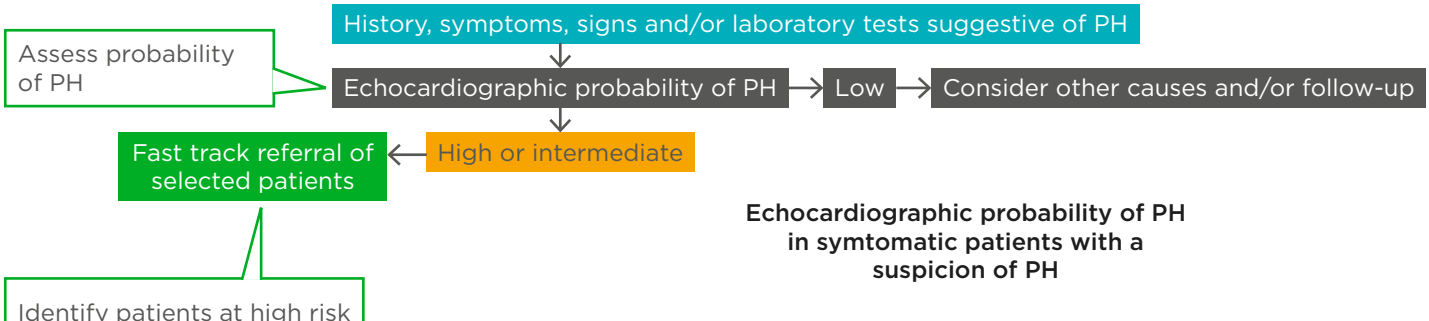
Making the Correct Diagnosis: Differentiating Pulmonary Arterial Hypertension from Pulmonary Hypertension Due to Left Heart Disease

Doctor Pilar Escribano

Globally, LHD is the most common cause of PH.[8] Among patients with LHD, PH is related to the severity of the underlying condition and impacts on symptoms, exercise capacity, treatment decision-making, and prognosis. LHD can cause PH when left ventricular (LV) dysfunction increases LV filling pressures, resulting in passive backward transmission to the pulmonary circulation and increased pulmonary pressure.[9] Ultimately, this can impact on the right heart, potentially resulting in RV failure, which is associated with a poor prognosis.[9]

PH-LHD is classified as postcapillary PH (mean pulmonary arterial pressure >20 mmHg; pulmonary arterial wedge pressure [PAWP] >15 mmHg), indicating backward transmission of increased left-sided pressure. Two types of postcapillary PH have been defined: isolated postcapillary PH (pulmonary vascular resistance [PVR] <3 Wood Units [WU]) and combined pre- and postcapillary PH (PVR ≥3 WU).[1] The former is easily distinguished from PAH, but the latter has much more overlap.

Echocardiography can be used to ascertain the probability of PH in patients with suspected PH (Figure 1).[10] Patients with high/intermediate probability who are part of a risk group (congenital heart disease, connective tissue disease, portal hypertension, and HIV infection) are recommended for fast track referral (Figure 1).[10]



Echocardiographic probability of PH in symtomatic patients with a suspicion of PH

Peak TRV (m/s)	Presence of other echocardiographic PHH signs	Echocardiographic probability of PH
≤2.8 or not meassurable	No	Low
≤2.8 or not meassurable 2.9–3.4	Yes No	Intermediate
2.9–3.4 >3.4	Yes Not required	High

Figure 1: A fast-track referral is recommended for patients with a high pretest probability for pulmonary arterial hypertension.

CHD: congenital heart disease; CTD: connective tissue disease; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; TRV: tricuspid regurgitation velocity.

Although various echocardiographic features can be used to help distinguish patients with precapillary PH (e.g., PAH) from those with postcapillary PH (e.g., PH-LHD),[1,11] distinction of the two conditions can be challenging. For example, mean pulmonary arterial pressure depends on volume load, so it can drop considerably after diuretics.[9] Furthermore, accurate PAWP measurement, which can be technically difficult, is very important as there is a cut-off for the identification of pre- and postcapillary PH (≤15 versus >15 mmHg).[1]

Among patients with severe PH and a clearly dilated right heart, a ventilation/perfusion scan should be performed to rule out chronic thromboembolic PH (CTEPH).[10] Such patients often have multiple comorbidities, and approximately 80% have a medical history of pulmonary embolism. Reliable diagnosis of CTEPH is particularly important because there are now various treatment options that can vastly improve pulmonary haemodynamics in these patients.[12]

A three-step pragmatic approach for the differential diagnosis between Group 1 PH (PAH) and Group 2 PH (mainly HFpEF) has recently been proposed.[13] Step 1 is the identification of a specific PH-LHD clinical phenotype: valvular heart disease, LV systolic dysfunction (heart failure with reduced ejection fraction), or LV diastolic dysfunction (HFpEF).[13] Of these, PH-HFpEF is the most difficult to distinguish from PAH. Step 2 is to define the pretest probability of PH-LHD.[13] Various factors indicate a high versus low probability of PH-LHD, including age >70 versus <60 years, three or more versus no risk factors (obesity, systemic hypertension, dyslipidaemia, impaired glucose tolerance/diabetes), previous versus no previous cardiac intervention, current versus no atrial fibrillation, structural LHD versus no structural LHD, and various parameters measured by electrocardiography,

echocardiography, cardiopulmonary exercise testing, or cMRI.[13] However, many patients are at intermediate probability, for example, those aged 60–70 years, with 1–2 risk factors, paroxysmal atrial fibrillation, etc.[13] Step 3 is haemodynamic assessment of PH-HFpEF.[13] If the pretest probability of PH-HFpEF is high, patients should be managed for LHD; if it is intermediate, right heart catheterisation should be considered (for patients with systemic sclerosis, risk factors for CTEPH, or unexplained dyspnoea, but no RV abnormality) or recommended (in case of RV abnormality). If PAWP is >15 mmHg, PH-HFpEF is considered confirmed (intermediate/high probability) or likely (low probability), in which case, LV end-diastolic pressure validation should be considered. If PAWP is 13–15 mmHg, precapillary PH is diagnosed (low probability) or PH-HFpEF cannot be excluded (intermediate/high), in which case provocative testing should be considered.[13]

The Importance of Imaging in Assessing Right Ventricular Function in Pulmonary Arterial Hypertension

Professor Stephan Rosenkranz

Although PAH is defined by increased pulmonary arterial pressure and vascular resistance, which has to be confirmed by right heart catheterisation, it is the impact of afterload increase on the right heart that is of higher importance.[14,15] Initially, structural changes in the heart enable the RV to keep working under strain; however, as PAH progresses, these adaptive changes are insufficient to deliver enough blood to the lungs. Ultimately, this can result in right heart failure, which is the primary cause of death among patients with PAH.[14]

Table 1: Risk assessment in patients with pulmonary arterial hypertension.

Determinants of prognosis	Estimated 1-year mortality		
	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
WHO functional class	I, II	III	IV
6-minute walk distance	>440 m	165–440 m	<165 m
Cardiopulmonary exercise test	Peak VO_2 >15 mL/min/kg (>65% predicted) VE/VCO_2 slope <36.0	Peak VO_2 11–15mL/min/kg (35–65% predicted) VE/VCO_2 slope 36.0–44.9	Peak VO_2 <11 mL/min/kg (<35% predicted) VE/VCO_2 slope ≥45.0
NT-proBNP plasma levels	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–300 ng/L NT-proBNP 300–1,400 ng/L	BNP >300 ng/L NT-proBNP >1,400 ng/L
Imaging (echocardiography, cardiac MRI)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 L/min/m^2 SvO_2 <60%

BNP: B-type natriuretic peptide; CI: cardiac index; NT-proBNP: N-terminal pro B-type natriuretic peptide; RA: right atrium; RAP: right atrial pressure; SvO_2: mixed venous oxygen saturation; VE/VCO_2: ventilatory equivalents for carbon dioxide; VO_2: oxygen consumption; WHO: World Health Organization.

Because RV structure and function are so important, ESC/European Respiratory Society (ERS) 2015 guidelines recommend regular imaging and haemodynamic assessments.[16,17] Along with other factors, these can be used to estimate 1-year mortality risk in PAH (Table 1).[16,17] For example, right atrial areas <18 cm^2, 18–26 cm^2, and >26 cm^2 indicate low (<5%), intermediate (5–10%), and high (>10%) 1-year mortality risk, respectively.[16,17] In the future, it may be possible to incorporate other imaging parameters into risk prediction models, if data of sufficient quality can be obtained from studies or registries.

Echocardiography is a key imaging tool for diagnosis and follow-up of patients with PH, and can also provide prognostic information.[18,19] However, although echocardiography is widely available and can be used to measure a range of RV structural and functional parameters, cMRI is considered the gold standard for a number of important RV parameters.[18,20] cMRI can be used to improve risk stratification,[21] but is not always available.

Various echocardiographic parameters have prognostic value in PH.[18] For example, among 47 patients with PAH, those with tricuspid annular plane systolic excursion ≥1.8 cm had significantly better survival than those with tricuspid annular plane systolic excursion <1.8 cm (approximately 90% versus 45% at 2 years; p=0.009).[22] N-terminal pro B-type natriuretic peptide level, a surrogate marker of right heart strain, is also prognostic. For example, in the placebo arm of the Phase III GRIPHON study (n=574), higher levels of N-terminal pro B-type natriuretic peptide (<271 ng/L, 271–1,165 ng/L, and >1,165 ng/L) decreased the chance of remaining free from a morbidity/mortality event (approximately 75%, 50%, and 30%, respectively, at 30 months).[23]

Various cMRI variables have been correlated with improved survival, including stroke volume index >25 mL/m^2, RV end-diastolic volume (RVEDV) index <84 mL/m^2, and LV end-diastolic volume index >40 mL/m^2 in a study of 64 patients with IPAH.[15] In the same study, analysis of the change in various variables after 1-year follow-up showed that mean change in stroke volume index, RVEDV index, and LV end-diastolic volume index predicted mortality.[15] Therefore, early diagnosis of PAH and treatment to maintain or improve RV function are important for patient outcome.

In a study of 22 clinically stable patients with IPAH, those with progressive disease had increasing RVEDV and decreasing RV ejection fraction over ≥5-year follow-up, while those with stable disease had little change in RVEDV and increasing RV ejection fraction.[6] However, both groups of patients had similar 6-minute walk distance and World Health Organization (WHO) functional class results.[6] This indicates that progressive RV dilation precedes clinical worsening.

Overall, improving right heart function in PAH is key to improving patient prognosis,[15,24] and these improvements can be measured using noninvasive imaging techniques.

Achieving Best Long-Term Outcomes in Pulmonary Arterial Hypertension: How to Choose the Right Treatments and When to Start Them

Professor Nazzareno Galiè

PAH encompasses a group of rare diseases, with a prevalence of around 50 cases/million.[25] Although heterogeneous, there are some common findings, including pulmonary arteriopathy and right heart dilatation.

Various oral therapies are available, which target one of the endothelin pathways (single or dual ERA), the nitric oxide pathway (PDE-5i, soluble guanylate cyclase stimulators), and the prostacyclin pathway (prostacyclin analogues, nonprostanoid prostacyclin receptor agonists).[26] The first human epoprostenol (a prostacyclin analogue) study was published in 1984,[27] while those for bosentan[28] (an ERA) and sildenafil[29] (a PDE-5i) were published in 2000. Overall, 41 randomised controlled studies in 9,061 patients with PAH have been carried out: 21 monotherapy versus placebo or versus another monotherapy, 18 monotherapy and/or sequential combination versus placebo, and two initial combination versus monotherapy. The design and endpoints of these studies have evolved over time, from small, short studies of exercise capacity[30-39] to larger, longer outcome trials.[40-43] Between 1998 and 2015, the number of ESC/ERS 2015 guideline-

approved PAH drugs steadily increased, from one to 11, but the number of pathway classes has remained constant at three since 2003.[16] Drugs that have been approved according to the ESC/ERS 2015 PH guidelines[16,17] are ERA (ambrisentan, bosentan, macitentan), PDE-5i (sildenafil, tadalafil), a soluble guanylate cyclase stimulator (riociguat), and prostacyclin analogues (iloprost, treprostinil, epoprostenol); and more recently, a prostacyclin receptor, also termed IP, agonist (selexipag).[44]

Early trials tested monotherapies, but then studies moved on to test sequential combinations, and then initial combinations. In the SERAPHIN study, 742 patients with PAH were randomised to macitentan 3 mg, 10 mg, or placebo.[41] Among 308 patients who were already receiving background PAH therapy (mainly [97.4%] a PDE-5i) at baseline and were randomised to placebo or macitentan 10 mg (i.e., sequential combination), the addition of macitentan reduced the risk of a morbidity/mortality event by 38% (hazard ratio [HR]: 0.62; 95% confidence interval [CI]: 0.43–0.89; p=0.009).[45]

In the GRIPHON trial, 1,156 patients with PAH were randomised to selexipag (the only oral treatment that targets the prostacyclin pathway that is approved in Europe) or placebo.[42] Among 376 patients who were already receiving a PDE-5i and an ERA, the addition of selexipag (i.e., third drug in sequential combination) was associated with a 37% reduction in morbidity/mortality when compared with double combination therapy (HR: 0.63; 95% CI: 0.44–0.90).[46] This beneficial effect was more pronounced among patients with mild symptoms (WHO functional Class II; n=115) (64% risk reduction; HR: 0.36; 95% CI: 0.14–0.91) than among those with more advanced symptoms (WHO functional Class III; n=255) (26% risk reduction; HR: 0.74; 95% CI: 0.50–1.10),[46] highlighting the importance of early intervention to delay disease progression.

In the AMBITION study, 500 treatment-naïve patients with PAH were randomised 1:1:2 to ambrisentan, tadalafil, or both (i.e., initial combination).[43] Those who started on combination therapy had a 50% lower risk of a morbidity/mortality endpoint than the pooled monotherapy population (HR: 0.50; 95% CI: 0.35–0.72; p<0.001).

Macitentan plus tadalafil has been tested as an initial combination therapy in 46 treatment-naïve patients with PAH in the single-arm OPTIMA study.[47] PVR (primary endpoint) was reduced from 11.7±4.7 WU at baseline to 6.5±3.6 at 16 weeks (47% reduction; geometric mean ratio: 0.53; 95% CI: 0.47–0.59; p<0.0001). Six-minute walk distance (a secondary endpoint) also improved, from 352±135 m to 388±142 m (+36 m; 95% CI: 16–56; p=0.0008).[47]

In the most recent ESC/ERS guidelines,[16] patients with PAH can be stratified into estimated 1-year mortality risk categories (low <5%, intermediate 5–10%, high >10%) based on various factors. These risk levels can then be used to assign patients to an appropriate treatment option,[48] as discussed in more detail below, which is key to achieving the best long-term outcomes.

The ESC/ERS risk stratification has been validated in two retrospective registries.[49,50] The Swedish PAH registry (n=530) reported 5-year survival rates of approximately 84%, 52%, and 35% for low-, intermediate-, and high-risk patients, respectively,[49] which was similar to the COMPERA Registry (n=1,588) (approximately 77%, 53%, and 33%, respectively).[50] The French PAH registry reported decreasing transplant-free survival with decreasing numbers of low-risk criteria.[51]

The ESC/ERS guidelines recommend that PAH severity is assessed at diagnosis based on clinical assessment, exercise tests, biochemical markers, and echocardiographic and haemodynamic evaluations; with regular follow-up assessments every 3–6 months in stable patients (both Class I, level C).[16,17] In terms of treatment, they recommend the achievement/maintenance of a low-risk profile (Class I, level C). All these recommendations will be elevated to level B in the new guidelines, which are planned for 2022.

According to the 6th World Symposium on Pulmonary Hypertension (WSPH) 2018 treatment algorithm[48] and the 2015 ESC/ERS guidelines,[16,17] vasoreactive patients should be treated with calcium channel blockers. Nonvasoreactive patients should be treated according to risk: high-risk patients should receive an initial combination therapy including intravenous prostacyclin analogue, while intermediate/low-risk patients should be given an initial oral combination,

although initial monotherapy currently has a residual role (e.g., PAH and age >75 years; suspicion/high probability of pulmonary veno-occlusive disease; HIV; portal hypertension; very mild disease; or haemodynamic responders).[48] After 3–6 months of treatment, risk should be reassessed. If patients are low risk, their treatment should be continued; if they are intermediate/high risk, a triple sequential combination is recommended. If patients remain at intermediate/high risk after a further 3–6 months, maximal medical therapy and listing for lung transplantation are recommended.[48]

Closing Remarks

Doctor Irene Lang

Firstly, it is essential to differentiate pre- from postcapillary PH because vasodilators work best in precapillary disease. Secondly, although PAH is a pulmonary vascular disorder, it is RV function that determines survival. Thirdly, vasodilator treatments have improved 3-year survival rates from 30–40% to >85%.[52] Fourthly, treatment regimens are based on regular risk assessments (every 3–6 months). Lastly, the use of upfront combination medications is beneficial.

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The Lung, at the Heart of Pulmonary Arterial Hypertension

This symposium took place on 9th September 2020, as part of the European Respiratory Society (ERS) International Congress 2020

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Disclosure: Prof Sitbon has received grants/research support from Actelion Pharmaceuticals, Bayer, GlaxoSmithKline, MSD; and honoraria or consultation fees from Actelion Pharmaceuticals, Acceleron Pharma, Bayer, Ferrer, Gossamer Bio, and MSD. Dr Manes has received lecture fees from Actelion Pharmaceuticals/Janssen. Dr Blanco has not declared any conflicts of interest in association with this presentation, but has received personal fees, including speaker, consultant, and advisory board fees, from Actelion Pharmaceuticals/Janssen, MSD, GlaxoSmithKline, and Ferrer Pharma. Prof Gaine has received honoraria from Actelion Pharmaceuticals, United Therapeutics, and Bayer. Prof Hoeper has received lecture/consultation fees from Acceleron Pharma, Actelion Pharmaceuticals, Bayer, Janssen, MSD, and Pfizer. Prof Delcroix has received institutional research grants and speaker and consultant fees from Actelion Pharmaceuticals; institutional speaker and consultant fees from Bayer/MSD; and institutional consultant fees from Acceleron Pharma.

Acknowledgements: This report was written by Jenny Lloyd, Compass Medical Communications, Ltd., Kent, UK.

Disclaimer: The views and opinions expressed are those of the speakers and not necessarily those of Janssen.

Support: This content was funded by Janssen.

Citation: EMJ. 2020;5[Suppl 1]:10-17.

Meeting Summary

In this symposium at the virtual European Respiratory Society (ERS) International Congress 2020, co-chair Prof Sitbon introduced the symposium by highlighting that many patients with pulmonary arterial hypertension (PAH) are already classified as being in the World Health Organization (WHO) functional Class III/IV at diagnosis, as early symptoms are nonspecific. However, early diagnosis and management are important to improve prognosis. Furthermore, the importance of correctly diagnosing the aetiology of pulmonary hypertension (PH) was highlighted through two clinical cases from Dr Manes and Dr Blanco because the treatment options for these patients differ. This can be difficult, but Prof Gaine continued the symposium by presenting some pearls of wisdom to help with the differential diagnosis towards PAH. Prof Hoeper then said that risk assessment, at diagnosis and then 3–6 times monthly, is very important in PAH. Patients with low or intermediate risk of 1-year

mortality should usually receive initial double oral combination therapy, as this has been shown to be superior to initial monotherapy, while high-risk patients should receive initial combination therapy including an intravenous prostacyclin analogue. Patients who are not low-risk at follow-up should have their therapy escalated (with an additional drug) to improve prognosis. Lastly, co-chair Prof Delcroix closed the meeting by reminding the audience of the importance of differential diagnosis, risk assessment, and treatment strategies.

Introduction

Professor Olivier Sitbon

The objectives of this symposium were firstly to recognise the difficult diagnostic journey faced by patients with PAH, to learn expert tips on how best to differentiate between the PH groups and ways to facilitate the differential diagnosis of PAH, and to explore the tools for risk assessment in PAH and the risk-management approach to treatment decisions.

PAH causes cardiovascular remodelling and cardiac damage over time ultimately leading to right heart failure, which is the primary cause of death in patients with PAH.[1] However, PH starts in the lungs, initially causing dyspnoea during exercise, fatigue, and weakness.[2] Approximately 70–85% of patients with PAH are already categorised as WHO functional Class III/IV at diagnosis.[3-5] This is unfortunate, as 5-year survival estimates decrease with increasing WHO functional class at diagnosis: 72.2% for Class I, 71.7% for Class II, 60.0% for Class III, and 43.8% for Class IV.[6] Early diagnosis is challenging, however, because early symptoms, such as breathlessness, are nonspecific, so referral to a specialist can take 1–2 years.[7]

Conversely, early diagnosis and management of PAH can improve prognosis. For example, in the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), which included 1,588 patients, 5-year survival after diagnosis ranged from approximately 77% for low-risk patients, to 53% for intermediate-risk patients, and 33% for high-risk patients.[5] Similarly, the French Pulmonary Hypertension Registry (FPHR) reported decreasing transplant-free survival with decreasing numbers of low-risk criteria.[8]

The Challenging Journey to Pulmonary Arterial Hypertension Diagnosis: Learnings from Two Clinical Cases of Pulmonary Hypertension

The following clinical cases of patients with PH highlight why and how it is important to differentiate between the different PH subtypes as the prognosis, management, and treatment strategies differ by PH group.

Doctor Alessandra Manes

Case One was of a female patient who had been known to have allergic asthma in her teenage years and was diagnosed at age 32 years for asthmatic exacerbation, with mild increase of pulmonary pressures (Group 3 PH). At age 33 years, after progressive worsening of her symptoms, chest tightness, and recurrent exertional syncope, she was re-evaluated by right heart catheterisation (RHC) and diagnosed with idiopathic PAH (IPAH); she was treated with sildenafil 20 mg three times daily, to which macitentan 10 mg/day was added after 2.5 years following worsening symptoms. At age 39 years, she was classified WHO functional Class III and had marked right ventricular (RV) hypertrophy and dilatation. A vasoreactivity test showed that she was acutely vasoreactive; therefore, her treatment was switched to a calcium channel blocker (CCB) (amlodipine 10 mg twice daily). After 6 months, she had improved to WHO functional Class I, her exercise capacity had increased, there was marked reverse remodelling of the RV, and RV function had improved.

This case highlighted the importance of a vasoreactivity test, which is recommended early in the diagnostic process in the European Society of Cardiology (ESC)/ERS guidelines for patients with IPAH, heritable PAH, or drug-induced PAH.[2,9] This is important because patients with

vasoreactive IPAH who respond to CCB have very good survival rates.

Doctor Isabel Blanco

Case Two was of a male patient aged 70 years old who was diagnosed with chronic obstructive pulmonary disease (COPD) (Global Initiative for Chronic Obstructive Lung Disease [GOLD] criteria 4) at age 56 years. He also had Type 2 diabetes mellitus and systemic hypertension. At age 60 years, he had suspected Group 3 PH (progressive dyspnoea, New York Heart Association [NYHA] functional Class II–III) and was treated with bronchodilators. Eight years later, he was given long-term oxygen therapy as a result of progressive respiratory failure. At age 69 years, there were no changes in right atrial or RV dimensions. His pulmonary haemodynamics were similar at age 70 years to those at age 60 years (including mildly elevated mean pulmonary artery pressure [mPAP] at both timepoints), but his exercise capacity had diminished considerably, likely because of his COPD.

Although this patient had precapillary PH, PAH-specific treatments would not have been beneficial. It is, therefore, important to consider all relevant patient history and complementary tests (for example, echocardiography and pulmonary haemodynamics), and exercise capacity tests are vital for differential diagnosis. More detailed information on the differential diagnosis of PH, and why it is so important, is included in the next section.

Differential Diagnosis of Pulmonary Hypertension: Pearls for the Pulmonologist

Professor Sean Gaine

Symptoms of PH can be nonspecific, commonly including exertion-induced dyspnoea, fatigue, weakness, angina, and syncope.[9] Patients with advanced disease can have peripheral oedema and abdominal distension.[9] The nonspecific nature of PH symptoms can lead to delays between symptom onset and diagnosis, delays being ≥2 years for 32% of patients in a recent UK study.[10] This could potentially be improved through better education of primary and secondary care providers about PH and earlier use of echocardiography in patients with unexplained breathlessness, notably looking at the right-sided chambers of the heart.

It is crucial to establish the correct PH diagnosis, as different forms of PH have different treatment approaches.[9] In a patient with suspected PH, the first step is clinical assessment: patient history and physical examination. Then, various diagnostic tests should be undertaken, such as echocardiography, ventilation/perfusion (V/Q) scan, CT, pulmonary function tests, diffusing capacity of the lungs for carbon monoxide (DLCO), blood tests, and RHC.[11]

The most common type of PH is Group 2 (PH due to left heart disease [LHD]), which accounts for 68% of cases, followed by Group 5 (unclear/multifactorial; 15%), and Group 3 (PH due to lung diseases/hypoxia; 9%).[12,13] Therefore, Group 1 (PAH) and Group 4 (PH due to pulmonary artery obstructions, for example, chronic thromboembolic PH [CTEPH]) are the least common, but it is important to identify such patients as there are a range of effective treatments. For Groups 2, 3, and 5, treatments tend to target the underlying disease.

For Group 2 PH (PH-LHD), echocardiography is a key diagnostic tool, and can be used to assess left ventricular (LV) systolic and diastolic dysfunction, and estimate pulmonary artery systolic pressure.[14] Several echocardiographic parameters differ between PH-LHD (Group 2) and precapillary PH (Groups 1, 3, 4, 5), so this can help with differential diagnosis.[14] Clinical assessment of risk factors for LHD (including hypertension, atrial fibrillation, diabetes, and obesity) can also help to recognise patients in Group 2.[14] **Pearl 1:** an enlarged left atrium is very indicative of PH-LHD.[15]

Group 3 PH includes obstructive and/or restrictive lung diseases, hypoxia without lung disease (sleep apnoea, for example), and developmental lung disorders.[15,16] Chest X-ray can be used to diagnose Group 3 PH by identifying lung diseases such as emphysema and interstitial lung disease.[17] It can also show signs indicative of other PH groups, for example, Kerley B lines and pleural effusion in Group 2 PH.[18] **Pearl 2:** a descending right pulmonary artery diameter ≥20 mm is strongly correlated with PH in patients

with COPD.[19,20] Further, on CT imaging, a main pulmonary artery diameter to ascending aorta diameter ratio ≥1 may predict PH.[17,19-21] Contrast CT can be used to visualise right heart dimensions, giving an indication of the severity of RV dysfunction.[21] CT can also reveal abnormalities in the lung parenchyma, which can help to discriminate between Groups 1 and 3 PH.[17,21] **Pearl 3:** an RV:LV ratio ≥1.0 is strongly associated with mortality or lung transplantation in patients with Group 3 PH.[22] Pulmonary function tests can be used to identify clinically significant obstruction or restriction as risk factors for Group 3 PH. DLCO is reduced in patients with PAH,[22,23] and a severely reduced DLCO should raise suspicion for pulmonary veno-occlusive disease, pulmonary capillary haemangiomatosis, or scleroderma-associated PAH.[24] **Pearl 4:** a severely reduced DLCO in IPAH is associated with older age, male sex, smoking history, and poor outcome, and has been termed 'vanishing capillary syndrome'.[24]

V/Q scanning is vitally important for the diagnosis of Group 4 PH, as a V/Q mismatched defect (pattern of preserved ventilation and regional absent perfusion) is a key feature of CTEPH.[9,24,25] Specific diagnostic signs for CTEPH can also be seen by CT pulmonary angiography, MRI, or conventional pulmonary angiography, including ring-like stenoses, webs, and chronic total occlusions (pouch lesions or tapered lesions).[9] **Pearl 5:** a diagnosis of CTEPH can be made if mPAP is ≥25 mmHg and pulmonary artery wedge pressure ≤15 mmHg after 3 months of effective therapeutic anticoagulation.[9] However, mPAP >20 mmHg may be a more appropriate cut-off in the future.[9] Group 5 PH includes haematological disorders, metabolic disorders, and sarcoidosis.[16] Patients with sarcoidosis can have PH as a result of direct granulomatous involvement of vessels, mediastinal fibrosis, or direct parenchymal involvement.

Group 1 PH (PAH) is partly diagnosed by a process of elimination, i.e., patients with a high probability of PH (by echocardiography), but with a negative V/Q scan, and no clinically significant LHD or lung disease.[11] Such patients should be referred to a PH expert centre, where PAH can be confirmed by RHC haemodynamics.[9] Of note, patients at high risk of developing PAH (e.g., those with connective tissue disease, HIV, or portal hypertension) should have a fast track referral to an expert centre.[11] **Pearl 6:** markers of RV function (e.g., RA pressure and cardiac index) are more important in determining prognosis than mPAP in patients with PAH.[9] Haemodynamics that indicate precapillary PH include mPAP ≥25 mmHg, pulmonary artery wedge pressure ≤15 mmHg, and pulmonary vascular resistance ≥3 Wood units.[9] There have been proposals to reduce the threshold for a diagnosis of PH from an mPAP of 25 mmHg to 20 mmHg,[12] but this has not yet been agreed in guidelines.

How to Assess Risk and Optimise Treatment in Patients with Pulmonary Arterial Hypertension

Professor Marius Hoeper

Risk assessment, at diagnosis and every 3–6 months during follow-up, is very important for patients with PAH as treatment options (Figure 1) vary depending on whether they are considered to have a low, intermediate, or high risk of 1-year mortality based on clinical evaluation, exercise capacity, and RV function (Table 1).[2,9,26] At diagnosis, most patients with PAH are nonvasoreactive and at low/intermediate risk, indicating initial oral combination therapy. Initial monotherapy is generally reserved for select patients: age >75 years, suspicion/high probability of pulmonary veno-occlusive disease, HIV, portal hypertension, very mild disease, or patient responders with IPAH on high-dose CCB.[26] Patients who present at high risk should receive initial combination therapy including intravenous prostacyclin analogues.[2,9,26]

Overall risk can be calculated by assigning 1, 2, or 3 points for low, intermediate, or high risk, respectively, for each row of Table 1 and then calculating the average 'score'. Patients with a mean score of 1.00–1.49, 1.50–2.49, and 2.50–3.00 are then considered to be low, intermediate, or high risk, respectively. This approach was seen in the Swedish PAH Register (SPAHR)[27] and the COMPERA registry.[5] Both registries showed good discrimination between risk groups for 5-year survival, with similar results (SPAHR: approximately 84%, 52%, and 35%;[27] COMPERA: approximately 77%, 53%, and 33%,[5] for low-, intermediate-, and high-risk patients, respectively; both $p<0.001$). The FPHR took a

different approach, and categorised patients based on how many low-risk values they had out of four criteria from Table 1 (WHO functional Class, 6-minute walk distance [6MWD], right atrium pressure, and cardiac index).[8] They reported decreasing transplant-free survival with decreasing numbers of low-risk criteria (p<0.001).[8]

Mortality risk can also be assessed using the REVEAL scores.[28] REVEAL 2.0 assigns points for 11 weighted clinical parameters (WHO Group I subgroup, demographics, comorbidities, NYHA/WHO functional Class, vital signs, all-cause hospitalisations ≤6 months, 6MWD, B-type natriuretic peptide [BNP], echocardiogram, pulmonary function, and RHC), which are summed to estimate risk.[28] REVEAL registry patients at low risk had higher 1-year survival rates than those at intermediate or high risk (approximately 98%, 93%, and 75%, respectively).[28]

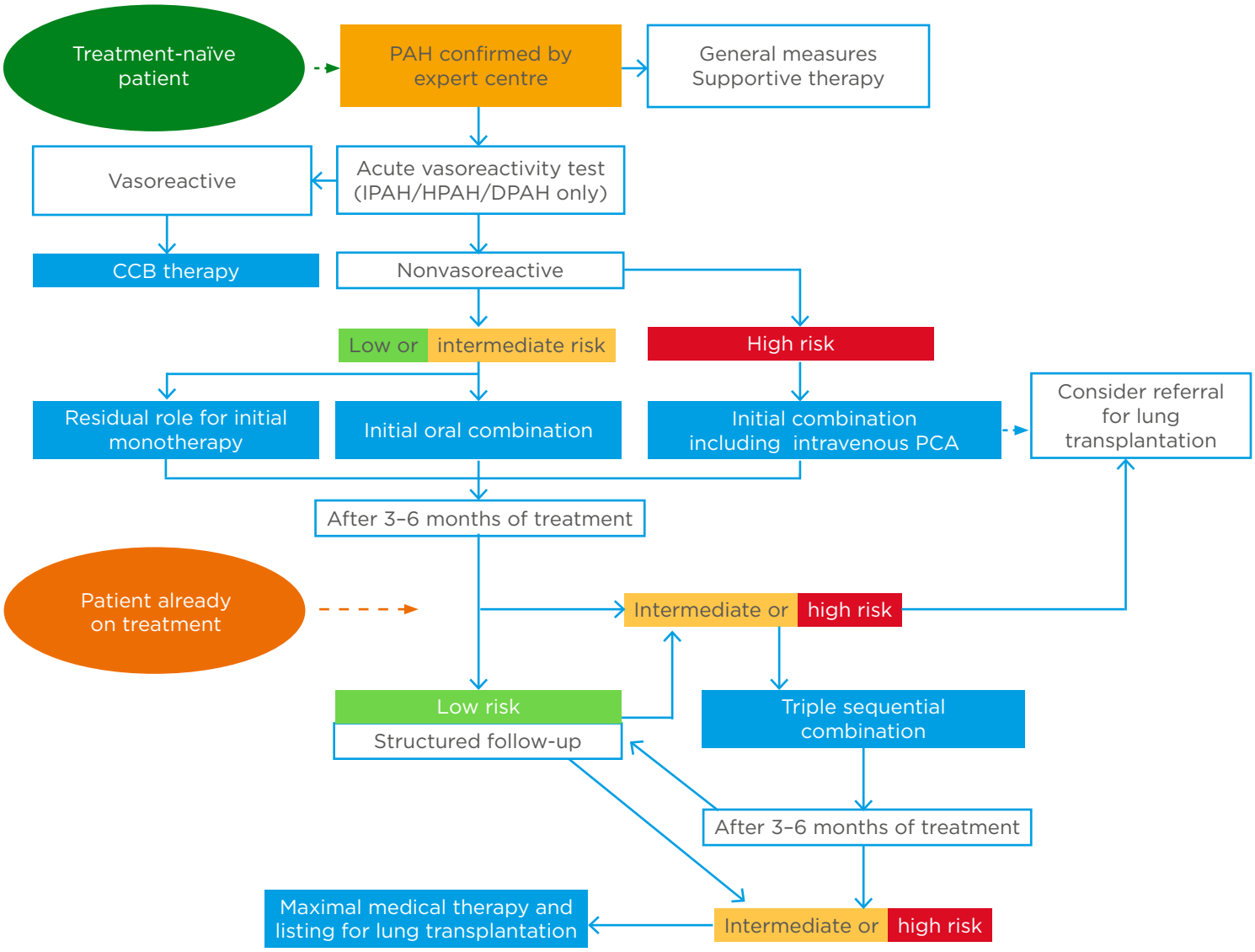

Figure 1: Treatment algorithm for patients with pulmonary arterial hypertension.

CCB: calcium channel blockers; DPAH: drug-induced pulmonary arterial hypertension; HPAH: heritable pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; PAH: pulmonary arterial hypertension; PCA: prostacyclin analogue.

Table 1: Risk assessment in patients with pulmonary arterial hypertension.

Determinants of prognosis	Estimated 1-year mortality		
	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
WHO functional class	I, II	III	IV
6-minute walk distance	>440 m	165–440 m	<165 m
Cardiopulmonary exercise test	Peak VO_2 >15 mL/min/kg (>65% predicted) VE/VCO_2 slope <36.0	Peak VO_2 11–15mL/min/kg (35–65% predicted) VE/VCO_2 slope 36.0–44.9	Peak VO_2 <11 mL/min/kg (<35% predicted) VE/VCO_2 slope ≥45.0
NT-proBNP plasma levels	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–300 ng/L NT-proBNP 300–1,400 ng/L	BNP >300 ng/L NT-proBNP >1,400 ng/L
Imaging (echocardiography, cardiac MRI)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 L/min/m^2 SvO_2 <60%

BNP: B-type natriuretic peptide; CI: cardiac index; NT-proBNP: N-terminal pro B-type natriuretic peptide; RA: right atrium; RAP: right atrial pressure; SvO_2: mixed venous oxygen saturation; VE/VCO_2: ventilatory equivalents for carbon dioxide; VO_2: oxygen consumption; WHO: World Health Organization.

REVEAL Lite 2 includes blood pressure, heart rate, estimated glomerular filtration rate/renal insufficiency, BNP/N-terminal pro B-type natriuretic peptide, NYHA/WHO functional Class, and 6MWD, while REVEAL Lite 1 also includes age, sex, and PAH aetiology.[29]

For low-/intermediate-risk patients, initial combination therapy is generally recommended over initial monotherapy (Figure 1).[2,9,26] This is because the AMBITION study showed that treatment-naïve patients with PAH randomised to initial combination therapy (ambrisentan plus tadalafil) had a 50% lower risk of a morbidity/mortality endpoint than those randomised to initial monotherapy (pooled ambrisentan or tadalafil) (hazard ratio [HR]: 0.50; 95% confidence interval [CI]: 0.35–0.72; p<0.001).[30]

As PAH is a chronic condition, it is also important to assess risk during treatment (Figure 1).[2,9,26] In the SPAHR,[27] patients who transitioned from intermediate-/high-risk at diagnosis to low-risk at follow-up had similar 5-year survival to those who were stable low-risk (approximately 96% and 89%, respectively). This indicated that the goal of treatment should be to achieve and maintain a low-risk profile.

The benefit of escalating treatment has been shown in the SERAPHIN[31] and GRIPHON studies.[32] In the SERAPHIN study, among 308 patients who were already receiving background PAH therapy (mainly [97.4%] a phosphodiesterase-5 inhibitor [PDE-5i]) at baseline and were randomised to placebo or macitentan 10 mg, the addition of macitentan reduced the risk of morbidity/mortality by 38% (HR: 0.62; 95% confidence limit: 0.43–0.89; p=0.009).[31]

In the GRIPHON study, among 376 patients who were already receiving a PDE-5i and an endothelin receptor antagonist at baseline, the addition of selexipag was associated with a 37%

reduction in morbidity/mortality versus placebo (HR: 0.63; 95% CI: 0.44–0.90).[32] This beneficial effect was seen in patients with mild symptoms (WHO functional Class II) (64% risk reduction; HR: 0.36; 95% CI: 0.14–0.91) and, albeit to a somewhat lesser extent, those with more advanced symptoms (WHO functional Class III) (26% risk reduction; HR: 0.74; 95% CI: 0.50–1.10).[32] Among all patients in GRIPHON (i.e., including 780 who were not receiving a PDE-5i and an endothelin receptor antagonist at baseline), the patients randomised to selexipag were more likely to have improved risk than those randomised to placebo (p<0.001).[33] Among all patients, selexipag had a more pronounced treatment effect if it was initiated closer to the time of PAH diagnosis (≤6 months: 55% reduction; HR: 0.45; 95% CI: 0.33–0.63, >6 months: 30% reduction; HR: 0.70; 95% CI: 0.54–0.91; Figure 2),[34] highlighting the importance of early intervention.

Closing Remarks

Professor Marion Delcroix

Regarding differential diagnosis, clinical symptoms and physical signs of PH can be difficult to distinguish in patients with respiratory disorders;[9] however, establishing a correct diagnosis of PH and the specific group are crucial in order to tailor treatment.[9] Multiparametric risk assessments should be undertaken at diagnosis and 3–6-monthly during follow-up to assess disease severity, predict survival, and guide treatment decisions.[9,26] Assessment of risk changes over time is also essential for making treatment decisions. Most low-/intermediate-risk patients with PAH should receive initial double-combination therapy,[9,26] with early escalation to triple-therapy in those not at low risk within the first 3–6 months[26] as targeting multiple pathological pathways in PAH is key to improving patient outcomes.

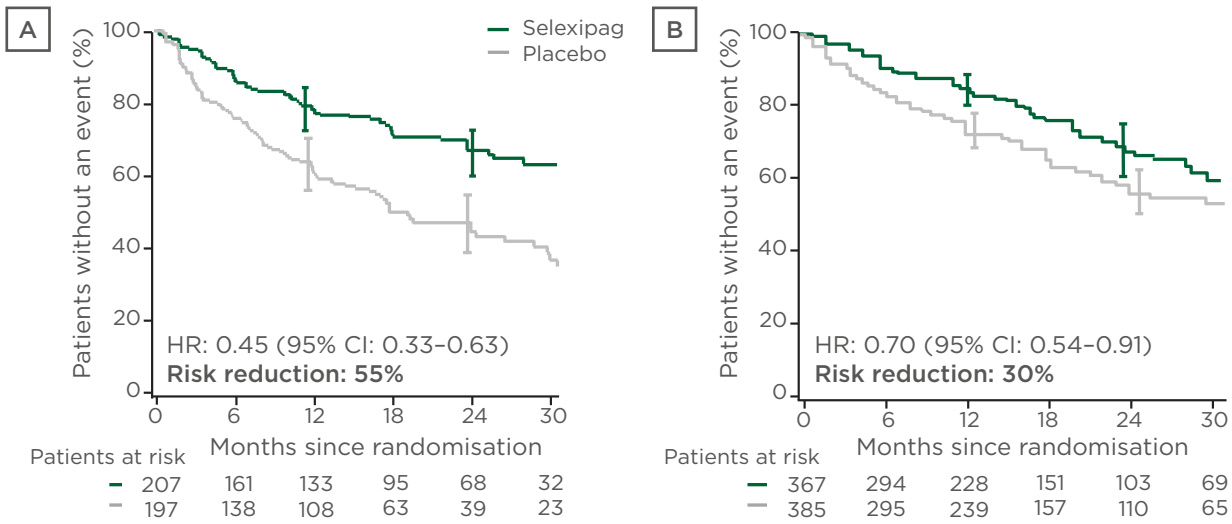

Figure 2: Time from randomisation to first morbidity/mortality event in patients with pulmonary arterial hypertension.

A) Pulmonary arterial hypertension diagnosed ≤6 months before baseline; and **B)** pulmonary arterial hypertension diagnosed >6 months before baseline.

CI: confidence interval; HR: hazard ratio.

Adapted with permission from Gaine et al.[34]

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Date of preparation: November 2020
EM-48981