Phenotypes and treatment outcomes in idiopathic pulmonary arterial hypertension patients with comorbidities

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Patients with IPAH and comorbidities have a poorer prognosis than patients without comorbidities. To improve therapy outcome combination therapy may be considered for IPAH patients with well-controlled comorbidities considering risk factors. https://bit.ly/3N9Sn8H

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Abstract

Idiopathic pulmonary arterial hypertension (IPAH) is often diagnosed in elderly patients with many comorbidities. Whereas a clear treatment strategy and risk assessment is recommended for patients with rare classical IPAH, monotherapy with phosphodiesterase type 5 inhibitors or endothelin receptor antagonists followed by regular follow-up and individualised therapy should be used for patients with many cardiopulmonary comorbidities. Here, we focus on these patients with IPAH and comorbidities, present a review of the literature with a focus on recently published work and summarise factors that may help to provide guidance for individualised treatment approaches in such patients.

Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is a severe, yet incurable, disease that affects the small pulmonary arteries with vasoconstriction and vascular proliferation, leading to remodelling and an increased pulmonary vascular resistance. The increased right ventricular afterload results in right ventricular failure and ultimately leads to death [1–3].

Based on the underlying pathophysiology, group 1 pulmonary arterial hypertension (PAH) can be divided into different subtypes. The most common subtypes (according to PAH registries) are IPAH, followed by PAH associated with connective tissue disease, PAH associated with congenital heart disease and portal hypertension (porto-pulmonary hypertension) [3]. IPAH is used to categorise patients with pre-capillary pulmonary hypertension (pre-capillary pulmonary hypertension = median pulmonary arterial pressure >20 mmHg and pulmonary arterial wedge pressure ⩽15 mmHg and pulmonary vascular resistance >2 Wood units [3] of unknown origin. IPAH was originally observed mainly in young otherwise healthy individuals particularly females [3, 4], but since then, several types of patients with IPAH have been identified. The heterogeneity of these phenotypes in PAH, especially in IPAH, becomes increasingly evident. Recent data from USA and Europe suggest that IPAH is now frequently diagnosed in older patients (*i.e.* those aged ⩾65 years) who often present with cardiovascular comorbidities [3]. In a cluster analysis of the European COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) registry, out of 841 patients with IPAH, >80% had comorbidities and were older

than 70 years [5]. It is not clear what significance this has for the diagnostic criteria, risk stratification and treatment outcomes. Especially when keeping in mind that, contrary to current clinical experience, most randomised controlled drug trials have excluded elderly patients with multiple comorbidities so far. However, there is a growing number of studies focusing on these patients, respectively examining data by *post hoc* analyses, notably because such patients may respond less well to targeted therapies and may display a reduced drug tolerability. Therefore, it seems to be evident that elderly patients with comorbidities are treated later and are less likely to receive combination therapy than younger ones [4–6].

Objective

The study selection for this review is based on a systematic search for current data in PubMed (search period 2016–2022), analyses of pulmonary hypertension registries and *post hoc* analyses of pivotal studies for pulmonary hypertension-targeted drugs. The year 2016 was chosen as the cut-off, due to the Cologne Consensus Conference (KKK) in 2015 and the approval of two new specific PAH drugs (macitentan and selexipag) in 2014 and 2016, which led to a surge in available publications on IPAH and comorbidities. The following terms were used for the databank search: ((clinical phenotype) or comorbidities or comorbidity) PAH pulmonary arterial hypertension and ((clinical phenotype) or comorbidities or comorbidity) pulmonary hypertension and ((phenotype) or comorbidities or comorbidity). Further important data sources were papers from renowned PAH working groups and registries as well as the 2022 P(A)H-Guidelines by Humbert *et al*. [3]. Only papers on treatment in PAH with comorbidities (not pulmonary hypertension) were considered. Papers on pulmonary hypertension group II and III were therefore excluded. As data on treatment of patients with comorbidities are scarce, data from registry analyses that refer not only to IPAH but to all forms of PAH are included.

This review aims to describe what is known about different phenotypes in PAH with a focus on IPAH and which types have been identified so far. Moreover, it is intended to clarify whether significant differences were found between different types of patients regarding risk stratification, prognosis and treatment outcome. This work aims to serve as a summary and overview of the current state of knowledge and gaps in evidence. Also, it may support clinical decision-making in a complex field with limited evidence.

Results

Studies in phenotyping/clustering on IPAH

The issue of “phenotypes” was already evident and discussed in previous registry analyses. In 2016 Opitz *et al*. [7] used registry data to compare clinical characteristics, haemodynamics and treatment responses in patients with “typical IPAH”, “atypical IPAH” (⩾three risk factors for left heart disease) and pulmonary hypertension–heart failure with preserved ejection fraction (PH-HFpEF) receiving PAH-targeted therapies. As a result, it was shown that patients with atypical IPAH share features of both typical IPAH and PH-HFpEF. The authors concluded that there may be a continuum between these conditions and that patients with IPAH diagnosis do not form a homogeneous group. In the same year, experts of the Cologne Consensus Conference introduced two new terms: “typical IPAH” and “atypical IPAH”. In addition to younger patients with “typical” or “classic IPAH”, they stated that German-speaking countries observed an unusually high number of older patients who had been diagnosed with IPAH based on the applicable definitions and haemodynamic criteria of pulmonary hypertension and PAH. Naturally, such elderly patients commonly present with comorbidities and risk factors for left heart disease or lung disease, and they are now specified as “IPAH with comorbidities” [8]. Experts demand a stronger focus on this aspect. The aim should be to carry out clinical studies in expert centres to investigate the effectiveness and safety/tolerability of targeted PAH therapies and new therapeutic principles for the treatment of “classical IPAH” and “IPAH with comorbidities” as well as other forms of pulmonary hypertension [8].

Influence of age and comorbidity in IPAH

In 2018, Hjalmarsson *et al*. [6] investigated the effects of age and comorbidity on risk stratification and outcome of patients with IPAH. They analysed 264 patients with an IPAH diagnosis. All data were based on the Swedish PAH & Chronic Thromboembolic Pulmonary Hypertension registry (SPAHR), where all seven Swedish PAH centres enrol patients into SPAHR. They categorised patients into four age groups: 18–45, 46–64, 65–74 and ⩾75 years, with individual risk profiles and assessed the presence of seven common comorbidities: arterial hypertension, diabetes mellitus, ischaemic stroke, ischaemic heart disease, atrial fibrillation, obesity and kidney dysfunction. Comorbidity was more frequent in the two oldest age groups, in which 20% had at least four comorbidities. The change in risk group (according to the risk assessment instrument from the 2015 pulmonary hypertension guidelines [9, 10]) and survival from baseline to first follow-up (median 5 months) were compared across age groups. As a result, it was found that in the two youngest age groups, a significant number of patients improved, moving from the intermediate- or high-risk group at baseline to the low-risk group at follow-up (18–45 years $Z = -4.613$,

p<0.001; 46–64 years Z= −2.125, p=0.034). In contrast, there was no significant difference in risk group distribution between baseline and follow-up in the two oldest age groups (65–74 years Z= −0.707, p=0.480; ⩾75 years Z= −0.832, p=0.405). 5-year survival was highest in patients aged 18–45 years (88%), while the survival rates were 63%, 56% and 36% for patients in the age groups of 46–64, 65–74 and ⩾75 years, respectively (p<0.001). As the authors discussed, the worse survival rate of the older patients might reflect the natural effect of age, as well as the deleterious effect of specific comorbidities on outcome, but it could also be due to delayed diagnosis in elderly patients, or to a different "IPAH phenotype" with a worse treatment response. Moreover, ischaemic heart disease and kidney dysfunction were the only independent predictors of survival among the investigated comorbidities.

Owing to therapy outcome in this patient group, elderly patients were less often initially treated with combination PAH-targeted therapy and had a poorer outcome. In conclusion, it was suggested to add age and specific comorbidity as prognostic markers of outcome to risk assessment algorithms. Because of the relatively small patient population in this study, further data were necessary to prove this hypothesis.

Cluster analyses show heterogeneity of IPAH

Subsequent studies used cluster analysis as a widely used exploratory and hypothesis-generating approach in describing subtypes in complex disorders. For example, clinical characterisation of the scleroderma pulmonary hypertension population has benefited from clustering approaches. Badagliacca *et al*. [11] published an analysis in 2020 in order to improve phenotyping of patients with IPAH and to analyse long-term clinical outcome. It was the first application of cluster analysis to identify distinct clinical phenotypes in IPAH. However, the authors mentioned that this study was not intended to suggest a phenotype classification for IPAH. They decided to use the simplest and commonly used parameters in clinical practice for clustering.

Two larger registry analyses underline the occurrence of different phenotypes in IPAH with heterogeneous outcome. In 2020, Hoeper *et al*. [5] focused on 841 patients with IPAH from the European COMPERA registry. They identified three clusters based on the following parameters: age, sex, diffusion capacity of the lung for carbon monoxide (D_{LCO}) (<45% *versus*⩾45% predicted, the D_{LCO} cut-off value of <45% *versus* 45% or more was derived from previous studies that determined prognostic value of this threshold), smoking status and presence of comorbidities (obesity, hypertension, coronary heart disease and diabetes mellitus). All three clusters were characterised by severe pre-capillary pulmonary hypertension:

- patients with a classical IPAH phenotype – cluster 1 (n=106; 12.6%): median age 45 years, 76% female, no comorbidities, mostly never-smokers, D_{LCO} typically ⩾45% pred
- patients with a HFpEF-like phenotype – cluster 2 (n=301; 35.8%): median age 75 years, 98% female, many comorbidities, no smoking history, D_{LCO} mostly ⩾45% pred
- patients with a cardiopulmonary phenotype – cluster 3 (n=434; 51.6%): median age 72 years, 72% male, many comorbidities, typically history of smoking and mainly low D_{LCO} (<45% pred)

The objectives of this investigation were to demonstrate different clusters of adult patients with IPAH in this setting and to examine the response to medical therapy and survival more closely. Thereby, different therapy strategies in cluster 1, in contrast to clusters 2 and 3, became evident: at baseline, 38% of the patients in cluster 1 received combination therapies, which increased to 63% at 1 year follow-up. By contrast, patients in clusters 2 and 3 received combinations of PAH drugs merely in 13% and 15% of cases at baseline, and in 28% and 39% of cases 1 year later. All clusters showed a different response to PAH therapy, and different survival rates. Patients in cluster 1 had a better response to PAH treatment than patients in the two other clusters. Concerning survival rates over 5 years, patients in cluster 1 showed a survival rate of 84.6%. In cluster 2 (59.2%) and cluster 3 (42.2%), survival rates were clearly lower (unadjusted p<0.001 for comparison between all groups).

It is still unclear whether these differences in survival were related to the pulmonary vascular disease and/or comorbidities itself, or to a less aggressive therapeutic regime or to a poorer treatment outcome. However, this study emphasises the diversity within the population of patients diagnosed with IPAH.

The most recent and comprehensive study confirms this conclusion and goes one step further [4]. Among patients diagnosed with IPAH it is striking that there is a lung phenotype characterised by a low diffusion capacity for carbon monoxide (D_{LCO}) and a smoking history. The aim of the study was to characterise these patients in detail. The authors raised the question if the findings could or should lead to a reclassification of some forms of pulmonary hypertension. The analysis was based on data from two European registries, COMPERA and Assessing the Spectrum of Pulmonary hypertension Identified at a

REferral centre (ASPIRE). In total, data derived from 2005 patients were evaluated, and three patient groups have been characterised:

- Patients with classical IPAH (128 from COMPERA and 185 from ASPIRE): these patients were younger than patients from the other two groups, had no risk factors for left heart disease (defined by body mass index (BMI) $\geqslant 30\ kg \cdot m^{-2}$, hypertension, diabetes and coronary heart disease) and had a D_{LCO} typically of 45% or more. This cluster included the highest female proportion.
- Patients with IPAH and a lung phenotype (268 from COMPERA and 139 from ASPIRE) of normal or near normal spirometry, a severe reduction in D_{LCO} (<45% pred), no or a mild degree of parenchymal lung involvement on chest computed tomography and a smoking history.
- Patients with pulmonary hypertension due to lung disease (group 3 pulmonary hypertension) (910 from COMPERA and 375 from ASPIRE).

Patient characteristics, response to therapy (available from COMPERA at first follow-up – median 4.7 months after baseline) and survival of the three cohorts were compared in this study. Improvements in World Health Organization functional class (WHO-FC) were seen in more than half of the patients with classical IPAH, but only in about a quarter of the patients with IPAH and a lung phenotype and 22% of the patients with pulmonary hypertension due to lung disease.

Median improvements in 6-min walking distance (6MWD) were 63 m, 25 m and 23 m for these three cohorts (p=0.0015 for classical IPAH *versus* IPAH and a lung phenotype, and p=0.64 for IPAH and a lung phenotype *versus* group 3 pulmonary hypertension).

Median reductions in N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) were 58%, 27% and 16%. This comparatively (concerning patients with classical IPAH) poor response to therapy in patients with IPAH and a lung phenotype could be explained by a different type of pulmonary vasculopathy, less aggressive therapy, comorbidities or a combination thereof.

Survival rates of patients with IPAH and a lung phenotype (1 year, 89% in COMPERA and 79% in ASPIRE; 5 years, 31% in COMPERA and 21% in ASPIRE) and group 3 pulmonary hypertension (1 year, 78% in COMPERA and 64% in ASPIRE; 5 years, 26% in COMPERA and 18% in ASPIRE) was worse than survival of patients with classical IPAH (1 year, 95% in COMPERA and 98% in ASPIRE; 5 years, 84% in COMPERA and 80% in ASPIRE).

The results of this comprehensive analysis clearly show that patients diagnosed with IPAH by definition and additional lung-related criteria (smoking history, low D_{LCO}) are more similar to patients with pulmonary hypertension due to lung disease than patients with classic IPAH. This led the authors to discuss adding a phenotypic component to the classification of unexplained pre-capillary pulmonary hypertension. They also made specific suggestions for parameters that consider smoking history, D_{LCO}, chest computed tomography findings and risk factors for left heart disease. Hoeper *et al*. [4] concluded that IPAH patients with a pulmonary phenotype may be better classified as group 3 pulmonary hypertension (pulmonary hypertension associated with lung disease).

These data are supported by Peacock *et al*. [12] who also discussed that patients with IPAH and a normal lung function, but minor coexisting lung disease on thoracic computed tomography, are a separate subgroup of IPAH with different phenotype characteristics and worse survival compared to IPAH without coexisting signs of a lung disease.

The role of smoking (on phenotyping) in PAH

A pathogenetic role of tobacco smoke exposure in PAH patients has been assumed for several years [13–15]. For example, it was shown in a mouse model that extensive tobacco exposure in mice leads to apoptosis of the endothelial cells in the pulmonary capillaries before emphysema develops [16]. Hoeper *et al*. [4] speculated that exposure to tobacco smoke might be a contributor or even a main cause of severe pre-capillary pulmonary hypertension. Frost *et al*. [17] took up the topic by analysing data from 3046 patients of the US Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL), asking whether there is an association between PAH (IPAH as well as other forms of PAH) and smoking prevalence. In this registry analysis, ever-smoking status was more prevalent in males (61.7%); also patients in this group were older at diagnosis and enrolment than never-smoking patients. It is remarkable that time to first hospitalisation, transplant-free survival and survival did not differ between ever- *versus* never-smokers overall. However, the subgroup of newly diagnosed ever-smoking males was associated with earlier death, composite of transplant or death and earlier first hospitalisation. In contrast, this did not apply to newly diagnosed ever-smoking women.

An overview on reviewed publications on studies describing different IPAH phenotypes, specific clusters of IPAH with respect to risk factors for left heart disease and comorbidities published since 2016 is provided in table 1.

Comorbidities and age determine therapeutic outcome – more evidence needed

Managing PAH requires a comprehensive treatment strategy and multidisciplinary care. Targeted drugs such as ERA (*i.e.* ambrisentan, bosentan, macitentan), PDE5i (*i.e.* sildenafil, tadalafil), a soluble guanylate cyclase stimulator (*i.e.* riociguat), prostacyclins and their analogues, and a prostacyclin IP-receptor agonist (*i.e.* selexipag) are an essential part of PAH care. <10% of patients with IPAH, hereditary PAH (HPAH) or drug-induced PAH (DPAH) respond favourably to vasoreactivity testing and hence are candidates for a treatment with high-dose calcium channel blockers [18, 19].

A comprehensive algorithm for the treatment of patients with IPAH, HPAH, DPAH or PAH associated with connective tissue disease (CTD-PAH) is provided by the recently updated European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines (figure 1) [3]. This algorithm considers phenotypes of patients diagnosed with IPAH and distinguishes between patients without or with cardiopulmonary comorbidities.

In contrast to the recommendations for upfront combination therapies for non-vasoreactive patients with IPAH, HPAH or DPAH without comorbidities, a less aggressive approach is recommended for patients who present with cardiopulmonary comorbidities. Specific guideline recommendations for these patients suggest that an initial monotherapy with a PDE5i or an ERA should be considered; for patients who remain at intermediate or high risk of death at follow-up while receiving monotherapy it is suggested that additional medication on an individual basis should be considered (in collaboration with a pulmonary hypertension expert centre) [3].

As primary treatment for IPAH patients with comorbidities, most physicians today use PDE5i; ERAs or PDE5i/ERA combinations are occasionally used, but the drug discontinuation rate is higher than in patients with classical IPAH [3, 7, 20]. According to the current guidelines, IPAH patients with cardiopulmonary comorbidities are generally more likely to discontinue their medication (due to efficacy failure or lack of tolerability), respond less well to specific PAH drugs, are less likely to meet the therapy goal of reaching a low-risk status regarding expected 1-year mortality, and have a higher mortality risk – in comparison to patients without such comorbidities [3]. Age-adjusted mortality of patients with the left heart phenotype is described as similar to that of patients with classical IPAH, whereas patients with a cardiopulmonary phenotype and a low D_{LCO} have a particularly high mortality risk [3, 5, 7, 14, 21, 22]. It is also stated that a lack of evidence leaves treatment recommendations for (elderly) patients with IPAH and cardiopulmonary comorbidities challenging [3]. The guidelines recommend that patients with comorbidities should consider an optimisation of therapy on an individual basis (class IIb), while acknowledging that a low-risk profile may not always be achievable [3, 6, 23–25].

Ironically, the largest subgroup has the least evidence of targeted therapies: IPAH patients with comorbidities, diagnosed with and treated for PAH. Consequently, guideline recommendations have remained vague for these patients. Nevertheless, a growing body of data provides a more profound insight into the quality, outcome and clinical practice of managing IPAH patients with cardiopulmonary comorbidities. Some of these data may help to guide treatment decisions in specific subgroups of IPAH phenotypes.

Different outcomes in patients with and without risk factors for LV diastolic dysfunction

The results of the AMBITION (Initial Use of Ambrisentan and Tadalafil in Patients with PAH) study [26] showed markedly better treatment outcomes regarding exercise tolerance and disease progression with initial combination therapy using ambrisentan and tadalafil, compared to monotherapy with each of these compounds [26]. In AMBITION, patients with multiple risk factors for left ventricular diastolic dysfunction (LVDD) were excluded from the primary analysis set (PAS) and referred to as ex-primary analysis set (Ex-PAS). To compare PAH patients with and without multiple risk factors for LVDD that had been enrolled in AMBITION, a *post hoc* analysis [27] was carried out. Here, discontinuation rates in patients receiving initial combination therapy were 33% in patients who had ⩾three comorbidities compared to 14% in patients who had fewer or no comorbidities [27]. For ERA monotherapy, the corresponding numbers were 38% *versus* 19%, and for PDE5i monotherapy it was 23% *versus* 15%, respectively [27]. Patients in the PAS (patients without multiple risk factors for LVDD, n=500) were younger (mean 54.4 *versus* 62.1 years) with greater baseline 6MWD (median 363.7 *versus* 330.5 m) and

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TABLE 1 Overview of reviewed publications on studies describing different IPAH phenotypes, specific clusters of IPAH with respect to risk factors for left heart disease and comorbidities published since 2016

Study/registry	Method/collective	Therapy	End-point
Badagliacca *et al.* [11], 2020	Patients with IPAH from two reference centres (Italy/USA) Cluster analysis based on clinical, haemodynamic and echocardiographic assessment and cardiopulmonary exercise test. Using a 4-cluster model, variables with a z-score >0.5 and <−0.5 were identified as the most important variables: age, weight, mPAP, RVEDA, O_2 pulse were the most significant determinants of cluster membership 4 clusters identified: Cluster 1: young, mild PH, mild RV dilation, high O_2 pulse Cluster 2: severe PH, RV dilation, high O_2 pulse Cluster 3: male patients, severe PH, RV dilation, low O_2 pulse Cluster 4: older, more female, overweight, mild PH and RV dilation, low O_2 pulse n=252	All treated with PAH-targeted drugs	Clinical worsening defined as reduction in exercise capacity, worsening in WHO functional class, non-elective hospitalisation for IPAH, all-cause mortality
Frost *et al.* [17], 2023	Patient data of US REVEAL Registry Prevalence, demographics and outcomes in ever- *versus* never-smokers with any form of PAH were determined n=3046	No data available	Analysis of putative associations between PAH and smoking prevalence as well as: • Time to first hospitalisation • Transplant-free survival • Survival
Hjalmarsson *et al.* 2018 [6]	Patients with IPAH (Swedish registry SPAHR)/categorised into four age groups: 18–45, 46–64, 65–74 and ⩾75 years Individual risk profiles were determined according to a risk assessment instrument (based on the European Society of Cardiology and the European Respiratory Society guidelines) n=264	PAH-targeted therapy (single/dual/triple)	Change in risk group and survival (baseline to follow-up (median 5 months) compared across age groups
Hoeper *et al.* [5], 2020	Patients with IPAH (COMPERA registry) Cluster analysis based on age, sex, diffusion capacity of the lung for carbon monoxide (D_{LCO} <45% *versus* ⩾45% predicted), smoking status, presence of comorbidities (obesity, hypertension, coronary heart disease and diabetes mellitus). A hierarchical agglomerative clustering algorithm was performed using Ward's minimum variance 3 clusters identified: • Cluster 1: IPAH phenotype, median age 45 years, mostly females, no comorbidities, mostly never-smokers, D_{LCO} ⩾45% • Cluster 2: HFpEF-like phenotype, median age 75 years, mostly females, many comorbidities, no smoking history, D_{LCO} mostly ⩾45% • Cluster 3: cardiopulmonary phenotype, median age 72 years, mostly males, many comorbidities, history of smoking, low D_{LCO} n=841	Patients with combination therapy at baseline: • 38% cluster 1 • 13% cluster 2 • 15% cluster 3 Patients with combination therapy 1 year after baseline: • 63% cluster 1 • 28% cluster 2 • 39% cluster 3	Survival, response of PAH therapy (expressed as changes from baseline to follow-up in functional class, 6-minute walking distance, cardiac biomarkers, risk)

Continued

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TABLE 1 Continued

Study/registry	Method/collective	Therapy	End-point
Hoeper *et al.* [4], 2022	Data of COMPERA and ASPIRE registries 3 patient groups: • Classical IPAH: younger, no risk factors for left heart disease (defined by BMI ⩾30 kg·m^{-2}, hypertension, diabetes, and coronary heart disease), D_{LCO} of 45% or more. This cluster includes, mostly female patients • IPAH and a lung phenotype: normal or near normal spirometry, severe reduction in D_{LCO}, no or a mild degree of parenchymal lung involvement, smoking history • PH due to lung disease (group 3 pulmonary hypertension) n=2005	Data only available from COMPERA at first follow-up – median 4.7 months after baseline: Monotherapy: • 63% classic IPAH • 8% IPAH with lung phenotype • 96% group 3 PH Combination therapy: • 37% classic IPAH • 18% IPAH with lung phenotype • 4% group 3 PH	Response to therapy (change in 6-min walk distance, change in WHO functional class, change in NT-proBNP), survival
Opitz *et al.* [7], 2016	Retrospective analysis of patients with IPAH from the COMPERA registry Definition and comparison of patients with typical *versus* atypical IPAH[#] Considered risk factors for left heart disease in this differentiation are: arterial hypertension, coronary artery disease, diabetes mellitus, atrial fibrillation, body mass index >30 kg·m^{-2} • Typical IPAH=patients with <3 risk factors for left heart disease (n=421) • Atypical IPAH=patients with ⩾3 risk factors for left heart disease (n=139) • PH-HFpEF (n=226) receiving PH-targeted therapy In total: n=787	Description of PH-targeted therapy in patients with or without ⩾3 risk factors for left heart disease or HFpEF: Combination therapy at baseline: • IPAH with <3 risk factors: 17.8% • IPAH with ⩾3 risk factors 7.9% • HFpEF: 2.7% Combination therapy at 1 year treatment • IPAH with <3 risk factors: 44.4% • IPAH with ⩾3 risk factors 25.9% • HFpEF: 7.4%	Characterisation of similarities and differences among patient populations with either PH-HFpEF or IPAH (with <3 or ⩾3 risk factors for left heart disease)

IPAH: idiopathic pulmonary arterial hypertension; mPAP: mean pulmonary artery pressure; RVEDA: right ventricular end-diastolic area; PH: pulmonary hypertension; RV: right ventricular; PAH: pulmonary arterial hypertension; WHO: World Health Organization; REVEAL: US Registry to Evaluate Early and Long-term PAH Disease Management; SPAHR: Swedish PAH & Chronic Thromboembolic Pulmonary Hypertension registry; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; D_{LCO}: diffusion capacity of the lung for carbon monoxide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; HFpEF: heart failure with preserved ejection fraction; ASPIRE: Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre; BMI: body mass index. [#]: risk factors for left heart disease – arterial hypertension, coronary artery disease, diabetes mellitus, atrial fibrillation, body mass index ⩾30 kg·m^{-2}.

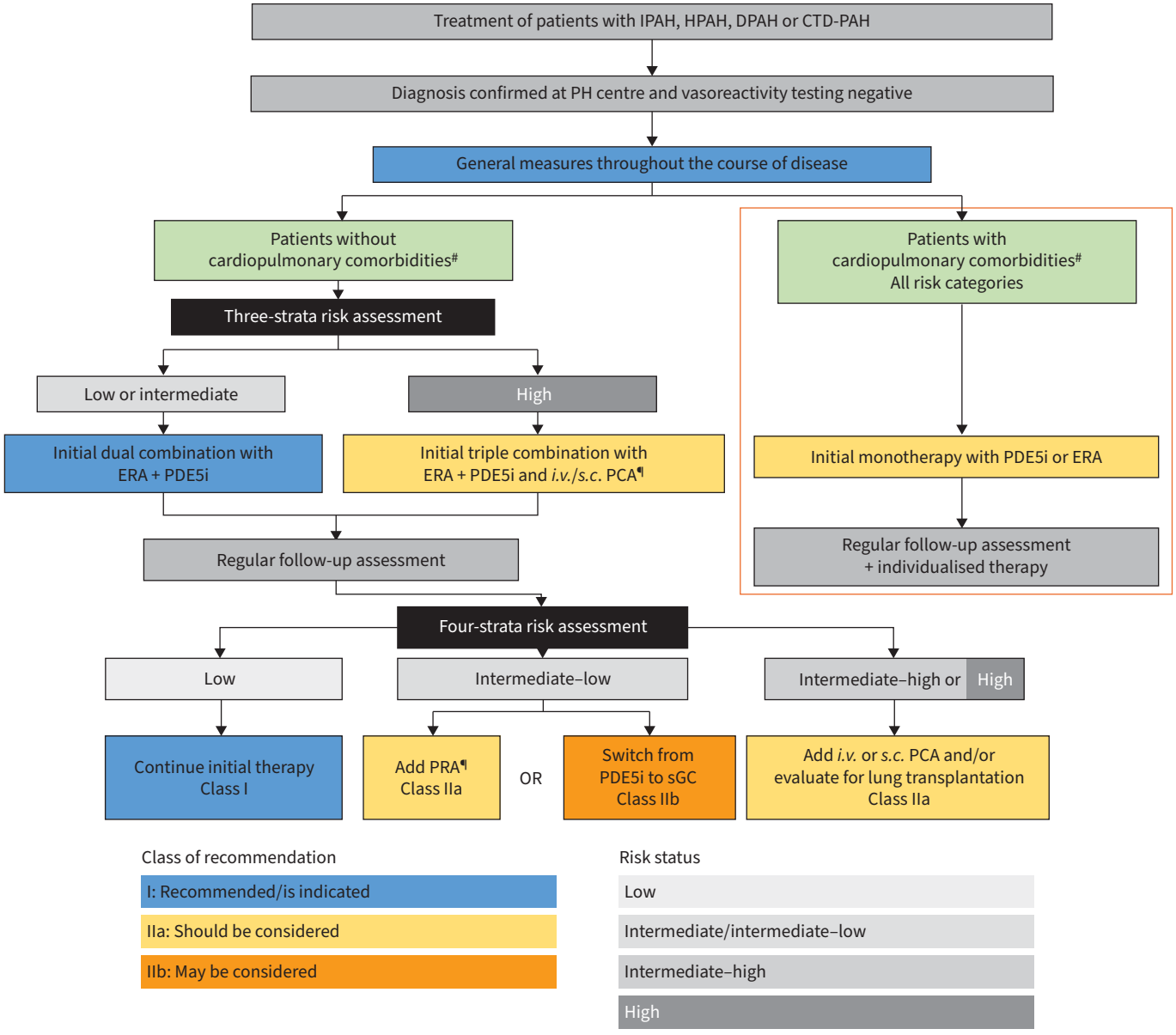

FIGURE 1 Treatment algorithm for pulmonary arterial hypertension (PAH) (European Society of Cardiology/European Respiratory Society Guideline 2022): an evidence-based framework for IPAH, HPAH, DPAH and CTD-PAH and some CHD-PAH patients (CHD-PAH patients with small/coincidental or with corrected defects should also be treated according to this treatment algorithm). IPAH: idiopathic PAH; HPAH: hereditary PAH; DPAH: drug-induced PAH; CTD-PAH: PAH associated with connective tissue disease; CHD-PAH: pulmonal arterial hypertension associated with congenital heart disease; PH: pulmonary hypertension; ERA: endothelin receptor antagonist; PDE-5i: phosphodiesterase-5 inhibitors; PCA: prostacyclin analogues; PRA: prostacyclin receptor agonist; sGCs: stimulator of soluble guanylate cyclase. #: cardiopulmonary comorbidities are conditions associated with an increased risk of left ventricular diastolic dysfunction and include obesity, hypertension, diabetes mellitus and coronary heart disease; pulmonary comorbidities may include signs of mild parenchymal lung disease and are often associated with a low diffusing capacity of the lung for carbon monoxide (<45% of the predicted value). ¶: PRA refers to selexipag whilst PCA refers to *i.v./s.c.* prostacyclin. Modified from [3].

fewer comorbidities (*e.g.* hypertension and diabetes) in comparison to patients comprising the Ex-PAS (with multiple risk factors for LVDD, n=105) [27]. In conclusion:

- PAH patients with multiple risk factors for LVDD experienced higher rates of clinical failure events and the response to combination therapy *versus* monotherapy was attenuated [27].
- However, with respect to the primary end-point (time to clinical failure), both the PAS group (hazard ratio (HR) 0.50, 95% CI 0.35–0.72) and Ex-PAS group (HR 0.70, 95% CI 0.35–1.37) were in favour of upfront combination therapy [27].

- Tolerability was better in patients without multiple risk factors than in patients with multiple risk factors for LVDD [27].
- Nevertheless, the benefit–risk balance for PAH patients with multiple risk factors for LVDD was positive overall.

Age affects outcome of treatment with macitentan

A *post hoc* analysis [28] of the event-driven, multicentre, double-blind, placebo-controlled, phase 3 study SERAPHIN (Study with Endothelin Receptor Antagonist in PAH to Improve cliNical outcome*)* [29] addressed the efficacy and safety of long-term therapy with the ERA macitentan (10 mg daily *versus* placebo) in 407 patients aged 18–64 years and in 71 elderly patients aged ⩾65 years [28]. It revealed that – although attenuated – the treatment effect of macitentan on morbidity/mortality was consistent in both groups (interaction p=0.89) with a positive risk–benefit profile: Macitentan showed a largely similar side-effect pattern in the elderly as in younger patients: oedema-related adverse events (AEs) tended to be more frequent in the elderly cohort (26% macitentan *versus* 25% placebo) than in the adult cohort (21% *versus* 20%), whereas AEs related to haemoglobin decrease as well as liver-related AEs were similar in both age groups [28].

A further *post hoc* analysis [30] of SERAPHIN [29] identified prognostic age groups and determined treatment effects of macitentan by age. Here, age <35 years was identified as a risk factor, the prognostic significance of age ⩾65 years was confirmed while patients in all age groups showed a response to macitentan in terms of reducing the risk for a morbidity/mortality event (composite primary end-point) [30]. However, the greatest treatment effects were observed in the younger and middle-aged patients: age <35 years (HR 0.44, 95% CI 0.25–0.78); age 35–64 years (HR 0.50, 95% CI 0.33–0.76); age ⩾65 years (HR 0.69, 95% CI 0.30–1.58) [30].

Comorbidity status does not impair prostacyclin receptor agonist treatment effects

In GRIPHON (Prostacyclin [PGI2] Receptor agonist In Pulmonary arterial HypertensiON) [30], 1.156 PAH patients (with or without PAH background therapy) were randomised to receive placebo or the selective oral prostacyclin IP-receptor agonist *selexipag*. This included patients aged 18–75 years with IPAH, HPAH, CTD-PAH, corrected-congenital shunts and HIV infection as well as drug or toxin exposure. Selexipag significantly reduced the risk of meeting the primary composite end-point (death or a complication related to PAH) *versus* placebo.

A *post hoc* analysis [32] of GRIPHON [31] explored the effect of *selexipag* in PAH (several forms) patients with cardiovascular comorbidities (using the AMBITION criteria). In this *post hoc* analysis, patients were classified as follows: 1) two subgroups defined by comorbidity count and restrictive haemodynamic criteria – subgroup A (<three comorbidities and/or haemodynamic criteria met; n=962) and subgroup B (⩾three comorbidities and/or haemodynamic criteria not met; n=144) (comorbidities included BMI ⩾30 $kg \cdot m^{-2}$, essential hypertension, diabetes, history of coronary artery disease); 2) by number of comorbidities, with addition of atrial fibrillation; or 3) by presence of individual comorbidities [32]. The risk of a morbidity/mortality event (composite primary end-point) was reduced compared with placebo in both subgroup A (HR 0.66, 95% CI 0.53–0.82) and subgroup B (HR 0.50, 95% CI 0.26–0.96), with no evidence of an inconsistent treatment effect between subgroups (interaction p=0.432), whereas consistent results were observed in analyses by number and by specific type of comorbidity [32].

The findings suggest that the comorbidity status does not influence the treatment effect of selexipag on the primary composite end-point [32]. Although an increased risk of selexipag discontinuation due to AEs in patients with ⩾three comorbidities compared to patients with fewer or no comorbidities (21% *versus* 13%) was observed in GRIPHON, in the *post hoc* analysis the proportion of patients with AEs leading to treatment discontinuations was similar in selexipag-treated patients in both subgroups, indicating that the tolerability of selexipag did not substantially differ between patients with and without comorbidities [32].

The most common AEs in the selexipag group were consistent with the known side-effects of drugs targeting the prostacyclin pathway, including headache, diarrhoea, nausea and jaw pain [31].

More combination therapies: patients with cardiovascular comorbidities benefit from targeted treatment

A recent analysis [33] of registry data from COMPERA suggests that IPAH patients with cardiovascular comorbidities also benefit from targeted PAH therapies, albeit to a lesser extent than patients without comorbidities. This was found for noninvasive parameters utilised for risk assessment in PAH, such as improvements in WHO-FC, 6MWD, brain natriuretic peptide (BNP)/NT-pro-BNP and mortality risk [33].

In addition, the analysis showed that the refined four-strata tool for risk stratification, as described in the 2022 ESC/ERS guidelines [3], predicted outcome irrespective of the presence of comorbidities [33]. However, only a few patients with comorbidities achieved a low-risk profile during follow-up, which can be partly explained by significantly worse baseline values in patients with (multiple) comorbidities, making it unrealistic to reach the thresholds defining low risk. Importantly, comorbid patients who reach an intermediate–low risk status at follow-up had a much better survival than patients at intermediate–high or high risk [33], so that this may be regarded as a realistic and meaningful treatment goal.

Temporal trends in PAH treatment patterns and survival were investigated in a further COMPERA analysis [34]. It addressed how new treatment options and strategies, as well as demographic changes, have affected treatment patterns and survival between 2010 and 2019. A total of 2531 patients with PAH were included. For survival analyses, annualised data and cumulated data comparing the periods 2010–2014 and 2015–2019 were used. The results were as follows [34]:

- When comparing the 2010–2014 and 2015–2019 periods, 1-year survival estimates were similar (HR 89.0%, 95% CI 87.2–90.9% and HR 90.8%, 95% CI 89.3–92.4%, respectively).
- There was a slight but non-significant improvement in 3-year survival estimates (HR 67.8%, 95% CI 65.0–70.8% and HR 70.5%, 95% CI 67.8–73.4%, respectively).
- The proportion of patients receiving combination therapy 1 year after diagnosis increased from 27.7% to 46.3%.
- Use of early combination therapy (within 3 months after diagnosis) increased from 10.0% in patients diagnosed with PAH in 2010 to 25.0% in patients diagnosed with PAH in 2019.
- Most patients still received monotherapy.

In conclusion, the use of combination therapy increased from 2010 to 2019, yet most patients still received monotherapy and survival rates measured 1 year after diagnosis did not change over time [34]. The authors state that future studies need to determine whether the observed trend suggesting an improved 3-year survival rate can be confirmed. With reference to patients who were aged ⩾65 years at the time of diagnosis, combination therapy was used much less frequently than in younger patients, both initially and 1 year after diagnosis. Overall, these older patients tended to be treated less aggressively, respond less well to PAH medications, have a higher likelihood of discontinuing their PAH medications and have a higher mortality risk [34].

Targeted PAH therapy for IPAH patients with significant comorbidities or LVDD risk

A retrospective analysis [35] of 253 treatment-naïve IPAH patients (with a confirmed diagnosis after right heart catheterisation) from the Amsterdam University Medical Centre (AUMC), diagnosed between 1989 and 2019, aimed at evaluating treatment effects according to the established H_2FPEF score, where a score ⩾5 indicated a higher probability of (masked) LVDD. It revealed that IPAH patients with a high H_2FPEF score are older, more often male, overweight and have more comorbidities; a high H_2FPEF score was associated with poorer prognosis and with evidence of LVDD. However, a favourable haemodynamic and functional response to treatment was found in all IPAH patients regardless of the H_2FPEF score [35]. The authors concluded that there are no compelling reasons to withhold targeted PAH treatment from patients with pre-capillary pulmonary hypertension diagnosed as IPAH and significant comorbidities or additional risk factors for LVDD.

Another retrospective analysis [36] in 181 patients with IPAH, CTD-PAH and CHD-PAH from the Italian Pulmonary Hypertension Network (iPHNET) database assessed the impact of comorbidities on haemodynamic and clinical response to initial oral combination therapy. It suggested that initial combination therapy with ERA+PDE5i is able to improve WHO-FC, exercise capacity and NT-proBNP at 6 months (weaker response in patients with cardiovascular risk factors). These data were consistent with those of the above-mentioned AUMC analysis and those of the AMBITION study [36].

Recent publications on studies or registry analyses assessing the impact of comorbidities (risk factors for left heart disease) and age on PAH therapy, treatment efficacy and safety since 2016 are shortly summarised in table 2.

Discussion

In this review, we focused on the distinct heterogeneity of IPAH phenotypes which became apparent over the last years. All studies we reviewed emphasise the diversity within the population of patients diagnosed with IPAH. The data also reveal differences in prognosis and therapy outcome for the named patient types (table 3). Obviously, patients with IPAH and comorbidities are less likely to receive maximal PAH therapy,

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TABLE 2 Publications on Studies or registry analyses assessing impact of comorbidities (risk factors for left heart disease) or age on PAH therapy, treatment efficacy and safety since 2016

Study/ registry	Method/collective	Therapy	End-point	Outcome	Adverse events
Badagliacca *et al.* [36], 2022	Retrospective analysis at 11 centres of Italian Pulmonary Hypertension Network (iPHNet), January 2013 to December 2018: 181 patients with IPAH, CTD-PAH or CHD-PAH who received initial combination therapy of ERA and PDE-5i in three groups: • Group A: no cardiac comorbidities 53.0% (n=96) • Group B: one cardiac comorbidity 29.8% (n=54) • Group C: ⩾two cardiac comorbidities 17.2% (n=31)	ERA, PDE-5i With majority of patients (62%) on ambrisentan/ tadalafil combination therapy	Assessing the impact of comorbidities on haemodynamic and clinical response to initial oral combination therapy	Improvement in risk status according to three-strata model from baseline to follow-up in patients without, respectively one or at least two cardiovascular comorbidities: • Patients without comorbidities were 2.3 times more likely to achieve/ maintain a low-risk status in comparison to patients with comorbidities • Patients with two comorbidities or more had 3.8 times higher probability of treatment failure *versus* patients without comorbidities Significant differences in reduction of PVR were observed in group A, B and C with median reduction of −45.0%, −30.3% and −24.3% respectively	Drug-related AEs occurred with similar frequency between groups; most frequent side-effects were reported as: • peripheral oedema (Group A, 27 patients: 28%; Group B, 16 patients: 30%; Group C, 10 patients: 32%), • headache (Group A, 37 patient: 38%; Group B, 19 patients: 35%; Group C, 11 patients: 35%) and • nasal congestion (Group A, 20 patients: 21%; Group B, 12 patients: 22%; Group C, 6 patients: 19%; p=NS) None of the patients discontinued dual oral combination therapy due to severe side-effects
Channick *et al.* [30], 2021	*Post hoc* analysis of SERAPHIN and GRIPHON to identify prognostic age groups and macitentan treatment effect by age. SERAPHIN and GRIPHON were event-driven, double-blind phase 3 RCTs with a time to M/M primary end-point • n=250 (SERAPHIN) • n=582 (GRIPHON) Cox regression models adjusted for FC, PAH background therapy, region, PAH aetiology, sex, and race/ethnicity were used to determine the macitentan 10 mg treatment effect in SERAPHIN by age group	Macitentan (SERAPHIN) Selexipag (GRIPHON) On PAH background therapy	Treatment effect on composite primary end-point of time to M/M related to PAH	The analysis of the two studies identified three age thresholds: <35, 35–64 and ⩾65 years: The risk of M/M event was higher in younger and older patients than in patients 35–64 years: In the SERAPHIN placebo arm (n=250), patients <35 years had a 73% greater risk of M/M than those 35–64 years (HR 1.73, 95% CI 1.10–2.72), and patients ⩾65 years had a 55% greater risk (HR 1.55, 95% CI 0.89–2.69). In the GRIPHON placebo arm (n=582), patients <35 years had an 82% greater risk of M/M than those 35–64 years (HR 1.82, 95% CI 1.29–2.57) and patients ⩾65 years had a 7% greater risk (HR 1.07, 95% CI 0.75–1.54) Macitentan reduced the risk of M/M *versus* placebo in all age groups: • <35 years: HR 0.44, 95% CI 0.25–0.78 • 35–64 years: HR 0.50, 95% CI 0.33–0.76 • ⩾65 years: HR 0.69, 95% CI 0.30–1.58	Incidence of AEs leading to macitentan discontinuation was similar across age groups

Continued

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TABLE 2 Continued

Study/ registry	Method/collective	Therapy	End-point	Outcome	Adverse events
Hoeper *et al.* [34], 2022	Analysis of prospectively collected variables: • n=2531 overall • Comorbid conditions: ○ n=810 obesity ○ n=1329 hypertension ○ n=554 coronary heart disease ○ N=590 diabetes mellitus	Monotherapies: ERA, PDE-5i, sGC, PCA/ selexipag, CCB, other Combination therapies: • ERA + PDE-5i • other than ERA + PDE-5i • ERA + PDE-5i + PCA • Triple combination therapy including *i.v.* or *s.c.* PCA	Assessment of temporal trends in the use of combination therapy (within 3 months and 1 year after diagnosis) and 1- and 3-year survival rates of patients with newly diagnosed PAH between 2010 and 2019	Increased use of oral combination therapies overall/use remains on a low level in patients ⩾65 years at the time of diagnosis, combination Therapy was used much less frequently than in younger patients, both initially and 1 year after diagnosis; 3-year survival improved slightly Older patients with PAH had more comorbidities, were less likely to receive combination therapy and had a higher mortality risk than younger patients	Not assessed
Hoeper *et al.* [4], 2022	Data of COMPERA and ASPIRE registries Three patient groups: • Classical IPAH: younger, no risk factors for left heart disease (defined by BMI ⩾30 kg·m^{-2}, hypertension, diabetes and coronary heart disease), D_{LCO} of 45% or more. This cluster includes mostly females • IPAH/PAH lung phenotype with normal or near normal spirometry, severe reduction in D_{LCO}, no or a mild degree of parenchymal lung involvement, smoking history • PH due to lung disease (group 3 pulmonary hypertension) n=2005	Data only available from COMPERA at first follow-up – median 4.7 months after baseline: Monotherapy: • 63% in classic IPAH • 82% in IPAH with lung phenotype • 96% in group 3 PH Combination therapy: • 3% in classic IPAH • 18% in IPAH with lung phenotype • 4% in group 3 PH	Response to therapy (change in 6-min walk distance, change in WHO functional class, change in NT-proBNP), survival	Improvements in WHO functional class: • 54% classical IPAH • 26% IPAH with a lung phenotype • 22% group 3 PH Median improvements in 6-min walking distance: • 63 m classical IPAH • 25 m IPAH with a lung phenotype • 23 m group 3 PH Median reductions in NT-proBNP: • 58% classical IPAH • 27% IPAH with a lung phenotype • 16% group 3 PH Survival: • IPAH/PAH lung phenotype ○ 1 year: 89% in COMPERA/79% in ASPIRE ○ 5 years: 31% in COMPERA and 21% in ASPIRE) • Group 3 pulmonary hypertension ○ 1 year: 78% in COMPERA and 64% in ASPIRE ○ 5 years: 26% in COMPERA and 18% in ASPIRE) • Classical IPAH ○ 1 year: 95% in COMPERA and 98% in ASPIRE ○ 5 years: 84% in COMPERA and 80% in ASPIRE	Not assessed

Continued

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TABLE 2 Continued

Study/ registry	Method/collective	Therapy	End-point	Outcome	Adverse events
Kianzad *et al.* [35], 2022	Retrospective analysis of 253 treatment-naïve IPAH patients; IPAH patients were stratified according to H_2FPEF score (⩾5 indicating left ventricular diastolic dysfunction): 24% (n=60) with low (⩽1), 54% (n=136) with intermediate (2–4) and 22% (n=57) with high score (⩾5) Follow-up RHC measurements available for n=150	Mono/dual/triple therapy with ERA, PDE-5i, CCB, prostacyclin	The study aimed to determine whether the H_2FPEF score identifies a subgroup of IPAH patients with blunted response to PAH-targeted treatment	High H_2FPEF score is associated with poorer prognosis IPAH patients with a high H_2FPEF score are older, more often male, overweight and have more comorbidities; increase of high H_2FPEF scores in incident IPAH patients, 30% in 30 years Improvement in risk status according to four-strata model from baseline to follow-up also in patients with high H_2PFEF score, which is indicative of IPAH patients with LVDD Haemodynamic and functional improvements at follow-up independent of H_2FPEF score	Drug discontinuation in patients under initial PAH therapy • with low H_2FPEF score: monotherapy 57%, dual therapy 42%, triple therapy 2% (ERA: 63%; PDE-5i: 43%; CCB: 18%; prostacyclin 22%) • with intermediate H_2FPEF score: monotherapy 51%, dual therapy 46%, triple therapy 3% (ERA: 60%; PDE-5i: 65%; CCB: 4%; prostacyclin 24%) • with high H_2FPEF score: monotherapy 61%, dual therapy 37%, triple therapy 2% (ERA: 61%; PDE-5i: 65%; CCB: 4%; prostacyclin 11%)
Langleben *et al.* [28], 2020	*Post hoc* analysis of patients in an event-driven double-blind phase 3 RCT on macitentan (SERAPHIN) Multicentre, double-blind, randomised, placebo-controlled, event-driven, phase 3 trial (NCT00660179) Analysis of efficacy and safety of long-term macitentan 10 mg *versus* placebo in 71 elderly patients (⩾65 years) *versus* 407 adults (18–64 years) n=71 (⩾65 years of age, ⩾one comorbidity)	Macitentan in comparison to placebo, as monotherapy or as sequential combination therapy (ca. 65% of total patients with PDE5i)	Treatment effect on composite primary end-point morbidity/ mortality: death or a complication related to PAH (as described above)	Consistent treatment effect on combined morbidity/mortality in patient aged 18–64 and in elderly patients above 65 years; macitentan was generally well tolerated	Oedema-related AEs, AEs related to haemoglobin decrease and liver-related AEs were reported: • Discontinuations due to AEs ○ 15% macitentan *versus* 25% placebo-treated elderly patients ○ 10% of adults<65 years in both treatment arms • PAH worsening: ○ Elderly: 33% macitentan *versus* 34% placebo ○ Adults: 21% *versus* 34% • Oedema in the elderly (26% macitentan *versus* 25% placebo) and in adults (21% *versus* 20%) • Haemoglobin decrease ○ Elderly: 19% macitentan *versus* 7% placebo ○ Adults: 16% *versus* 5% • Liver-related AEs ○ Elderly 7% macitentan *versus* 14% placebo ○ Adults 9% *versus* 15% • Cases of death: ○ Elderly five (7%; one macitentan; four placebo) ○ Adults 29 (7%; 13 macitentan; 16 placebo)

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TABLE 2 Continued

Study/ registry	Method/collective	Therapy	End-point	Outcome	Adverse events
McLaughlin *et al.* [27], 2019	Pre-specified ex-primary analysis of the AMBITION study, an event-driven, double-blind RCT to compare efficacy and safety in PAH patients with <three or ⩾three risk factors for left ventricular diastolic dysfunction • PAS patients with <three risk factors for left ventricular diastolic dysfunction (HFpEF), n=500/median age 54.4 years/ baseline 6MWD (median, 363.7 m) • Ex-PAS patients with ⩾three risk factors for left ventricular diastolic dysfunction n=105), median age 62.1 years/baseline 6MWD (median 330.5 m) HPpEF risk factors: • BMI ⩾30 kg·m^{-2} • History of essential hypertension • Diabetes mellitus (any type) • Historical evidence of significant coronary artery disease n=605	Initial combination therapy (ambrisentan and tadalafil) compared to monotherapy with each of these	Primary end-point: time from randomisation to first adjudicated clinical failure event (=first occurrence of a composite of morbidity and mortality events)	Efficacy of initial combination therapy versus monotherapy similar for PAS and Ex-PAS patients (with multiple risk factors for ventricular diastolic dysfunction) Initial combination therapy reduced the risk of clinical failure compared with pooled monotherapy PAS: HR 0.50, 95% CI 0.35–0.72, Ex-PAS: HR 0.70, 95% CI 0.35–1.37 Clinical failure events: PAS 25% *versus* Ex-PAS: 33% of patients Satisfactory clinical response: PAS: 34% *versus* Ex-PAS: 24% of patients	Tolerability was better in patients without multiple risk factors Permanently withdrawn from study because of AEs: PAS *versus* EX-PAS patients: 16% *versus* 31% Rates of serious AEs: primary analysis: 36% Ex-PAS: 57% for patients on initial combination therapy, 36% *versus* 58% for those on ambrisentan monotherapy, and 41% *versus* 43% for those on tadalafil monotherapy

Risk factors for left heart disease: arterial hypertension, coronary artery disease, diabetes mellitus, atrial fibrillation, body mass index >30 kg·m^{-2}. PAH: pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; CTD-PAH: PAH associated with connective tissue disease; CHD-PAH: pulmonal arterial hypertension associated with congenital heart disease (CHD); ERA: endothelin receptor antagonist; PDE-5i: phosphodiesterase-5 inhibitors (sildenafil/tadalafil); PVR: pulmonary vascular resistance; AEs: adverse events; RCTs: randomised controlled trials; M/M: morbidity/mortality event; FC: functional class; sGCs: stimulator of soluble guanylate cyclase (riociguat); PCA: prostacyclin analogues; CCB: calcium channel blocker; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; BMI: body mass index; D_{LCO}: diffusion capacity of the lung for carbon monoxide; PH: pulmonary hypertension; WHO: World Health Organization; NT-proBNP: N-terminal pro-brain natriuretic peptide; RHC: right heart catheterisation; LVDD: left ventricular diastolic dysfunction; 6MWD: 6-min walk distance; HFpEF: heart failure with preserved ejection fraction; PAS: primary analysis set; Ex-PAS: ex-primary analysis set.

TABLE 3 Phenotypes of idiopathic pulmonary arterial hypertension based on COMPERA analyses and updated recommendations of Cologne Consensus Conference 2018 [4, 5, 8]

Phenotype	Characteristics
1) **Classic** [5]	• Mostly younger • Mostly women • No/few relevant comorbidities
2) **Left heart** [5]	• Mostly older • Mostly women • Risk factors for HFpEF (RR↑, BMI↑, diabetes mellitus, coronary heart disease) • History of atrial fibrillation (∼30%)
3) **Cardiopulmonary** [5]	• Mostly older • Mostly men • Mostly D_{LCO} <45% of predicted value • Mostly P_{aO_2}↓ • Risk factors for left heart disease • Often smoking history
4) **Lung phenotype** [4]	• Older • Smoking history (100%) • D_{LCO} <45% of predicted value • Typically mild parenchymal changes • Vascular changes

HFpEF: heart failure with preserved ejection fraction; RR: (Riva Rocci) blood pressure; BMI: body mass index; D_{LCO} : diffusion capacity of the lung for carbon monoxide; P_{aO_2}: arterial oxygen tension.

such as combination therapy, than patients with a classic IPAH phenotype. At the same time, the above-listed studies support the efficacy and safety/tolerability of PAH-specific drugs (in combination either) at least in a subset of well-characterised (elderly) patients with cardiovascular comorbidities. We should take this into account when treating such patient groups and make every effort to obtain more solid data.

There are limitations to our review. First, the definition of phenotypes and the clinical parameters to be determined for classification are the subject of current research and scientific discussions and are not yet finalised (table 3). The cardiopulmonary and the lung phenotype are especially difficult to differentiate. Both are associated with a smoking history, and smoking is known to damage not only the lung parenchyma but also other blood vessels in the body. Therefore, one could expect that vascular changes also occur in the cardiopulmonary phenotype. Furthermore it is not guaranteed that right heart catheterisation was performed with oxygen in patients with the lung phenotype; oxygen may improve pulmonary artery pressure. Likewise, we cannot provide any information about whether fluid challenge or exercise were applied to differentiate from left heart disease. For lung assessment, smoking history and D_{LCO}, in addition to chest computed tomography findings and pulmonary function testing are important. For the left heart phenotype, the interpretation of cardiovascular comorbidities and their impact on classification and treatment strategies remain challenging.

Considering risk stratification, recent data suggested that current strategies for risk stratification can be applied to patients with (cardiovascular) comorbidities [32]. However, low risk was achieved in few patients with comorbidities, while intermediate–low risk appeared as a realistic goal in these patients and was associated with better outcomes as compared to intermediate–high or high risk.

Registry data and *post hoc* analyses from clinical trials have consistently shown that comorbidities can mitigate the therapeutic response to PAH therapies. However, such data are difficult to interpret, as the treatment regimens differed between phenotypes, with combination therapies prescribed much less in patients with comorbidities. The latter is partly explained by poorer drug tolerability and a higher rate of discontinuations (particularly ERA) in such phenotypes [7, 32], as well as reluctancy to prescribe combination therapies in IPAH patients with multiple comorbidities [37]. Thus, it is not entirely clear whether lower treatment efficacy is due to comorbidities or because patients receive combination therapies less frequently. Furthermore, it is currently unknown to what extent these experiences of an overall positive benefit *versus* risk profile of (combination) therapy in IPAH patients with comorbidities can also be transferred to patients with associated PAH such as CTD-PAH, as most analyses from studies and registries were only performed for patients with IPAH and therefore the data for other forms of PAH are even rarer.

To achieve therapeutic improvements, earlier diagnosis, a profound phenotyping, early initiation of PAH therapy according to guidelines and a tight follow-up are needed.

Management of such complex patients requires experience with PAH as well as left heart and lung conditions, and decision-making should be performed in expert centres. It seems to be of crucial importance not only to distinguish between with and without comorbidities, but also to consider severity and number of comorbidities as well as the age of patients for treatment decision resp. escalation of therapy. As a basis for deciding between combination and monotherapy in clinical practice, a list of factors that may help to guide treatment decisions is provided in box 1. Summarised, phenotypes comprising substantial haemodynamic impairment should not be undertreated, provided the concomitant diseases are well controlled.

BOX 1 Factors to consider when initiating combination therapy in IPAH patients with cardiopulmonary comorbidities

Phenotype of IPAH
Age
Haemodynamics (PVR)
Number/severity of comorbidities/HFpEF risk factors
Results of risk stratification (ESC/ERS guideline 2022)
Response to initial PAH-specific pulmonary vasoactive treatment
- Risk stratification
- Quality of life
- Physical endurance
- Drug tolerance
- Patient satisfaction

Individual treatment decision in patients with comorbidities [37]: up to now only data on treatment of pulmonary arterial hypertension (PAH) patients with comorbidities is available for cases with left heart phenotype or patients with heart failure with preserved ejection fraction (HFpEF) risk factors and elderly patients (>65 years). IPAH: idiopathic PAH; PVR: pulmonary vascular resistance; ESC/ERS: European Society of Cardiology/European Respiratory Society.

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References

1 D'Alonzo GE, Barst RJ, Ayres SM, *et al.* Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991; 115: 343–349.
2 Swiston JR, Johnson SR, Granton JT. Factors that prognosticate mortality in idiopathic PAH: a systematic review of the literature. *Respir Med* 2010; 104: 1588–1607.
3 Humbert M, Kovacs G, Hoeper MM, *et al.* 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2022; 43: 3618–3731.
4 Hoeper MM, Pausch C, Dwivedi K, *et al.* Phenotyping of idiopathic pulmonary arterial hypertension: a registry analysis. *Lancet Respir Med* 2022; 10: 937–948.
5 Hoeper MM, Pausch C, Grünig E, *et al.* Idiopathic pulmonary arterial hypertension phenotypes determined by cluster analysis from the COMPERA registry. *J Heart Lung Transpl* 2020; 39: 1435–1444.
6 Hjalmarsson C, Rådegran G, Kylhammar D, *et al.* Impact of age and comorbidity on risk stratification in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2018; 51: 1702310.
7 Opitz CF, Hoeper MM, Gibbs JSR, *et al.* Pre-capillary, combined, and post-capillary pulmonary hypertension: a pathophysiological continuum. *J Am Coll Cardiol* 2016; 68: 368–378
8 Rosenkranz S, Ghofrani HA, Grünig E, *et al.* Cologne consensus conference on pulmonary hypertension – Update 2018. *Int J Cardiol* 2018; 272: 1–3.
9 Galiè N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). *Eur Heart J* 2016; 37: 67–119.
10 Galiè N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). *Eur Respir J* 2015; 46: 903–975.
11 Badagliacca R, Rischard F, Papa S, *et al.* Clinical implications of idiopathic pulmonary arterial hypertension phenotypes defined by cluster analysis. *J Heart Lung Transplant* 2020; 39: 310–320.
12 Peacock AJ, Ling Y, Johnson MK, *et al.* Idiopathic pulmonary arterial hypertension and co-existing lung disease: is this a new phenotype? *Pulm Circ* 2020: 10: 2045894020914851.
13 Schiess R, Senn O, Fischler M, *et al.* Tobacco smoke: a risk factor for pulmonary arterial hypertension? A case-control study. *Chest* 2010; 138: 1086–1092.
14 Trip P, Nossent EJ, de Man FS, *et al.* Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses. *Eur Respir J* 2013; 42: 1575–1585.
15 Keusch S, Hildenbrand FF, Bollmann T, *et al.* Tobacco smoke exposure in pulmonary arterial and thromboembolic pulmonary hypertension. *Respiration* 2014; 88: 38–45.
16 Seimetz M, Parajuli M, Pichl A, *et al.* Inducible NOS inhibition reverses tobacco-smoke-induced emphysema and pulmonary hypertension in mice. *Cell* 2011; 147: 293–305.
17 Frost A, Zhao C, Farber HW, *et al.* Smoking history and pulmonary arterial hypertension: demographics, onset, and outcomes. *J Heart Lung Transplant* 2023; 42: 377–389.
18 Sitbon O, Humbert M, Jais X, *et al.* Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005; 111: 3105–3111.
19 Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; 327: 76–81.
20 Hoeper MM, Huscher D, Ghofrani HA, *et al.* Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. *Int J Cardiol* 2013; 168: 871–880.
21 Olsson KM, Fuge J, Meyer K, *et al.* More on idiopathic pulmonary arterial hypertension with a low diffusing capacity. *Eur Respir J* 2017; 50: 1700354.
22 Lewis RA, Thompson AAR, Billings CG, *et al.* Mild parenchymal lung disease and/or low diffusion capacity impacts survival and treatment response in patients diagnosed with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2020; 55: 2000041.
23 Hoeper MM, Kramer T, Pan Z, *et al.* Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J* 2017; 50: 1700740.
24 Hjalmarsson C, Kjellström B, Jansson K, *et al.* Early risk prediction in patients with idiopathic *versus* connective tissue disease-associated pulmonary arterial hypertension: call for a refined assessment. *ERJ Open Res* 2021; 7: 00854-2020.
25 Weatherald J, Boucly A, Launay D, *et al.* Haemodynamics and serial risk assessment in systemic sclerosis associated PAH. *Eur Respir J* 2018; 52: 1800678.
26 Galiè N, Barberà JA, Frost AE, *et al.* Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; 373: 834–844.
27 McLaughlin VV, Vachiery JL, Ouidiz RJ, *et al.* Patients with pulmonary arterial hypertension with and without cardiovascular risk factors: results from the AMBITION trial. *J Heart Lung Transplant* 2019; 38: 1286–1295.

28 Langleben D, Channick R, Delcroix M, *et al.* Safety and efficacy of macitentan in elderly patients with pulmonary arterial hypertension (PAH): insights from SERAPHIN. *J Am Coll Cardiol* 2020: 75: Suppl. 1, 2090–2092.

29 Pulido T, Adzerikho I, Channick RN, *et al.* Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013; 369: 809–818.

30 Channick R, Medrek S, Delcroix M, *et al.* Effect of macitentan across prognostic age groups in patients with pulmonary arterial hypertension (PAH). *Pulm Circ* 2021; 11: Suppl., Abstract 0015.

31 Sitbon O, Channick R, Chin KM, *et al.* Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2015; 373: 2522–2533.

32 Rosenkranz S, Channick R, Chin KM, *et al.* The impact of comorbidities on selexipag treatment effect in patients with pulmonary arterial hypertension: insights from the GRIPHON study. *Eur J Heart Fail* 2022; 24: 205–214.

33 Rosenkranz S, Pausch C, Coghlan J, *et al.* Risk stratification and response to therapy in patients with pulmonary arterial hypertension and comorbidities: a COMPERA analysis. *J Heart Lung Transplant* 2023; 42: 102–114.

34 Hoeper MM, Pausch C, Grünig E, *et al.* Temporal trends in pulmonary arterial hypertension: results from the COMPERA registry. *Eur Respir J* 2022; 59: 2102024.

35 Kianzad A, van Wezenbeek J, Celant LR, *et al.* Idiopathic pulmonary arterial hypertension patients with a high H_2FPEF-score: insights from the Amsterdam UMC PAH-cohort. *J Heart Lung Transplant* 2022; 41: 1075–1085.

36 Badagliacca R, D'Alto M, Ghio S, *et al.* Relevance of comorbidities on initial combination therapy in pulmonary arterial hypertension. *ERJ Open Res* 2022; 8: 00298-2022.

37 Wissmueller M, Xanthouli P, Benjamin N, *et al.* Profiles and treatment patterns of patients with pulmonary arterial hypertension on monotherapy at experienced centres. *ESC Heart Fail* 2022; 9: 2873–2885.