




Age, risk and outcomes in idiopathic pulmonary arterial hypertension

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Older patients with IPAH often present with distinct phenotypes and show less improvements with targeted therapy than younger patients <http://ow.ly/vsCb30jqOB3>

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The current European pulmonary hypertension (PH) guidelines recommend a risk-based therapeutic approach to patients with idiopathic pulmonary arterial hypertension (IPAH) [1, 2]. The goal is reaching and maintaining a low risk profile. Recent studies from the French PH registry and from the European PH registry COMPERA have confirmed that IPAH patients who meet 3–4 distinct low risk criteria with targeted therapies have 5-year survival rates of 95% or higher [3, 4]. Unfortunately, this was accomplished only in 19% of the patients in the French series and 9% of the patients in COMPERA [4, 5]. The reasons why the majority of patients fail to reach a low risk profile with targeted therapies have not been fully explored.

In this issue of the *European Respiratory Journal*, HJALMARSSON *et al.* [6] present data from the Swedish PH registry showing that the likelihood that IPAH patients meet a low risk profile with targeted therapies diminishes with increasing age. Almost 80% of patients aged between 18 and 45 years reached the low risk category with PAH treatment, compared with approximately 20% of patients aged ≥ 65 years and less than 10% of patients aged ≥ 75 years. Improvements in risk category were rarely observed in patients aged ≥ 65 years. Similar data have been recently reported from COMPERA [3]. In the present Swedish series, the 5-year transplantation-free survival decreased from 88% in patients aged 18–45 years to 36% in patients aged ≥ 75 years.

The high mortality risk of older IPAH patients is probably due to various reasons including comorbidities, unique disease phenotypes, different treatment patterns, and a diminished response to PAH targeted therapies. These factors are tightly interconnected but can be assessed separately.

Increasing age and mortality in IPAH

The mean age of patients enrolled between 1981 and 1985 in the US National Institutes of Health (NIH) registry was 36 years at the time of diagnosis; only 9% of the patients were more than 60 years of age [7]. Since then, the age of IPAH patients has increased considerably, at least in Western countries [4, 8–11]. In Germany, the mean age of patients newly diagnosed with IPAH in 2014 was 65 years [12]. In a recent Swedish registry, the mean age at diagnosis was 69 years [13]. Naturally, older patients have a higher mortality risk in general, but it has already been shown that older patients (>65 years) diagnosed with IPAH have a significantly higher mortality risk than younger patients (18–65 years), even when adjusted for their respective statistical life expectancies [14].

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Comorbidities and disease phenotypes

Not unexpectedly, increasing age in the Swedish cohort was accompanied by a higher prevalence of comorbidities, in particular systemic hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation and renal insufficiency. All these comorbidities are known to increase the risk of death. Coronary heart disease and renal insufficiency were independent predictors of mortality in the Swedish IPAH cohort. The high prevalence of these comorbidities among older patients diagnosed with IPAH raise the questions whether these patients truly suffer from IPAH, or whether at least some of them actually have PH due to left heart disease, in particular heart failure with preserved ejection fraction (HFpEF). The normal pulmonary artery wedge pressure (PAWP; mean 9 mmHg) in the Swedish patients does not rule out HFpEF, which can present with normal PAWP levels at rest [15]. There is as yet no consensus among experts about how to best classify these patients [15, 16].

Another striking feature of the Swedish cohort was a male predominance among older patients with IPAH, while the younger patients were predominantly female, as has been seen in various previous series [7–9]. Several groups have recently reported on a distinct IPAH phenotype of mostly elderly male patients with precapillary PH, a history of smoking, no signs of parenchymal lung disease, but a low diffusion capacity of the lung for carbon monoxide (DLCO) [17–19]. Those patients respond poorly to PAH therapies and have an exceptionally high mortality risk [19]. In the Swedish cohort, DLCO was also significantly lower in the older patients, probably indicating that this cohort included patients with this unique “low diffusion capacity” phenotype that could suggest pulmonary capillary and vein involvement.

Today, IPAH is no longer a relatively homogeneous disease affecting mostly younger patients, but a condition where new phenotypes have been emerging predominantly, but not exclusively, among older patients. We do not even know if what we call IPAH in older patients presenting with the phenotypes described above is the same disease as the “classic” form of IPAH that we used to see back in the days of the US NIH registry, and that we still see today, albeit less frequently than older patients with more complex disease phenotypes.

Treatment and treatment response

Perhaps the most important clue to the findings by HJALMARSSON *et al.* [6] is a better understanding of how older patients respond to PAH targeted therapies. Such patients were not well represented in PAH studies. Some of the recent clinical trials in PAH had an upper age limit of 75 years, and the average age of the enrolled patients ranged from 48 to 54 years [20, 21]. Hence, most of the available data on treatment responses in older patients have been derived from registries. OPITZ *et al.* [22] have shown recently that older patients diagnosed with IPAH 1) often present with risk factors for left heart disease, 2) have little clinical improvement with PAH targeted therapies, 3) frequently experience side-effects and drug discontinuations due to side-effects when exposed to PAH targeted therapies, and 4) usually do not receive combination therapies or parenteral prostacyclin analogues. The present findings from Sweden confirm and expand these observations.

The current study from Sweden does not come without limitations. Registries usually do not have the quality of rigorous clinical studies, and missing data, as well as incorrect data entries, may have affected the results. The age stratification was arbitrary and other stratifications may have yielded different results. The sample size was relatively small (n=264 at baseline; n=220 with follow-up visits), and follow-up right heart catheterisation data were available for only 87 patients. Despite these limitations, this study adds to our understanding of treatment responses in older patients with IPAH and highlights the need to look further into this patient population.

Taken together, the increasing age of patients diagnosed with IPAH and the accompanying clinical features have substantial impact on clinical practice. Clinical trials in the PAH field have enrolled mostly younger patients with a “classical” phenotype and few comorbidities. Risk assessment and risk-based treatment strategies have been developed and validated primarily for these patients. There is, however, a considerable gap between clinical trial populations and real-world patients. Registry data show that PAH drugs are widely used in older patients with multiple comorbidities, but little is known about their safety and efficacy in these patients. The present paper by HJALMARSSON *et al.* [6] reinforces this notion by demonstrating absence of substantial clinical improvements in the majority of older IPAH patients receiving PAH therapies. Registry data help to better characterise and understand these patients, but eventually, adequate representation in randomised trials is necessary to determine the best possible care for this increasingly relevant group of patients.

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