

Management of pulmonary arterial hypertension in patients aged over 65 years

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KEYWORDS

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Historically, pulmonary arterial hypertension (PAH) has been considered a disease of young adults, but over the last three decades, the average age at diagnosis has increased, presenting clinicians with some unique challenges. Clinical symptoms of PAH, including shortness of breath and reduced functional capacity, are not specific for the disease and may be present in older patients because of their age or as a result of comorbid conditions. Eliminating other causes for these symptoms can delay PAH diagnosis and initiation of PAH-specific treatment compared with younger patients. Currently, there are no specific guidelines relating to PAH in older patients and existing guidelines for identifying patients at potential risk of PAH may not be appropriate for patients aged over 65 years. Even though older patients tend to be diagnosed with more advanced symptoms, and evidence suggests that they are less responsive to PAH-specific therapies, treatment is often less aggressive than in younger patients. Even after adjusting for age, survival rates remain disproportionately lower in the older vs. younger PAH populations. Specific guidelines for diagnosis and treatment of older patients with PAH are needed to improve care and outcomes in this growing population. This review aims to assess the challenges associated with diagnosing and managing PAH in older patients, based on literature searches, authors' experiences, and expert opinions.

Introduction

Pulmonary arterial hypertension (PAH) has historically been considered to affect young adults and predominantly women. However, data from PAH registries suggest that, over recent years, the demographics of PAH populations are changing with increases in the average age at diagnosis, the number of older patients and the proportion of male patients being reported.¹⁻³ The exact reasons for the increased incidence of PAH in older patients are unknown, but contributing factors include increased awareness and understanding of the disease; improved screening/diagnostic methods; the overall ageing of western populations; and associated increases in common age-related

comorbidities linked with vascular endothelial dysfunction.^{4,5} Improvements in PAH survival rates over the past two decades, due to a combination of new treatments and improved patient-support strategies,⁶ may also have contributed to greater life expectancy for patients with PAH in general, and particularly older patients.

The diagnosis of PAH in patients aged over 65 years is impeded by a number of factors and can be clinically challenging.⁷ Older patients tend to present with multiple comorbidities that may mask the symptoms of PAH and delay diagnosis.⁴ Furthermore, as they generally have reduced exercise capacity, older patients are more likely to be diagnosed with more advanced symptoms than younger patients.^{4,5,8}

The journey to a PAH diagnosis can have a substantial impact on a patient's quality of life, as well as living with the disease itself.⁹⁻¹¹ Most studies on patient-reported outcomes in PAH are generally concerned with aspects that are

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more relevant to non-elderly patients, such as being unable to work and the consequent financial concerns and feelings of social isolation.^{9,10} However, PAH adversely affects patients' quality of life regardless of age¹²⁻¹⁴ and being mindful of its impact on patients' daily lives can be particularly important when treating elderly patients, for whom maintenance or improvement of quality of life may be the main treatment goal. Few studies have investigated patient-reported outcomes in elderly PAH patients but a separate review in this supplement¹⁵ is devoted to the patient's perspective and discusses measures to improve disease management in more detail.

Older patients also present unique challenges in terms of treatment and management. Treatment selection is complicated by the susceptibility of many older patients to adverse events. Moreover, these patients may already be receiving a range of concomitant medications to treat comorbidities, therefore, the potential for drug-drug interactions needs to be assessed when selecting therapy. In addition, family and social support may also present more of a challenge in this population.

Despite these difficulties, no guidelines for the management of PAH in older patients currently exist. This review aims to assess the challenges associated with diagnosing

and managing PAH in older patients and address potential approaches to overcoming these challenges.

The changing profile of pulmonary arterial hypertension: registry data

For the past 30 years, PAH registries from around the globe have collected data on the demographic, clinical and haemodynamic characteristics of more than 6100 patients¹⁶⁻²³ (Table 1). In the oldest PAH registry, established by the US National Institutes of Health (NIH) in 1981,²² patients had a mean age at diagnosis of 36 years and 118/187 (63%) were female. More recent, PAH registries have since reported higher mean ages at diagnosis (Table 1), most notably in the European COMPERA (comparative, prospective registry of newly initiated therapies for pulmonary hypertension) registry established in 2007, where 63% of the 587 patients were aged >65 years.²³ One exception was in a Chinese registry, established in 1999, where the mean age at diagnosis was similar to the US NIH registry. This discrepancy has been attributed to a lack of diagnosis of PAH in older patients in China perhaps due to shortcomings in the healthcare system and poor economic conditions.²⁵

Table 1 Demographics and pulmonary arterial hypertension characteristics of patients included in registries^a

Registry	US NIH ²²	Switzerland ²⁰	China ¹⁶	UK/Ireland ²¹	France ¹⁸	US REVEAL ²⁴	COMPERA ^{23b}	Czech Republic ¹⁷	Spain ¹⁹
Year of initiation	1981	1998	1999	2001	2002	2006	2007	2007	2007
Year of first data report	1987	2015	2007	2012	2006	2010	2013	2014	2012
Number of patients	187	517	72	482	674	2525	587	191	866
Study cohort									
Incident ^c	✓	-	✓	✓	-	-	✓	-	-
Incident and prevalent ^d	-	✓	-	-	✓	✓	-	✓	✓
Age (years), mean (SD)	36 (15)	57 (16)	36 (12)	50 (17)	50 (15)	53 (14)	71 (16) ^e	52 (17)	45 (17)
Female (%)	63.1	60.0	70.8	69.9	65.3	79.5	60.3	65.5	71.0
Time from first symptoms to diagnosis (months), mean (SD)	24.4 (58.8)	NP	26.4 (27.6)	18 (9-36) ^e	27 ^f	35.6 (37.9)	NP	39 (48)	42 (73)
6MWD (m), mean (SD)	NP	357 (137)	NP	292 (123) ^g	329 (109)	366 (126)	293 (126)	324 (120)	363 (120)
Haemodynamics, mean (SD)									
RAP (mmHg)	10 (6)	9 (4)	12.8 (5.6)	10 (6) ^h	8 (5)	9 (6)	8 (5)	10 (5)	9 (5)
mPAP (mmHg)	60 (18)	48 (15)	64.1 (17)	54 (14) ⁱ	55 (15)	51 (14)	44 (12)	59 (63)	54 (16)
PVR (Wood units)	NP	9.4 (5.6) ^j	20.4 (8.0)	12.8 (6.3) ^k	NP	NP	9.6 (5.5)	NP	12 (6)
PVRI (Wood units·m ²)	26.2 (13.8)	NP	NP	23.1 (10.1) ^l	20.5 (10.2)	21.1 (12.5)	NP	NP	NP

6MWD, 6-min-walk distance; COMPERA, comparative, prospective registry of newly initiated therapies for pulmonary hypertension; mPAP, mean pulmonary arterial pressure; NIH, National Institutes of Health; NP, not presented; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; RAP, right atrial pressure; SD, standard deviation.

^aPulmonary arterial hypertension-only where reported, idiopathic pulmonary arterial hypertension otherwise.

^bAustria, Belgium, Germany, Italy, the Netherlands, Switzerland, and UK.

^cNewly diagnosed patients.

^dPreviously diagnosed patients.

^eMedian (interquartile range).

^fSD not provided.

^gn = 260.

^hn = 439.

ⁱn = 457.

^jn = 440.

^kn = 395.

^ln = 355.

Table 2 Demographics and pulmonary arterial hypertension characteristics of patients included in registries^a by age

Registry	Switzerland ²⁰		UK/Ireland ²¹		COMPERA ^{23b}	
Cohort	Diagnosis before 2000	Diagnosis 2009-2012	≤50 years	>50 years	18-65 years	>65 years
Number of patients	24	171	NP	NP	209	378
Age (years), mean (SD)	42 (16)	60 (15)	36.5 (9.3)	65.1 (8.3)	54 (16) ^c	75 (8) ^c
Female (%)	66.7	55.6	73.2	66.5	69.4	55.3
Time from first symptoms to diagnosis (months), median (IQR)	NP	NP	12 (6-24)	24 (12-36)	NP	NP
6MWD (m), mean (SD)	341 (120)	366 (139)	330 (119)	246 (112)	340 (131)	266 (114)
Haemodynamics, mean (SD)						
Cardiac index (L/min ⁻¹ /m ²)	2.6 (0.9)	2.6 (0.8)	2.1 (0.7)	2.1 (0.7)	2.2 (0.7)	2.2 (0.7)
RAP (mmHg)	9 (4)	9 (8)	10.0 (5.8)	10.2 (6.1)	9 (5)	8 (5)
mPAP (mmHg)	55 (18)	46 (12)	57.2 (14.9)	51.0 (12.2)	50 (13)	41 (10)
PVR (Wood units)	10.1 (5.4)	8.5 (5.2)	13.9 (6.7)	11.8 (5.8)	12.0 (6.3)	8.3 (4.5)

6MWD, 6-min-walk distance; COMPERA, comparative, prospective registry of newly initiated therapies for pulmonary hypertension; IQR, interquartile range; mPAP, mean pulmonary arterial pressure; NP, not presented; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SD, standard deviation.

^aPAH-only where reported, IPAH otherwise.

^bAustria, Belgium, Germany, Italy, the Netherlands, Switzerland, and UK.

^cMedian (interquartile range).

Results from registries that reported data by year of diagnosis or by age at diagnosis also showed increases in the mean age of diagnosis²⁰ and the proportion of male patients being diagnosed²³ (Table 2). Although older patients are more likely to have more severe symptoms and lower percent diffusing capacity of the lung for carbon monoxide (DL_{CO}), and shorter 6-min-walk distance (6MWD),^{21,23} they tended to have less severe haemodynamics (Table 2).

Diagnosis of pulmonary arterial hypertension in older patients

General considerations

The diagnosis of PAH is complex, and even more so as patients age. Consequently, patients may be referred to various specialists resulting in delays to diagnosis confirmation.²⁶ Across the registries, the mean duration between symptom onset and diagnostic confirmation of PAH ranged from 24 to 36 months (Table 1) with the UK/Ireland registry reporting that the median duration of symptoms prior to diagnosis in older patients was double that for younger patients (24 vs. 12 months)²¹ (Table 2). Older patients often present with multiple comorbidities²¹ that may complicate and delay a diagnosis of PAH. Systemic hypertension, ischaemic heart disease, dyslipidaemia, diabetes, and arrhythmia are among the most common comorbidities reported in older patients,^{21,27,28} and they are more prevalent in this population compared with younger adults, as evidenced across two studies that defined older as >50 years of age,²¹ and ≥75 years of age.²⁷ Comorbid cardiovascular and metabolic diseases are also commonly observed in the general PAH population²⁴ and management of PAH in these cases is fully discussed in a separate review in this supplement.²⁹

Identification of PAH as the leading pulmonary hypertension (PH) diagnosis in older patients is important so as not to mix the true PAH population with patients in whom disorders relating to PH Group 2 (left heart disease), Group 3 (lung pathology/hypoxia), or even Group 4 [chronic thromboembolic PH (CTEPH)] are the primary condition responsible for disease progression.²⁶ Incorrect diagnoses could result in inappropriate treatment choices being made, particularly as therapies for treating PAH are often contraindicated for Group 2 and Group 3 PH.²⁶ In order to form a correct diagnosis, it is also important to discriminate PAH from secondary causes commonly seen in older populations, such as coronary artery disease (CAD), left ventricular diastolic dysfunction, or dyspnoeic conditions like chronic obstructive pulmonary disease.^{4,30,31}

Differentiating clinical signs of PAH from those related to ageing or comorbidities add to the time required for diagnosis. PAH is a progressive disease and greater deterioration as a consequence of delayed diagnosis may be one of the reasons older patients with PAH are typically less responsive to therapy. However, older patients with PAH do tend to present with less severe haemodynamic measures associated with worse functional impairment than in younger adults with PAH, suggesting that a slightly different mechanism of disease progression may be at work, and it is also possible that this is the reason for poorer response to PAH treatment in older populations. Nevertheless, timely diagnosis is important for this vulnerable population.^{3,21,23}

Pulmonary arterial hypertension should, therefore, always be considered in older patients presenting with appropriate symptoms, but care must be taken to ensure that appropriate steps are taken to determine the correct diagnosis.

Diagnostic process

The diagnostic process for PAH in older patients should follow that recommended in the current guidelines for PAH,^{32,33} but with additional considerations specific for older patients. The recommended process involves clinical examination, electrocardiogram, chest radiography, pulmonary function tests, 6MWD, arterial blood gas analysis, echocardiography, ventilation/perfusion scanning, and high-resolution computed tomography prior to mandatory confirmation via right heart catheterization (RHC).³² In older patients, challenges in undertaking some of these examinations need to be taken into consideration.

Clinical examination

The main clinical symptoms of PAH at initial presentation (e.g. shortness of breath, reduced exercise tolerance) are non-specific and shared with a variety of other, much more common, age-related comorbid conditions, including left heart disease, aortic stenosis, and impaired lung function.^{4,28,30} Consequently, PAH may not be an immediate consideration for the cause of the symptoms. Physician awareness of PAH is, therefore, particularly important when dealing with older patients so that further diagnostic testing and potential specialist referral can take place in a timely manner.³²

Echocardiography

Echocardiography is a vital tool for the screening and monitoring of PAH.³² However, the measurement of certain echocardiographic parameters can be less reliable in older patients. Atrial fibrillation, which is often seen in older patients who have cardiac/valvular comorbidities, can complicate echocardiographic analyses, reducing the reliability of atrial size measurements and estimates of left ventricular filling pressures and mitral annular velocities.³⁴⁻³⁸ In addition, distinguishing between echocardiographic changes due to PAH from those due to, for example, age or left heart disease can be challenging in older patients.⁴

Exercise testing

The physical condition of older patients should be considered when interpreting 6MWD data. Age-related changes in a number of pulmonary function parameters (e.g. progressive decline in lung function), as well as pulmonary and systemic haemodynamic measures, may lead to reduced exercise tolerance in older patients and should be considered separately from changes that may be due to pulmonary vasculopathy. It should also be considered that older patients often exhibit reduced mobility due to additional factors such as osteoporosis, arthritis, or other musculoskeletal pathology (e.g. hip/knee fractures or hip replacement).

Ventilation/perfusion scanning

Ventilation/perfusion should be used to rule out a diagnosis of CTEPH.³²

Right heart catheterization

A 2018 study concluded that RHC could be successfully used in the diagnosis of PH regardless of age.³⁹ However, it

should be noted that certain difficulties can present in the recording and interpretation of RHC results in older patients.

Measurement of pulmonary artery wedge pressure (PAWP) allows differentiation between PAH (pre-capillary PH) and PH due to heart failure with preserved left ejection fraction, which is common in elderly patients and those with Group 2 PH classification (post-capillary). However, PAWP can be falsely low/normal in patients who do actually have elevated left ventricle end-diastolic pressure (LVEDP), for example with patients treated with diuretics.⁴⁰ Therefore, it is often necessary to use exercise or fluid challenge during RHC to determine the true resistive properties of the pulmonary vessels. However, measuring PAWP during exercise testing is a complex procedure and, moreover, as exercise capacity and mobility may be reduced in the elderly, fluid challenge may be preferable.⁴¹ In patients with an increased PAWP, the diastolic pulmonary gradient can be used to help distinguish patients with a true pre-capillary component in a post-capillary setting.^{1,4} Similarly, the transpulmonary pressure gradient can be used to discriminate between 'passive' PH and 'reactive' PH, but this can be influenced by pulmonary circulation characteristics and age-related vascular stiffness, so should be interpreted with caution.^{1,4}

Taking all these factors into account, *Figure 1* illustrates a proposed algorithm for diagnosing PAH in older patients based on haemodynamic evaluations.

Management of pulmonary arterial hypertension in older patients

General considerations and treatment goals

Older patients with PAH are more likely to have more severe symptoms compared with a younger cohort, although haemodynamic impairments tend to be less extensive. While younger patients with PAH are more likely to be diagnosed in New York Heart Association (NYHA)/World Health Organization (WHO) functional Class I/II, older patients generally have a more severe functional class (III/IV), and lower exercise tolerance.^{21,23} Furthermore, a subgroup of PAH patients who present with low DL_{CO} (<45% predicted) has been identified. These patients were more frequently older, male, and smokers, had more comorbidities (including coronary disease), a poorer prognosis, and worse pulmonary function, exercise capacity and survival rate than other patients with PAH.⁴⁵ However, their haemodynamic profile is similar to other age-matched patients and they are without bone morphogenetic protein receptor Type 2 gene (*BMPR2*) mutations, the most important genetic predisposition factor for PAH.⁴⁶ This low DL_{CO} patient subgroup, who present with different risk factors and comorbidities to patients with higher DL_{CO} values, may be enriched in older populations and could account for the increased mortality seen in older vs. younger patients.

Another reason for poorer survival in older patients may be that treatment goals differ from those for younger patients. The primary focus of treatment in older patients is likely to be improvement or maintenance of quality of life and palliative care. It should also be considered that, in

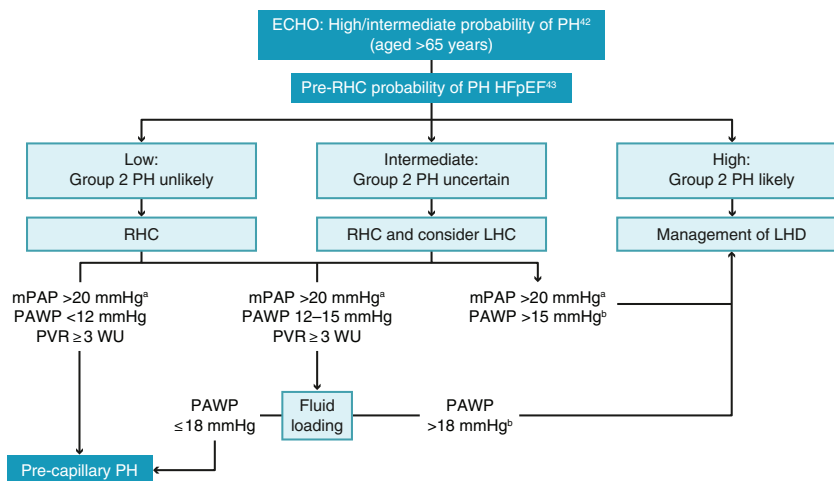


Figure 1 Algorithm for haemodynamic evaluation of suspected pulmonary arterial hypertension in patients aged >65 years.^{42,43} This reflects the recommendation from the 6th World Symposium on Pulmonary Hypertension to consider this threshold as the upper limit of normal value.⁴⁴ Please note the 2015 ESC/ERS Guidelines use the threshold value of 25 mmHg for mean pulmonary arterial pressure measurements.³² ^bConsider left ventricle end-diastolic pressure validation. ECHO, echocardiography; HFpEF, heart failure with preserved ejection fraction; LHC, left heart catheterization; LHD, left heart disease; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WU, Wood units.

general, the systemic and pulmonary vasculature of older patients is less responsive to vasodilation due to vascular stiffening and reduced left heart compliance (with progressive left ventricular diastolic dysfunction)^{30,47} and may be less responsive to PAH-specific therapies.^{23,48} In addition, improvement in exercise capacity should be individualized based on patient age and take into account any comorbidities present, particularly those affecting mobility. Given the reduced survival times seen in older patients, there is a need to individually optimize treatment, especially in those patients with very low DL_{CO}, which could represent covert pulmonary veno-occlusive disease.

Despite a generally worse prognosis for older patients, they tend to be treated less aggressively than younger patients. In the UK/Ireland registry, significantly fewer patients aged >50 years vs. ≤50 years received sequential combination therapy (34.5% vs. 57.6%, $P < 0.001$), triple combination therapy (1.3% vs. 10.6%, $P < 0.001$) or prostacyclin analogues (28.1% vs. 51.8%, $P < 0.001$).²¹ Similarly, in the COMPERA registry, in the first 3 months following diagnosis, fewer patients aged >65 years (compared with those aged 18–65 years) received prostacyclin analogues (6.3% vs. 14.4%, $P = 0.003$), endothelin receptor antagonists (ERAs) (63.2% vs. 71.3%, $P = 0.056$), and combination therapy (12.7% vs. 19.2%; $P = 0.07$).²³

These differences in therapeutic approaches between older and younger patients may have contributed to the corresponding disparities seen in the COMPERA registry in the improvement in 6MWD after 1 year (median increases of 30 and 50 m, respectively, $P = 0.028$) and overall mortality rates (22.0% vs. 12.0%, $P = 0.003$).²³ Although the smaller improvement in 6MWD could be due to other age-related mobility issues, the difference in mortality rates remained statistically significant ($P = 0.001$) after adjustment for the survival estimates of age-/gender-matched populations.²³

Each patient's expectations of any prescribed treatment should always be considered. Discussions between patients and their physicians on considerations such as life expectancy, quality of life and the benefits and risks of treatment need to be undertaken throughout the disease course and particularly before any change in treatment.

Treatment approach and risk stratification

Treatments used in the management of PAH focus on three separate signalling pathways: the prostacyclin pathway targeted with prostacyclin analogues and prostacyclin receptor agonists, the endothelin pathway, targeted with ERAs, and the nitric oxide pathway targeted with phosphodiesterase-5 (PDE-5) inhibitors and soluble guanylate cyclase stimulators.³² In younger patients, combinations of these therapies may be prescribed, but in older patients, a sequential monotherapy approach to treatment is frequently adopted with combinations of treatments only administered to patients showing little or no improvement.^{8,49,50} This less aggressive approach taken with older patients may be because current risk scoring/stratification assessments for combination treatment of PAH are based on younger cohorts of patients and cannot reliably be extrapolated directly to older patients.⁸ For example, assessments of peripheral oedema/fluid management are more important in older patients, who are more likely to have decompensated right heart failure and/or renal dysfunction.⁸ Although it is not possible to tailor risk scoring/stratification assessments so that they are applicable to older patients in general, it is important that the severity of PAH and any comorbid conditions are evaluated in each patient to aid in the decision of what, if any, combination of therapies can be used.

In general, the range and frequency of follow-up assessments in older patients receiving PAH-specific therapies

are those recommended in the current European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines (i.e. to follow-up 3 months after treatment initiation).³² Detailed reassessments, particularly with catheterization, may be beneficial in the older patient to assess for unmasking of left heart disease. A final treatment consideration is how the age of the patient may affect planning of treatment and future treatment options. Lung transplantation may eventually be required, but the upper age limit for such operations is not globally consistent (e.g. 60 years in UK, but 70 years in France). All potential medicinal options should have been assessed before surgery is contemplated, taking into account the age limit and donor organ availability.

Tolerability

In the COMPERA registry, a significantly greater percentage of patients aged >65 years discontinued treatment with the ERAs bosentan, sitaxentan, and ambrisentan compared with patients aged 18–65 years (17.2% vs. 8.1%, $P=0.014$), mainly because of an apparent lack of efficacy (65.9% vs. 58.3% of patients who discontinued these treatments). A non-significantly higher percentage of discontinuations was also seen from treatment with PDE-5 inhibitors in the older patient group (6.7% vs. 4.5%).²³ Although the number of patients reporting side effects was not presented in the COMPERA registry manuscript, there was an age discrepancy in discontinuations related to side effects following treatment with PDE-5 inhibitors (47.4% vs. 14.3% of patients receiving PDE-5 who discontinued).²³

It has been reported that older patients can be more sensitive to side effects related to PAH-specific treatments, in particular, peripheral oedema resulting from fluid retention.²¹ As side effects of medications can have a significant impact on patient quality of life, treatment decisions need to be thoroughly considered and discussed with patients. This is particularly true of intravenous therapies, which can be particularly challenging for patients with arthritis, visual impairment, or social isolation.

The increased prevalence of comorbidities and associated co-medication in older patients may also increase the risk of drug-drug interactions with PAH-specific medications.¹ This, combined with the potentially greater risk of side effects, could result in a greater impact on patient quality of life compared with younger patients. These issues need to be thoroughly considered and discussed with patients, along with careful monitoring for any treatment-related complications.

Adherence to pharmacotherapy

Treatment adherence is an important issue in any chronic illness but can be especially challenging for older patients with PAH. Treatment often requires combination therapies to target multiple pathways and older patients are more likely to already be taking multiple medications for comorbid pathologies. A systematic literature review identified several variables that were significantly related to medication adherence in older patients.⁵¹ These included self-efficacy (belief of being able to perform a specific task under differing conditions), belief in the efficacy of the

treatment, confidence in the prescribing physician, views on natural products and home remedies, beliefs on control over their own health and perceptions of the illness. More technologically minded patients may benefit from the use of on-line or mobile phone apps to aid adherence to medications. Specialist nurses can be a vital point of contact, providing information and advice for older patients with PAH who might need help with adhering to therapy.

Outcomes in older patients

While overall patient clinical outcomes and survival have improved over recent years, in part due to the introduction of PAH-specific therapies, survival rates remain disproportionately lower in the older PAH population vs. younger patients.²

Progressively worsening survival rates were reported in older vs. younger patients over time in the COMPERA registry (1 year: 89.8% vs. 96.0%; 2 years: 78.6% vs. 90.9%; 3 years: 68.0% vs. 83.3%), and this finding persisted following adjustment for an age-/gender-matched population.²³ In the UK/Ireland registry,²¹ patients aged >50 years had a three-fold greater mortality risk vs. younger patients. These inferior survival rates may be related to a more limited response to pharmacotherapy in older patients, but it is not possible to confirm this due to the less aggressive treatment approach typically adopted in these patients.

Previous studies have shown that patients with PAH and risk factors for left ventricular diastolic dysfunction, such as CAD or with cardiac comorbidities do not display a reduced response to treatment.^{52,53} However, another study in PAH has shown that in addition to older age, cardiovascular risk factors may predict a reduced response to treatment.⁵⁴ The elucidation of whether treatment response in older, comorbid patients is similar or reduced when compared with younger patients requires further investigation.

The lower survival rate among older patients with PAH may be due to the right ventricle in older patients having less capacity to adapt following stress loading as seen by their lower pulmonary vascular resistance compared with younger patients. Lower survival rates are also likely to be related to a longer delay in diagnosis and a higher burden of comorbid conditions,²⁷ such as cardiac or lung disease associated with secondary PH.^{28,30} It has even been postulated that there is a different natural history of PAH in late-onset cases,⁵⁵ and this might be associated with older patients presenting with low DL_{CO} values, which carry a particularly poor prognosis.⁴⁵ Furthermore, it is not known why older patients should have worse symptoms but less severe haemodynamics. PAH symptom severity may be directly related to age itself, the number and severity of confounding comorbidities or physiological changes with age may decrease the response of the right ventricle to afterload. More research into these age-related differences is required.

Conclusions

The diagnosis and management of PAH in older patients are complicated by ageing *per se* and comorbid conditions associated with ageing, resulting in delays in starting

treatment and worse outcomes compared with younger patients. The goals, expectations, and treatment tolerability in older patients should be assessed on an individual basis, as they may differ from those usually experienced in a younger patient cohort. Importantly, guidelines relating specifically to older patients are needed to improve care and outcomes in this growing PAH population.

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