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Authors: Nicholas Rothbard, Abhinav Agrawal, Conrad Fischer, Arunabh Talwar, Sonu Sahni

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Pulmonary arterial hypertension in the elderly: Clinical perspectives

Nicholas Rothbard[1], Abhinav Agrawal[2], Conrad Fischer[1,3], Arunabh Talwar[2], Sonu Sahni[1, 3]
[1]Touro College of Osteopathic Medicine, Department of Primary Care, New York, NY, USA
[2]Northwell Health System, Department of Pulmonary, Critical Care and Sleep Medicine, New Hyde Park, NY, USA
[3]Brookdale University Hospital Medical Center, Department of Medicine, Brooklyn, NY, USA

Address for correspondence: Sonu Sahni, MD, Touro College of Osteopathic Medicine, Department of Primary Care, 230 W 125th Street, New York, NY 10027, USA, tel: (646) 981-4507, fax: (212) 678-1784, e-mail: sahni.sonu@gmail.com

Abstract

Pulmonary hypertension (PH) is a rare and devastating disease characterized by progressive increases in pulmonary arterial pressure and pulmonary vascular resistance, which eventually leads to right ventricular failure and death. Pulmonary arterial hypertension (PAH) (World Health Organization Group I), a subset of PH, and may be idiopathic in nature or associated with other systemic conditions and is thought to most commonly effect women, the majority of whom are of childbearing age. However, PAH in the elderly population is being increasingly diagnosed creating clinical considerations that had once not been considered. Often in an elderly population the diagnosis of PAH may be delayed due to chronic comorbid conditions such as coronary artery disease or other dyspneic conditions. Though survival and clinical outcomes have improved, the elderly population continues to have disproportionately lower survival rates. High clinical suspicion of PAH warrants a complete diagnostic workup with right heart catheterization. Upon diagnosis, PAH specific therapy should be initiated with possible drug interactions in mind. Adjuvant pulmonary rehabilitation should be considered as a conservative measure with definitive results. Finally, psychosomatic aspects of the disease should also be considered in elderly populations.

Key words: pulmonary hypertension, pulmonary arterial hypertension, pulmonary hypertension in the elderly, geriatric medicine, pulmonary vascular disease

Introduction

Pulmonary hypertension (PH) is a rare and devastating disease characterized by progressive increases in pulmonary arterial pressure and pulmonary vascular resistance, which eventually leads to right ventricular failure and death [1, 2]. Pulmonary hypertension is defined hemodynamically as a mean resting pulmonary artery pressure (mPAP) greater than or equal to 25 mmHg as confirmed by right heart catheterization (RHC). The World Health Organization (WHO) has proposed a classification system for PH based on common clinical features and etiology, which is outlined in Table 1 [3]. Regardless of classification efforts, PH remains to be a clinical challenge due to its complex pathogenesis, limited disease specific therapies and healthcare disparities [4].

Pulmonary arterial hypertension (PAH) (WHO Group I PH), may be idiopathic in nature or associated with connective tissue diseases, congenital heart disease, portal hypertension, HIV or drug induced and is thought to most commonly effect women, the majority of whom are of childbearing age [3, 5, 6]. Due to disease recognition and readily available advanced diagnostic modalities, PAH in the elderly population is being increasingly diagnosed. Recent data has shown that there was a shift in the demographics of PAH with initial diagnosis coming at an older age, creating clinical considerations once not thought of [7, 8]. Though the underlying causes of PAH are well studied, in the elderly it presents a clinical challenge to the standard therapeutic algorithm. This review article will serve to describe the changing epidemiology and challenges clinicians face in the diagnosis and management of PAH in the elderly population.

Methods

A comprehensive literature search was conducted of the National Library of Medicine's MEDLINE/PubMed with the objective of identifying all articles published in the English language between January 1980 and May 2018 with "elderly" and "pulmonary arterial hypertension" in the title. Combinations of medical subject heading terms including "pulmonary arterial hypertension," "changes with age" and "management of pulmonary hypertension in the elderly" were used. Recent publications were mainly selected, but older works were not excluded provided that they were widely referenced. Reference lists were also searched of all articles

identified by this search strategy and those that were judged to be relevant were also selected. All pertinent reports were retrieved and the relative reference lists were systematically searched in order to identify any potential additional studies that could be included. All data were accessed between January 2017 and May 2018.

General considerations

Pulmonary arterial hypertension is characterized by a specific pattern on pulmonary hemodynamics. During RHC, there is an added criterion of pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg) with an absolute increase in pulmonary vascular resistance (PVR) (> 3 WU), and is labeled as pre-capillary PH [9]. Histologically, this group of conditions is characterized by vascular specific changes such as endothelial and fibroblast dysfunction. These molecular level changes affect different pathways implicated in the specific therapy of PAH. Among them are the nitric oxide, endothelin and prostacyclin pathways.

The health care burden of PH has also increased in the recent decades [10]. Secondary causes of PH are the still the most common in the elderly population such as PH due to left heart disease (WHO Group 2 PH) and PH due to lung disease/hypoxia (WHO group 3 PH) [11]. The incidence of PH with heart failure with preserved ejection fraction (HFpEF) was noted to be between 36% to 83% based on recent studies [12–14]. In contrast to pre-capillary PH (PAH), left heart disease causes post-capillary PH secondary to backward transmission of elevated left-sided filling pressures into the pulmonary circulation. These patients may demonstrate either isolated post-capillary PH or combined post-capillary PH along with a component of pre-capillary PH. In these patients, invasive hemodynamics show a combination of elevated PCWP and increased PVR [9]. Thus, despite the presence of clear definitions an increasing number of patients are noted to have simultaneous existence of multiple categories of PH. This is especially relevant in the elderly population who have a have increased co-morbidities associated with HFpEF such has arterial hypertension, atrial fibrillation and age related diastolic dysfunction.

Pulmonary arterial hypertension remains a relatively rare diagnosis in the elderly as well as WHO Group IV, chronic thromboembolic PH (CTEPH) [15]. In the elderly, management of PH due to secondary causes is dictated by the etiology and disease severity. Diagnosis in the elderly is often elusive due to non-specific findings including shortness of breath, fatigue, weakness, angina and syncope; these symptoms are largely due to right ventricular dysfunction

[9]. In a study by Shapiro et al. [16] examining unexplained PH in the elderly population it was found that despite in the absence of secondary causes of PH the elderly population did not meet the diagnostic hemodynamic criteria for PAH due to elevated PCWP [16]. A strong clinical suspicion and complete diagnostic workup including a RHC should be considered if PAH is in the differential.

Epidemiology

Traditionally it has been thought that PAH is a disease of the young, however, studies have shown that the number of elderly patients (age ≥ 65 years) being diagnosed with PAH is increasing. United States registry data suggests that PAH has an older age at diagnosis as compared with the National Institute of Heath registry study performed in the 1980s, with nearly 17% of the cohort 65 years of age at the time of diagnosis in the last decade [17–19]. A multinational European registry has found that up to 63% of patients in a cohort of PAH were aged 65 years or older [8]. Baseline characteristics of PAH patients across various registries has been outlined in Table 2 [7, 8, 18–23].

There appears to be a trend of diagnosis of PAH occurring at a later age (Fig. 1). In the latest epidemiological registry results, it was found by Mueller-Mottet et al. [23] that since 2000, the age of Swiss PAH patients has been gradually getting older. A study by Hoeper et al. [8], the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) revealed the highest median age (71 ± 16 years) at diagnosis was reported in the literature with a majority of patients being of the elderly population. The Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL) found that being a male greater than 60 years of age showed an increased risk of mortality [24]. This observed trend may due to various reasons including delay in diagnosis as it is known that the mean duration between symptom onset and diagnostic catheterization has been reported to be approximately 2.8 years [18]. In the elderly population, this may hold especially true due to the rare nature of the disease and presence of other comorbid dyspneic conditions such as chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD). In a study by Shimony et al. [25] it was found that in the cohort of patients age 65 and older there was a 4.6 times greater prevalence of significant CAD than those individuals less than age 65, which may lead to dyspnea and further delay the diagnosis of PAH. Delays in diagnosis may be detrimental as elderly patients tend to

present at a worse functional class, which may due to their underlying comorbidities or even extrinsic factors such as socioeconomic status [26, 27].

Diagnostic considerations

The diagnosis of PH requires a high degree of clinical suspicion based on symptoms and physical examination. This is followed by a comprehensive set of investigations to assess the hemodynamics as well as to determine the etiology of the disease process. Basic work up includes electrocardiogram, chest radiograph, pulmonary function tests, 6-minute walk distance (6WMD), arterial blood gas, echocardiography, ventilation/perfusion scan and high-resolution computed tomography [6]. It is also important to assess for left atrial pressures to rule out group II PH. Pressure measurements include PAP measurements and PCWP as a surrogate of left atrial pressure. Derived variables include calculating a PVR and transpulmonary pressure gradient (TPG). A PVR > 3WU is required for diagnosis of PAH. TPG is calculated as the difference between mPAP and PCWP and has been used to distinguish 'passive' PH (TPG < 12 mmHg) from 'reactive' PH (TPG ≥ 12). Unfortunately, the limitation of this measurement is that it is influenced by multiple determinants of mPAP including flow, resistance and left heart filling pressures. Diastolic PAP on the other hand is less influenced by PCWP at any level of stroke volume. Therefore the 2015 PH guidelines recommends diastolic pulmonary gradient (DPG) defined as diastolic PAP — mean PCWP as the best approach to determine the presence of pulmonary vascular disease. Thus in a patient with mPAP ≥ 25 mmHg and PCWP > 15mm Hg, a DPG < 7 mmHg and/or PVR ≤ 3 WU reflects the presence of isolated post-capillary PH while a DPG ≥ 7 mmHg and/or PVR > 3 WU represents combined post-capillary and pre-capillary PH.

Pulmonary vasoreactivity testing during the RHC is also considered for patients with PAH. A positive response is defined as reduction of mPAP > 10 mmHg to reach an absolute value of mPAP of ≤ 40 mmHg with an increased unchanged CO. Coronary angiography should be considered in patients with risk factors of CAD or in patients being listed for pulmonary endarterectomy or lung transplantation [28].

Management

At present curative options for PAH are limited to lung transplantation which in the elderly has shown to carry an increased risk of mortality [29]. However, over the past decade

targeted pharmaceutical options have become available for the treatment of PAH (Table 3) [9, 30]. There are different classes of medications available with different mechanisms of actions, all of which net a vasodilatory and anti-proliferative effect [9, 30]. If PH is suspected all efforts must be made to exclude secondary causes. Once a definitive diagnosis of PAH has been made with RHC, drug specific therapy should be initiated. Certain considerations should be observed in this population relating to therapeutic response. In general, elderly patients are weaker responders to vasodilatory effects which may due to age related vascular stiffening of the pulmonary arteries. It has been shown that a significant age-related increase in pulmonary artery systolic pressure exists and increases about 1 mmHg annually [31, 32]. Additional special considerations need to be taken in the geriatric population while using PAH specific therapy. These considerations set forth by the Food and Drug Administration have been outlined in Table 4 [33].

Pharmacotherapy of PAH should be addressed in a cautious way. A majority of patients of the elderly age group diagnosed with PAH also tend to have underlying chronic comorbidities. In the United Kingdom PAH registry, it was found that in patients greater than age 50, nearly all patients suffered from systemic hypertension, more than half from diabetes as well as ischemic heart disease [7]. These patients should have their co-morbid conditions managed optimally to reduce the synergistic effects on PAH.

In the elderly population, delayed diagnosis usually means advanced disease at presentation. With evidence pointing towards initial combination therapy, the use of multiple drugs working on multiple PAH pathways creates the possibility of drug-drug interactions in the elderly population. The PDE-5 sildenafil is metabolized via the cytochrome P450 pathway specifically involving CYP3A4 and CYP2C9. There is an increase in sildenafil bioavailability and reduced clearance with CYP3A4 substrates and inhibitors and CYP3A4 substrates plus beta-adrenoceptor blockers. Drugs that are CYP3A4 inducers such as barbiturates, rifampicin and St. John's wort may lower sildenafil levels and should be used with caution. Sildenafil levels are modestly increased by fresh grapefruit juice, a weak inhibitor of CYP3A4 [34].

The ERA bosentan is an inducer of cytochrome P450 isoenzymes CYP3A4 and CYP2C9. Plasma concentrations of drugs metabolized by these isoenzymes will be reduced when co-administered with bosentan. Of note is that the combination of a potent CYP3A4 inhibitor (ketoconazole, ritonavir) and/or a CYP2C9 inhibitor (e.g. amiodarone, fluconazole) with

bosentan may cause a significant increase in plasma bosentan levels and thus is contraindicated. Interactions may theoretically occur with certain antifungals as well as immunosuppressive drugs. It is also important to note that bosentan is often administered concomitantly with sildenafil as part of dual PAH therapy. It has been found that bosentan significantly decreases the plasma concentration of sildenafil when co-administered to patients with PH [35]. A detailed outline of PAH specific medications and interactions with commonly used drugs is shown in Table 5 [36].

Currently there are no guidelines on treatment of PAH specifically in the elderly. Treatment of PAH is dictated by WHO functional class at presentation [9, 30]. However there has been a trend towards the use of oral medications such as Bosentan over intravenous or inhalation prostacyclins, possibly due to the ease of use and compliance [25]. In addition, it has been observed that there is a tendency to use monotherapy in the elderly as observed in the COMPERA trial as well as in the United Kingdom population [8].

Another aspect to consider in pharmacotherapy treatment of elderly patients diagnosed with PAH is the presence of risk factors for concurrent left heart disease. Several registries have documented a change in phenotype of patients with PAH with increasing age [7, 8]. The terms typical and atypical PAH have been proposed to distinguish between these two populations [12]. Opitz et al. [12] in their review of the COMPERA trial, noted that patients with atypical PAH share features of both typical PAH and PH-HFpEF indicating that there might be a continuum between these conditions. Multiple studies have demonstrated that these patients with risk factors of left heart disease presenting with pre-capillary PH (atypical PAH) may benefit from targeted therapies [12, 28, 37, 38]. Opitz et al. [12] also demonstrated the potential benefits of targeted PH therapies in patients with HFpEF and combined post-capillary and pre-capillary PH.

Thus, future studies are warranted to identify treatment strategies for this patient population. This is especially important in the elderly population, as there is a growing number of PH-HFpEF patients diagnosed as PAH, and the efficacy of specific PAH therapy may decline and side effects may become more prominent.

Pulmonary rehabilitation

Pulmonary rehabilitation (PR) is defined as a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not

limited to, exercise training, education, and behavior change, all designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote long-term adherence of health-enhancing behaviors [39]. The primary goal of PR programs is to improve function, disease related symptoms, optimize functional capacity and an overall improvement in quality of life (QoL) [40]. A multinational European study by Spruit et al. [41] found that there are still large differences among PR programs across continents. Their findings stress the importance of future development of processes and performance metrics to monitor PR programs to begin standardization, and to provide recommendations for internationally evidence based guidelines.

Pulmonary rehabilitation has been well-studied and has been demonstrated to reduce dyspnea, increase exercise tolerance and improve health-related QoL in patients with COPD and idiopathic pulmonary fibrosis in the elderly [39, 42, 43]. While there are fewer trials of PR in patients with PAH, they also show that PR improves exercise capacity, muscle strength and health-related QoL [44]. A recent study by Talwar et al. has shown that patients across all groups of PHTN with an average age of 67.7 ± 11.6 years there was improvement in exercise tolerance as measured by miles per hour. Being that PR is a conservative treatment, philosophy dictates consideration in pharmacologically optimized PAH patients, utilization in the elderly population may be beneficial. It may also be beneficial in patients who have been deemed unable to receive pharmacotherapy. Though these small trials have provided beneficence in an elderly population, certain precautions must be taken prior to initiation, including a pulmonary and cardiac clearance.

Several studies have also found that PR improves numerous clinical endpoints. Mereles et al. [45], found that 30 patients with either idiopathic PAH or CTEPH experienced improvements in 6MWD and QoL self-assessment scores; importantly, rehabilitation was well-tolerated and deemed to be safe. Another study found an improvement in 6MWD, resting heart rate, peak oxygen consumption, oxygen saturation and systolic pulmonary artery pressure in patients with PH due to connective tissue disease [46]. Though these study cohorts were not exclusively elderly patients it may be inferred that they provide a similar benefit.

Psychosomatic considerations

Pulmonary arterial hypertension is a debilitating lung disease characterized exertional dyspnea, exercise intolerance, palpitations, fatigue and even syncope. Besides the somatic effects of the disease the elderly population is more averse to the psychological effects of the disease. In the elderly population where disease severity may be at a peak or pharmacotherapy contraindicated, improving psychosomatic manifestations of the disease may be the only option. Assessing psychological and somatic effects of the disease may be difficult, however with the use of a standardized instrument may be advantageous. Recently the PAH-SYMPACT questionnaire demonstrated to be a valid patient self-reporting tool to measure the impact that PAH is having on an individual [47].

It has been well documented that depression and diminished mental functioning are part of the PAH picture [40, 48]. In addition, disease-specific symptoms such as shortness of breath can adversely affect health related QoL (HRQoL), increase anxiety and be independently related to depression [49–51]. HRQoL in patients with PAH has been shown to be correlated with 6MWD and may affect WHO functional class status [51]. Worsening HRQoL and depressive symptoms may result in a decrease in physical activity, which reduces exercise tolerance and worsens dyspnea — this notion is supported by evidence that exercise and PR has been demonstrated to improve exercise capacity and WHO functional class [46, 52]. As noted above, dyspnea is independently related to depressive symptoms; another study that patient self-reported dyspnea negatively correlates with a reduced mental and physical QoL [40]. Taken together, the evidence supports the possibility of a "vicious cycle" of worsening dyspnea resulting in decreased exercise tolerance and worsening depressive symptoms, leading to decreased HRQOL which then decreases physical activity further, perpetuating the cycle as the disease progresses.

Considerations of the relationship between dyspnea, HRQoL and depression are of particular note in the elderly as depression is already a significant problem in this population: 5% of community-dwelling older adults suffer from major depressive disorder and 8% to 16% of older adults have clinically significant depressive symptoms [53]. Furthermore, rates of major depressive disorder rise as medical morbidity increases. Jackson et al. [54] found that up to 37% of patients suffer from major depressive disorder after critical care hospitalizations. Therefore, it is important for practitioners to recognize depression in elderly patients with PH and provide appropriate interventions.

Another psychosomatic aspect of PAH, often overlooked, in the elderly is fatigue. Fatigue is defined as extreme, persistent tiredness and mental, physical weakness or exhaustion and represents a psychosomatic domain of the disease [55, 56]. In the setting of PH fatigue may have a multifactorial etiology, including many conditions that can underlie PH or be associated with PH such as heart failure, obstructive sleep apnea, depression, muscle weakness and osteoporosis, so recognition and effective treatment of other contributing factors is important [57]. The studies of fatigue in PAH are rare, however in a study by Sahni et al. [58] a cohort of 42 patients comprised of all WHO groups of PH, there was an elevated level of fatigue as measured by the fatigue severity scale. In an another study, Talwar et al. [57] found that in a cohort of 21 patients with a mean age 64.3 years with advanced lung disease (COPD and ILD) there was an elevated level of fatigue as measured by the Fatigue Severity Scale and also an improvement in fatigue symptoms after completion of a PR program.

Survival

Over the past decades, with the advent of PAH specific drugs, in general the outcomes of PAH have improved [59]. However, the elderly cohort is unique in that survival of PAH patients is not as favorable as in younger populations, which may be multifactorial. In an analysis of 587 patients from the COMPERA registry all-cause mortality was 18.4%. There were 108 deaths; 25 (mortality rate, 12.0%) in the younger cohort (< 65 years of age) and 83 (mortality rate, 22.0%) in the older one ($p = 0.003$) and in younger patients, the 1-, 2-, and 3-year survival rates were 96.0%, 90.9% and 83.3%, respectively. The corresponding survival rates in the older patients were 89.8%, 78.6% and 68.0% [8]. The authors attributed the lower survival rate in the elderly cohort to limited response to pharmacotherapy and a less aggressive approach relying on monotherapy over combination therapy. In a study that analyzed data from 6 randomized treatment trials patients were categorized into three age groups following traditional cut-offs (≤ 50, 50–65, and ≥ 65 years old). It was found though that mortality rates were generally lowacross the groups, there was a significantly higher rate of mortality as age groups increased, mortality rates were 16.6%, 24.6% and 28.6% in the three age groups, respectively ($p = 0.0004$) [27].

Conclusions

Pulmonary arterial hypertension in the elderly remains to be a rare diagnosis, however it is becoming more recognized. Often in an elderly population the diagnosis of PAH may be delayed due to chronic comorbid conditions such as CAD or other dyspneic conditions. Though survival and clinical outcomes have improved, the elderly population continues to have disproportionately lower survival rates. A high clinical suspicion of PAH warrants a complete diagnostic workup with right heart catheterization. Upon diagnosis of PAH, specific therapy should be initiated with possible drug interaction in mind. Adjuvant PR should be considered as a conservative measure with definitive results. Finally, psychosomatic aspects of the disease should also be considered in an elderly population.

Conflict of interest: None declared

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Table 1. World Health Organization Classification of Pulmonary Hypertension

Group I. Pulmonary arterial hypertension (PAH)
Idiopathic PAH
Heritable PAH (BMPR2, ALK1, endoglin, SMAD9, caveolin-1, KCNK3, unknown)
Drug and toxin induced
Associated with (i) Connective tissue disease, (ii) HIV infection, (iii) Portal hypertension, (iv)

Congenital heart disease, (v) Schistosomiasis Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis Persistent pulmonary hypertension of the newborn
Group II. Pulmonary hypertension due to left heart disease Left ventricular systolic dysfunction Left ventricular diastolic dysfunction Valvular disease Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Group III. Pulmonary hypertension due to lung diseases and/or hypoxia Chronic obstructive pulmonary disease Interstitial lung disease Other pulmonary diseases with mixed restrictive and obstructive pattern Sleep-disordered breathing Alveolar hypoventilation disorders Chronic exposure to high altitudes Developmental lung disease
Group IV. Chronic thromboembolic pulmonary hypertension
Group V. Pulmonary hypertension with unclear multifactorial mechanisms Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleimyomatosis Metabolic disorders: glycogen storage disease, Gaucher's disease, hypothyroidism Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension

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BMPR — bone morphogenic protein receptor type II; HIV — human Immunodeficiency virus

Table 2. Baseline epidemiologic characteristics of pulmonary arterial hypertension registries

Registry	**NIH**	**French**	**US**	**REVEAL**	**UK/Ireland**	**ASPIRE**	**COMPERA**	**Swiss**
Year	1987	2006	2007	2010	2012	2012	2013	2015
Number	187	674	578	2525	482	175	587	171
Mean age at diagnosis [years]	36±15	50±15	48±14	50.1±14.4	50.1±17.1	55±16	71±16	60±15
Women [%]	63.0	65.3	77.0	55.6	69.9	67.0	60.3	56.0

Table 3. Medications in the management of pulmonary arterial hypertension (PAH)

PAH specific therapies	**Mode of administration**
Phosphodiesterase type-5 (PDE) inhibitors	
Sildenafil (Revatio)	Oral
Tadalafil (Adcirca)	Oral
Prostacyclin analogues	
Epoprostenol (Flolan, Valetri)	Intravenous infusion, injection
Treprostinil (Remodulin, Tyvaso, Orenitram)	Intravenous infusion, inhalation, oral
Iloprost (Ventavis)	Inhalation
Prostacyclin receptor agonist	
Selexipag (Uptravi)	Oral
Endothelin receptor antogonists (ERAs)	
Bosentan (Tracleer)	Oral
Ambrisentan (Letairis, Volibris)	Oral
Macitentan (Opsumit)	Oral
Soluble guanylate cyclase (sGC) stimulator	
Riociguat (Adempas)	Oral

Table 4. Geriatric considerations of select pulmonary arterial hypertension specific medications.

Drug	**Geriatric consideration**
Sildenafil	Clinical studies of did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.
Tadalafil	No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age.
Riociguat	No overall differences in safety or effectiveness were observed between elderly and younger subjects.
Bosentan	No conclusive evidence from clinical trials.
Ambrisentan	The elderly (age ≥ 65 years) showed less improvement in walk distances with Letairis than younger patients did. Peripheral edema was more common in the elderly than in younger patients. Improvements in walk distance with Letairis were smaller for elderly patients (age ≥ 65) than younger patients. Peripheral edema was greater in elderly patients (age ≥ 65) receiving Letairis as compared to placebo.
Mactitentan	No overall differences in safety or effectiveness were observed between these subjects and younger subjects.
Epoprostenol/iloprost/treprostinil	No conclusive evidence from clinical trials or clinical experience. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.
Selexipag	No overall differences were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients

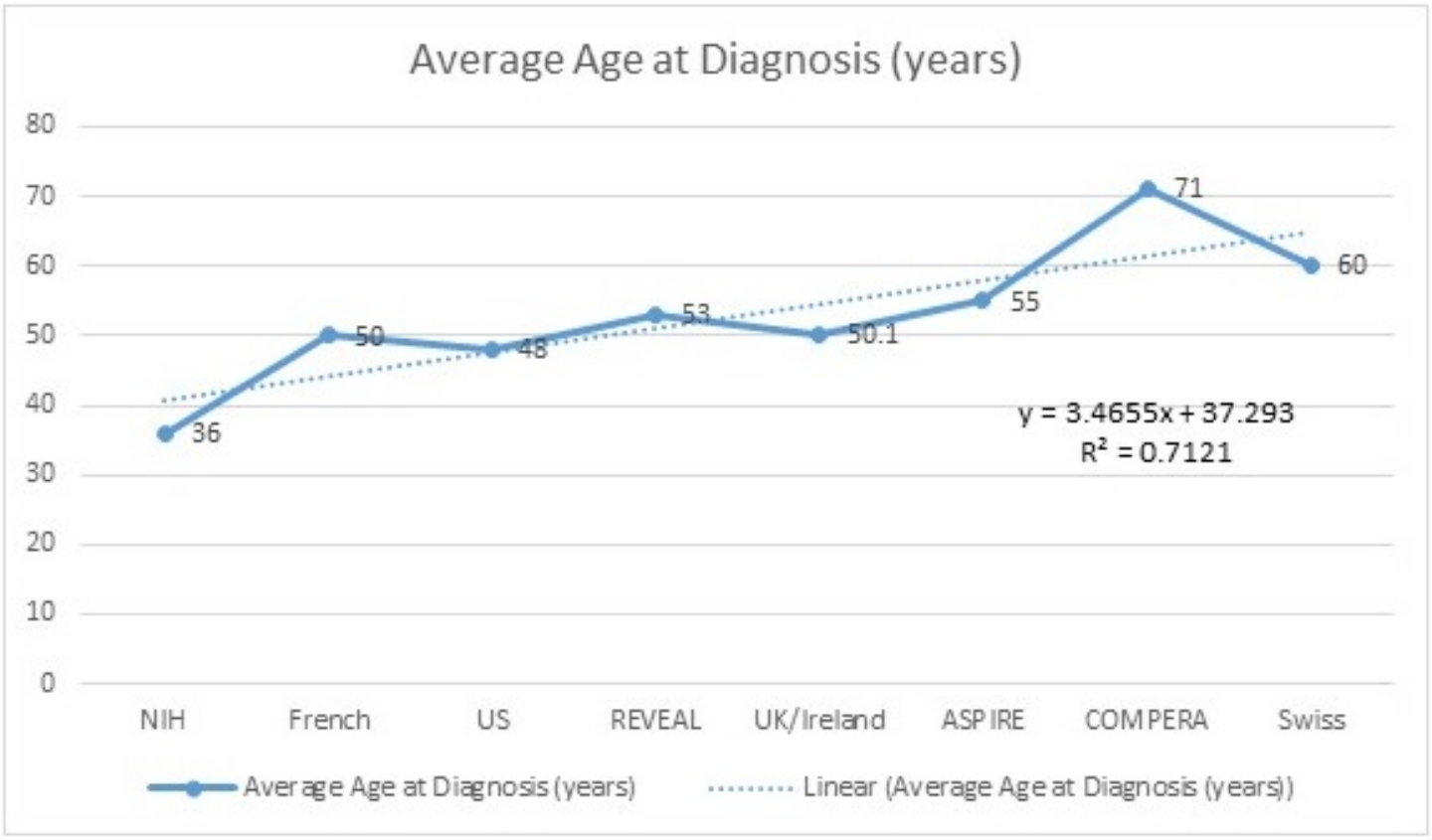
All considerations obtained from Federal Drug Administration (FDA) drug approved package inserts.

Table 5. Potential interactions between pulmonary arterial hypertension–specific medications for concurrent illnesses.

	Anti–platelets anticoagulants	**Statins**	**Digoxin**	**NSAIDs**	**SSRIs/TCAs**	**Sulph.**	**Beta–blockers**	**Barbiturates**	**Macrolides**	**Protease Inhibitors**	**Antifungals**	**Cyclosporine A**	**Hormonal contraceptives**
Prostacyclin analogues													
Epoprostenol	X	–	–	–	–	–	–	–	–	–	–	–	–
Treprostinil	X	–	–	X	–	–	–	–	–	–	–	–	–
Iloprost	X	–	–	–	–	–	–	–	–	–	–	–	–
Phosphodiesterase type–5 inhibitors													
Sildenafil	–	–	–	–	–	X	–	–	X	X	X	–	–
Tadalafil	–	–	–	–	–	–	–	–	X	–	X	–	–
Endothelin receptor antagonists													
Bosentan	X	X	–	–	–	X	–	X	X	X	X	X	X
Macitentan	–	–	–	–	–	–	–	X	X	X	X	X	X
Ambrisentan	–	–	–	–	–	–	–	–	X	–	–	–	–
Soluble guanylate ciclase stimulator													
Riociguat	–	–	–	–		X	–	X	X	–	X	–	–

NSAID — non–steroidal anti–inflammatory drug; SSRI — serotonin–selective re–uptake inhibitor; TCA — tricyclic acid; X — known interaction; ″–″ no known interaction or not clinically significant interaction

Figure 1. Chronological display of average age of diagnosis in pulmonary arterial hypertension registries.


Average Age at Diagnosis (years)
80
70
60
50
40
30
20
10
0
36
50
48
53
50.1
55
71
60
y = 3.4655x + 37.293
R² = 0.7121
NIH
French
US
REVEAL
UK/Ireland
ASPIRE
COMPERA
Swiss
Average Age at Diagnosis (years)
Linear (Average Age at Diagnosis (years))