Research Article

Pulmonary Circulation

Epidemiology and initial management of pulmonary arterial hypertension: real-world data from the Hellenic pulmOnary hyPertension rEgistry (HOPE)

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Abstract

Pulmonary arterial hypertension (PAH) is a heterogenous clinical entity with poor prognosis, despite recent major pharmacological advances. To increase awareness about the pathophysiology, epidemiology, and management of the disease, large national registries are required. The Hellenic pulmOnary hyPertension rEgistry (HOPE) was launched in early 2015 and enrolls patients from all pulmonary hypertension subgroups in Greece. Baseline epidemiologic, diagnostic, and initial treatment data of consecutive patients with PAH are presented in this article. In total, 231 patients with PAH were enrolled from January 2015 until April 2018. At baseline, about half of patients with PAH were in World Health Organization functional class II. The majority of patients with PAH (56.7%) were at intermediate 1-year mortality risk, while more than one-third were low-risk patients, according to an abbreviated risk stratification score. Half of patients with PAH were on monotherapy, 38.9% received combination therapy, while prostanoids were used only in 12.1% of patients. In conclusion, baseline data of the Greek PAH population share common characteristics, but also have some differences with other registries, the most prominent being a better functional capacity. This may reflect earlier diagnosis of PAH that in conjunction with the increased proportion of patients with atypical PAH could partially explain the preference for monotherapy and the limited use of prostanoids in Greece. Nevertheless, early, advanced specific therapy is strongly recommended.

Keywords

clinical characteristics, risk stratification, specific medical treatment, pulmonary arterial hypertension

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Introduction

Pulmonary arterial hypertension (PAH) is a rare heterogenous disease of the pulmonary vasculature, defined by an

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increased mean pulmonary artery pressure (mPAP) ≥25 mmHg, a pulmonary artery wedge pressure (PAWP) <15 mmHg, and increased pulmonary vascular resistance (PVR) ≥3 Wood Units.[1] PAH is characterized by an adverse remodeling of the small pulmonary arteries with progressive increase in PVR that eventually leads to right heart failure and death, if not treated promptly. It could be idiopathic, familial, induced by drugs and toxins, or may be associated with a wide spectrum of diseases, such as connective tissue disease (CTD), congenital heart disease (CHD), portal hypertension, or schistosomiasis.[2–4] A Task Force from the *6th World Symposium on Pulmonary Hypertension* recently proposed a new definition of pre-capillary pulmonary hypertension (PH), with mPAP > 20 mmHg, PAWP < 15 mmHg, and PVR ≥ 3 Wood Units; however, prospective trials are required to determine whether this PH population might benefit from specific management.[5]

Despite major advances in pharmacotherapy of PAH in the last 15 years,[6] we still lack thorough knowledge about the pathophysiology and the epidemiology of PAH. Although large national and international registries[7–15] have so far provided useful information on the epidemiology, the diagnosis, and management of patients with PAH, regional differences certainly exist regarding patients' characteristics, diagnostic workup, and treatment availability. Moreover, since the registries include a mix of PAH patients with advanced age and various comorbidities, there is a scientific need for more epidemiological data from different countries, with different healthcare organization and financial background, in order to obtain a more comprehensive view of PAH worldwide.

Prompted by the increasing number of patients with PH who have been treated in expert centers in Greece so far and by the lack of epidemiological and management data for the Greek population, the Hellenic Society for the Study of Pulmonary Hypertension established a national network on PH. In this initial observational study, we present baseline data regarding the epidemiology, diagnosis, and management of patients with PAH in Greece.

Methods

The Hellenic Pulmonary Hypertension Registry (HOPE) is a PH registry that was launched in January 2015 and continues to enroll patients, mainly with PAH. The HOPE registry has been approved by the Institutional Review Board of each one of the nine participating PH expert centers in Greece according to the Declaration of Helsinki. All patients provided written informed consent for their inclusion in the study. Documentation has been Internet-based (PAH tool by Inovultus Lda, Portugal) and includes demographics, type of PH according to the European Guidelines,[1] comorbidities, clinical symptoms and signs, World Heart Organization (WHO) functional class (FC), 6-minute walk distance (6-MWD), N-terminal pro-brain natriuretic peptide (NT-proBNP) serum levels, echocardiographic parameters, hemodynamics, lung function tests, computed tomography data, ventilation/perfusion scintigraphy, and detailed information about medications for PH, including supportive measures, such as oxygen therapy and anticoagulation, as well as PAH-specific medical therapy. The participating centers enter all of their eligible patients on a consecutive basis. Data are collected at the time of first visit of patients at the PH centers and at least in 6-month intervals or whenever the patient has a predefined clinical event (death, transplantation, PAH-related hospitalization, deterioration in FC, any unscheduled change in PAH therapy, or other serious adverse events).

The cut-off date for the data analysis of the present study was April 2, 2018. Inclusion criteria for this study were a diagnosis of PAH according to the definitions of the 2015 guidelines,[1] age ≥14 years, and availability of data from right heart catheterization showing an mPAP ≥25 mmHg, a PAWP ≤ 15 mmHg, and PVR ≥ 3 Wood units. The exception was patients with Eisenmenger syndrome who could be diagnosed only by echocardiography. Classification of specific PAH subtype was assigned by the investigator reporting the case to the registry. The present study focused only on patients' baseline data, that is data at the time of first visit of patients at the PH centers, since follow-up data were not available yet for the majority of PAH patients.

An abbreviated version of the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk stratification strategy was used to categorize patients as low, intermediate, or high risk, as proposed by Hoeper et al.[16] WHO FC, 6-MWD, NT-proBNP, right atrial pressure (RAP), cardiac index (CI), and mixed venous oxygen saturation at baseline were used for the risk stratification, if available.[16] The cut-off values proposed in the European guidelines[1] were graded 1–3 (1: low risk, 2: intermediate risk, and 3: high risk). For each patient, the sum of all grades was divided by the number of available variables and rounded to the next integer to define the risk group.[16,17]

Statistical methods

Data were presented as mean ± standard deviation for continuous variables with normal distribution, and as median and interquartile range for non-normally distributed variables. Categorical variables were presented as frequencies and percentages (%). Continuous variables were compared using the *t*-test for independent samples or the Mann–Whitney *U* test, while the chi-square test or the Fisher exact test was used to assess categorical variables. For multiple comparisons, one-way ANOVA or the Kruskal–Wallis test with post hoc analysis was used as appropriate.

A p-value < 0.05 was considered statistically significant in this study. Data were analyzed using the SPSS version 23.0.

Results

Baseline characteristics

Between January 2015 and April 2018, 231 patients with PAH from nine PH centers from all over Greece were enrolled. Figure 1 shows the distribution of 231 patients across the various types of PAH. The most frequent PAH subtypes were idiopathic PAH (IPAH) (82, 35%), PAH due to CTD (71, 31%), and PAH associated with CHD (60, 26%). Four patients (2%) had heritable PAH (HPAH), three patients (1%) had PAH induced by drugs and toxins, six patients (3%) had PAH due to portal hypertension, and five patients (2%) had PAH due to more than one etiology. The most frequent cause of PAH-CTD was systemic sclerosis in 63% of patients, while Eisenmenger syndrome was present in 36% of patients with PAH-CHD. In PAH-CHD, simple type defects were the most frequent etiology (76%).

Baseline demographic and clinical characteristics of the overall PAH population and among the three main PAH subgroups (IPAH/HPAH, PAH-CTD, and PAH-CHD) are presented in Table 1. About two-thirds of patients with PAH were women (mean age 51.8 ± 18.6 years). Female predominance was more prominent in PAH-CTD patients (78.8%), who were also older (60.9 ± 11.8 years) when compared with PAH-CHD patients (38.5 ± 22.1 years). Arterial hypertension and obesity were the most frequent comorbidities in the overall PAH population, being present in one-quarter of them. Furthermore, IPAH/HPAH subgroup presented notably more comorbidities than the other subgroups (Table 1).

About half of patients with PAH (55%) were mildly symptomatic at baseline in WHO FC II, with dyspnea and fatigue being the most frequent presenting symptoms. No significant differences were found among subgroups regarding their FC; however, PAH-CTD patients achieved shorter 6-MWD than the other PAH subgroups (326.3 ± 114.0 m, $p = 0.002$) (Table 2). Hemodynamics were reported on 212 patients (91.8 %). Vasoreactivity test was performed in 37 patients with PAH and was positive in 5 patients (13.5%). The mPAP (47.1 ± 15.5 mmHg) and PVR (8.1 (6.4) Wood units) were increased in PAH population, with the lowest values of both variables detected in the PAH-CTD subgroup ($p < 0.0001$). A significant increase of SVO_2 was also detected in PAH-CHD group in comparison to the

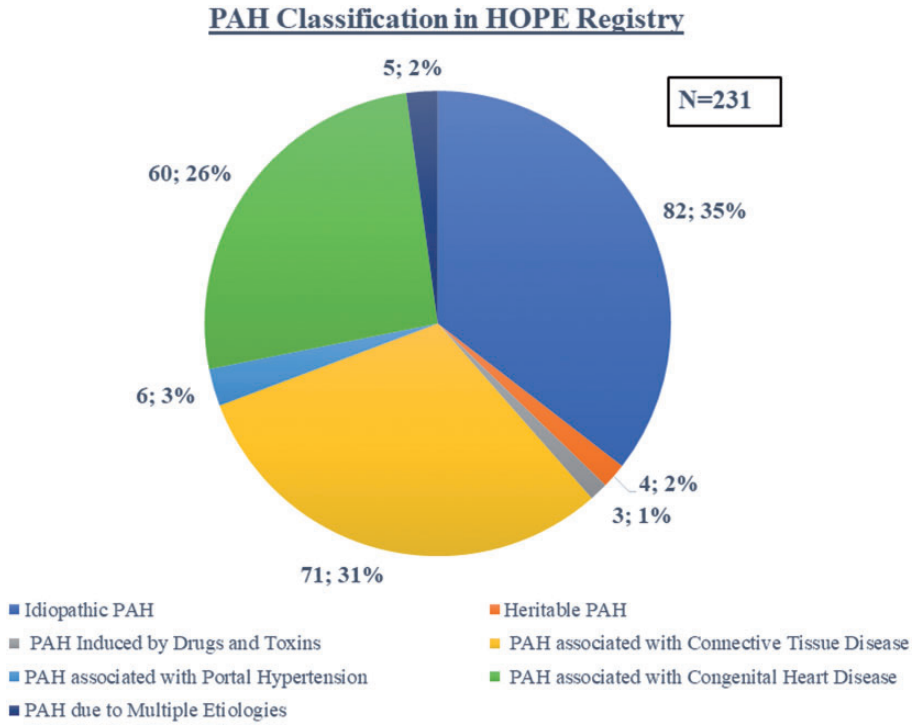

Figure 1. Classification of patients with PAH. The distribution of 231 patients across the various types of PAH in Greece (absolute number; %) is shown.
HOPE: Hellenic pulmOnary hyPertension rEgistry; PAH: pulmonary arterial hypertension.

Table 1. Baseline demographics and clinical characteristics of patients with PAH and differences among subgroups.

	PAH	IPAH/HPAH	PAH-CTD	PAH-CHD	*p* Value*
Subjects	231	86 (37.2)	71 (30.7)	60 (25.9)	
Female	149 (64.5)	48 (55.8)	56 (78.8)	37 (61.6)	**0.009**
Age (years)	51.8 ± 18.6	53.5 ± 15.5[§$]	60.9 ± 11.8[§#]	38.5 ± 22.1[$#]	<**0.0001**
BMI (kg/m^2)	25.5 (7.7)	27.5 (6.9)[$]	25.8 (8.0)	22.9 (6.6)[$]	<**0.0001**
Comorbidities					
Atrial fibrillation	10 (4.3)	4 (4.6)	2 (2.8)	4 (6.6)	0.578
Arterial hypertension	59 (25.5)	31 (36.0)	23 (32.4)	4 (6.6)	<**0.0001**
Dyslipidemia	29 (12.6)	11 (12.8)	15 (2.1)	2 (3.3)	**0.010**
Diabetes	30 (13)	17 (19.7)	8 (11.2)	2 (3.3)	**0.012**
CAD	16 (6.9)	9 (10.4)	6 (8.4)	0	**0.041**
Obesity	58 (25.1)	24 (27.9)	19 (26.7)	10 (16.6)	0.255
Hypothyroidism	39 (16.9)	12 (13.9)	16 (22.5)	11 (18.3)	0.377
Smoking	10 (4.3)	5 (5.8)	3 (4.2)	0	0.178
Symptoms					
Dyspnea	186 (80.5)	67 (77.9)	66 (92.9)	41 (68.3)	**0.002**
Fatigue	120 (51.9)	40 (46.5)	40 (56.0)	30 (50.0)	0.468
Palpitations	58 (25.1)	20 (23.2)	19 (2.7)	17 (28.3)	0.769
Chest pain	21 (9.1)	11 (12.8)	6 (8.4)	3 (5.0)	0.267
Syncope	16 (6.9)	6 (6.9)	4 (5.6)	4 (6.6)	0.941
RHF	6 (2.6)	28 (32.5)	21 (29.5)	10 (16.6)	0.09
Functional signs					
Loud P2	82 (35.5)	39 (45.3)	24 (33.8)	16 (26.7)	0.06
Cyanosis	42 (18.2)	13 (15.1)	15 (21.1)	14 (23.3)	0.42
Clubbing	22 (9.5)	8 (9.3)	6 (8.5)	8 (13.3)	0.62
JVD	37 (16)	8 (9.3)	13 (18.3)	12 (20.0)	0.14
Hepatomegaly	21 (9.1)	7 (8.1)	6 (8.5)	6 (10.0)	0.92
Hepatojugular reflux	27 (11.7)	10 (11.6)	8 (11.3)	7 (11.7)	0.97
Ascites	10 (4.3)	5 (5.8)	1 (1.4)	2 (3.3)	0.34
Edema	61 (26.4)	21 (24.4)	21 (29.6)	13 (21.7)	0.56
Systolic murmur	34 (14.7)	13 (15.1)	8 (11.3)	11 (18.3)	0.52

Note: Categorical variables are presented as frequency and percentage, n (%).
Continuous variables are presented as mean value ± standard deviation or median value with interquartile range.
*Statistical significance among the three PAH subgroups: $p < 0.05$
§$p < 0.05$ between IPAH/HPAH and PAH-CTD for continuous variables.
$$p < 0.05$ between IPAH/HPAH and PAH-CHD for continuous variables.
#$p < 0.05$ between PAH-CTD and PAH-CHD for continuous variables.
BMI: body mass index; CAD: coronary artery disease; HPAH: hereditary pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; JVD: jugular vein distension; PAH: pulmonary arterial hypertension; PAH-CHD; pulmonary arterial hypertension associated with congenital heart disease; PAH-CTD: pulmonary arterial hypertension associated with connective tissue disease; P2: pulmonary component of second cardiac sound; RHF: right heart failure.

other subgroups ($p = 0.002$). Moreover, the diffusion lung capacity was significantly decreased in PAH-CTD group ($35.3 \pm 16.4\%$, $p < 0.0001$), while PAH-CHD group presented signs of restrictive ventilatory impairment in spirometry (decreased forced expiratory volume and forced vital capacity) (Table 2). Finally, more than half of patients were considered as intermediate risk for 1-year mortality (56.7%), while patients with PAH-CHD were equally classified as low and intermediate risk, without however significant differences among subgroups ($p = 0.278$).

Medical therapy

Table 3 presents data about supportive and specific PAH medical therapy in the overall PAH population and among PAH subgroups. As far as supportive therapy is concerned, about one-fifth of patients with PAH received oxygen therapy at baseline, half of them were on diuretics, while nearly a quarter of them received an oral anticoagulant. Among PAH subgroups, 4 out of 10 patients with IPAH/HPAH received an oral anticoagulant and more than half of them

Table 2. Baseline clinical assessment and hemodynamics of patients with PAH and differences among subgroups.

	PAH	IPAH/HPAH	PAH-CTD	PAH-CHD	*p* Value*
Subjects	231	86 (37.2)	71 (30.7)	60 (25.9)	
WHO FC					
I	10 (4.3)	7 (8.1)	0	3 (5.0)	0.06
II	127 (55.0)	45 (52.3)	35 (49.3)	38 (63.3)	
III	84 (36.4)	28 (32.5)	33 (46.4)	18 (30.0)	
IV	10 (4.3)	6 (6.9)	3 (4.2)	1 (1.6)	
6-MWD (m) *N*=230 (76.6%)	373.4 ± 118.1	399.3 ± 118.2[§]	326.3 ± 114.0[§#]	384.7 ± 114.5[#]	**0.002**
NT-pro BNP (pg/mL) *N* = 155 (51.6%)	503.0 (1480.2)	535.0 (1071.5)	632.0 (2133.5)	261.0 (1690.0)	0.453
Risk stratification					
Low risk	85 (36.8)	28 (32.5)	24 (33.8)	29 (48.3)	0.278
Intermediate risk	131 (56.7)	51 (59.3)	41 (57.7)	29 (48.3)	
High risk	15 (6.5)	7 (8.1)	6 (8.4)	2 (3.3)	
Echocardiography					
RV hypertrophy	65 (43.6)	32 (37.2)	14 (19.7)	17 (28.3)	**0.006**
RVEDD (mm)	38.2 ± 8.8	39.0 ± 10.4	37.3 ± 8.5	37.6 ± 5.2	0.744
TAPSE (mm)	19.3 ± 4.9	19.3 ± 5.1	19.3 ± 4.1	18.4 ± 5.2	0.741
TR Vmax (m/s)	3.9 ± 0.7	4.0 ± 0.6	3.7 ± 0.6[#]	4.3 ± 0.7[#]	**0.001**
RVSP (mmHg)	71.2 ± 26.0	78.1 ± 24.6[§]	65.3 ± 22.6[§#]	89.7 ± 30.3[#]	<**0.0001**
Right heart catheterization, *N* = 212 (91.8%)					
mRAP (mmHg)	8.8 ± 5.0	9.1 ± 4.6	7.7 ± 4.7	9.7 ± 6.2	0.096
mPAP (mmHg)	47.1 ± 15.5	49.5 ± 12.8[§$]	39.9 ± 10.8[§#]	57.1 ± 20.8[$#]	<**0.0001**
PAWP (mmHg)	10.9 ± 3.8	10.6 ± 4.0	11.0 ± 3.6	11.3 ± 3.8	0.613
CO (L/min)	4.5 ± 1.5	4.6 ± 1.6	4.5 ± 1.4	4.2 ± 1.5	0.346
CI (L/min/m^2)	2.6 ± 0.8	2.5 ± 0.9	2.6 ± 0.6	2.8 ± 0.9	0.143
PVR (WU)	8.1 (6.4)	8.6 (5.5)[§$]	5.6 (4.8)[§#]	10.7 (11.8)[$#]	<**0.0001**
HR (bpm)	79.7 ± 12.6	76.9 ± 11.2[$]	80.5 ± 12.0	84.9 ± 14.6[$]	**0.005**
SVO_2 (%)	69.4 ± 8.1	67.4 ± 7.5[§]	68.2 ± 7.4[#]	73.8 ± 9.7[§#]	**0.002**
LFT, *N* = 105 (45.4%)					
FEV1 (%)	81.9 ± 20.1	86.2 ± 16.7[$]	79.5 ± 21.6	58.8 ± 19.9[$]	**0.008**
FVC (%)	84.1 ± 20.1	89.6 ± 17.3[$]	80.4 ± 22.3	64.1 ± 24.2[$]	**0.009**
FEV1/FVC (%)	81.5 ± 11.2	80.9 ± 1 2.7	82.5 ± 9.2	72.8 ± 9.2	0.25
DLCO (%)	47.6 ± 24.1	56.6 ± 23.7[§$]	35.3 ± 16.4[§]	88.5 ± 21.6[$]	<**0.0001**
CPET, *N* = 30 (13.0%)					
VO2max (mL/kg/min)	14.2 ± 3.6	14.3 ± 3.4	12.7 ± 3.6	16.2 ± 1.5	0.33
VO2max (%)	58.7 ± 17.1	60.4 ± 17.7	56.8 ± 17.6	46 ± 1.4	0.52

Categorical variables are presented as frequency and percentage, n (%).

Continuous variables are presented as mean value ± standard deviation or median value with interquartile range.

*Statistical significance among the three PAH subgroups: $p < 0.05$.

§$p < 0.05$ between IPAH/HPAH and PAH-CTD for continuous variables.

$$p < 0.05$ between IPAH/HPAH and PAH-CHD for continuous variables.

#$p < 0.05$ between PAH-CTD and PAH-CHD for continuous variables.

6-MWD: 6-minute walk distance; bpm: beats per minute; CI: cardiac index; CO: cardiac output; CPET: cardiopulmonary exercise testing; DLCO: diffusing capacity for carbon monoxide; FC: functional class; FEV1: forced expiratory volume during the first second of expiration; FVC: forced vital capacity; HPAH: hereditary pulmonary arterial hypertension; HR: heart rate; IPAH: idiopathic pulmonary arterial hypertension; LFT: lung function test; mPAP: mean pulmonary artery pressure; mRAP: mean right atrial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAH: pulmonary arterial hypertension; PAH-CHD: pulmonary arterial hypertension associated with congenital heart disease; PAH-CTD: pulmonary arterial hypertension associated with connective tissue disease; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; RV: right ventricle; RVEDD: right ventricular end-diastolic diameter; RVSP: right ventricular systolic pressure; SvO_2: oxygen saturation in pulmonary artery; TAPSE: tricuspid annular plane systolic excursion; TR Vmax: maximal velocity of tricuspid regurgitation; VO2max: oxygen consumption at maximum exercise; WHO: World Health Organization; WU: Wood units.

Table 3. Baseline medical therapy in patients with PAH and differences among subgroups.

	PAH	IPAH/HPAH	PAH-CTD	PAH-CHD	*p* Value*
Subjects	231	86 (37.2)	71 (30.7)	60 (25.9)	
Supportive therapy					
Oxygen therapy	50 (21.6)	22 (25.5)	24 (33.8)	4 (6.6)	**0.001**
Diuretics	111 (48.1)	49 (56.9)	36 (50.7)	21 (35.0)	**0.031**
OAC	60 (25.9)	35 (40.6)	16 (22.5)	9 (15.0)	**0.001**
Targeted PAH therapy	207 (89.6)	79 (91.8)	65 (91.5)	51 (85.0)	0.340
PDE5i	111 (48.1)	52 (60.5)	37 (52.1)	17 (28.3)	**0.001**
sGC	6 (2.6)	4 (4.6)	2 (2.8)	0	0.241
ERA	167 (72.3)	55 (63.9)	52 (73.2)	48 (80.0)	0.099
Prostanoids	28 (12.1)	16 (18.6)	10 (15.4)	1 (1.6)	**0.007**
iv epoprostenol	8 (28.6)	5 (31.2)	1 (10.0)	1 (100)	0.216
sc treprostinil	5 (17.6)	2 (12.5)	3 (30.0)	0	0.275
inh iloprost	15 (53.6)	9 (56.2)	6 (60.0)	0	**0.039**
Selexipag	3 (1.3)	2 (2.3)	0	1 (1.6)	0.451
No PAH therapy	24 (10.4)	7 (8.1)	6 (8.4)	9 (15.0)	0.340
Monotherapy	117 (50.6)	35 (40.6)	36 (50.7)	37 (61.6)	**0.044**
PDE5i	25 (21.4)	11 (31.4)	10 (27.7)	3 (8.1)	**0.005**
sGC	3 (2.6)	2 (5.7)	1 (2.7)	0	0.383
ERA	84 (71.8)	17 (48.5)	25 (69.4)	34 (91.9)	**<0.0001**
Prostanoids	2 (1.7)	2 (5.7)	0	0	0.119
Double combination	71 (30.7)	34 (39.5)	22 (28.2)	12 (20.0)	**0.043**
PDE5i + ERA	58 (81.6)	28 (82.3)	19 (86.3)	12 (100)	0.300
PDE5i + Prostanoid	8 (11.2)	5 (14.7)	2 (9.1)	0	0.345
ERA + Prostanoid	3 (4.2)	2 (5.8)	1 (4.5)	0	0.694
Triple combination	19 (8.2)	10 (11.6)	7 (12.7)	2 (3.3)	0.201

Note: Categorical variables are presented as frequency and percentage, n (%).
*Statistical significance among the three PAH subgroups: $p < 0.05$.
ERA: endothelin receptor agonists; HPAH: hereditary pulmonary arterial hypertension; inh: inhaled; IPAH: idiopathic pulmonary arterial hypertension; iv: intravenous; OAC: oral anticoagulant; PAH: pulmonary arterial hypertension; PAH-CHD; pulmonary arterial hypertension associated with congenital heart disease; PAH-CTD: pulmonary arterial hypertension associated with connective tissue disease; PDE5i: phosphodiesterase type 5 inhibitors; sc: subcutaneous; sGC: guanylate cyclase stimulator.

were on diuretics. Furthermore, oxygen therapy was prescribed in more than one-third of patients with PAH-CTD.

Only 1 out of 10 patients with PAH did not receive a targeted PAH medical therapy at baseline. About half of patients received a phosphodiesterase type 5 inhibitor (PDE5i), while nearly three-fourth of them received an endothelin receptor agonist (ERA). Prostanoid use was limited in 12.1% of patients with PAH. Half of patients with PAH were on monotherapy at baseline, mainly with an ERA (71.8%), while 38.9% of them received a combination therapy (mostly an ERA with a PDE5i) (Table 3).

Among PAH subgroups, oral combination therapy was most frequently used in IPAH/HPAH (51.1%). PDE5i and prostanoid use were also higher in this subgroup (60.5% and 18.6%, respectively). The majority of patients with PAH-CHD received an ERA (80%), either as monotherapy (56.6%) or combination therapy (23.3%) (Table 3). Calcium channel blockers (CCBs) were most frequently prescribed in PAH-CTD (19.7%), mainly due to digital ulcers and comorbidities, but also in five patients with IPAH due to positive vasoreactivity test.

Risk stratification in PAH

Table 4 presents the baseline characteristics of patients with PAH according to their 1-year mortality risk. All patients had available more than two out of six variables required for the calculation of modified PAH risk score. The majority of patients with PAH were at intermediate risk (56.7%), more than one-third were low risk (36.8%) and only 6.5% were high-risk patients. The estimated 1-year mortality risk was associated, as expected, with WHO FC, 6-MWD, NTproBNP, mean RAP, CI, and SVO_2, but also with age, body mass index, mPAP, PVR and echocardiographically derived right ventricular diameter at end-diastole, maximal tricuspid regurgitation velocity, and right ventricular systolic pressure. As for the medical therapy, mortality risk at baseline was associated with the number of administered

Table 4. Differences in baseline clinical assessment, hemodynamics, and therapeutic management of patients with PAH according to their 1-year mortality risk.

N = 231	Low risk	Intermediate risk	High risk	*p* Value*
Subjects	**85 (36.8)**	**131 (56.7)**	**15 (6.5)**	
Female	58 (68.2)	80 (61.0)	10 (66.7)	0.550
Age (years)	48.0 (27.0)[§$]	56.0 (20.0)[§]	58.0 (23.0)[$]	<**0.0001**
BMI (kg/m^2)	24.2 (7.8)[$]	25.7 (7.2)[#]	30.2 (8.7)[$#]	**0.025**
WHO FC				
I	8 (9.4)	2 (1.5)	0	<**0.0001**
II	64 (75.3)	62 (47.3)	1 (6.6)	
III	13 (15.3)	62 (47.3)	9 (60.0)	
IV	0	5 (3.8)	5 (33.3)	
6-MWD (m)	446.6 ± 87.9[§$]	341.5 ± 104.8[§#]	183.4 ± 109.1[$#]	<**0.0001**
NT-proBNP (pg/mL)	176.5 (175.3)[§$]	810.5 (1357.0)[§#]	4259.0 (3607.0)[$#]	<**0.0001**
Echocardiography				
RVEDD (mm)	34.0 (9.0)[$]	39.0 (12.0)[#]	54.0 (18.5)[$#]	**0.009**
TAPSE (mm)	20.0 (7.0)	18.0 (6.0)	17.0 (9.0)	0.1
TR Vmax (m/s)	3.6 (0.9)[$]	4.0 (0.8)[#]	4.6 (1.3)[$#]	**0.001**
RVSP (mmHg)	59.0 (31.2)[$]	70.0 (28.0)[#]	102.5 (41.5)[$#]	<**0.0001**
Right heart catheterization				
mRAP (mmHg)	6.0 (4.8)[§$]	9.0 (6.0)[§#]	16.5 (5.3)[$#]	<**0.0001**
mPAP (mmHg)	42.0 (20.5)[$]	45.0 (17.0)[#]	58.5 (16.3)[$#]	<**0.0001**
PAWP (mmHg)	9.8 ± 3.6[§$]	11.3 ± 3.7[§]	12.9 ± 4.1[$]	**0.013**
CO (L/min)	4.7 (2.3)[§$]	4.0 (1.6)[§#]	3.2 (0.6)[$#]	<**0.0001**
CI (L/min/m^2)	2.8 (0.9)[§$]	2.2 (0.9)[§#]	1.7 (0.3)[$#]	<**0.0001**
PVR (WU)	6.4 (5.9)[$]	8.1 (5.9)[#]	14.2 (7.4)[$#]	<**0.0001**
HR (bpm)	79.8 ± 12.1	79.1 ± 12.9	84.5 ± 13.1	0.43
SVO_2 (%)	74.3 ± 5.1[§$]	67.3 ± 7.8[§#]	59.7 ± 8.7[$#]	<**0.0001**
Supportive therapy				
Oxygen therapy	10 (11.7)	34 (25.9)	6 (40.0)	**0.010**
Diuretics	29 (34.1)	70 (53.4)	12 (80.0)	**0.001**
OAC	16 (18.8)	40 (30.5)	4 (26.6)	0.159
Targeted PAH therapy	80 (94.1)	113 (86.2)	14 (93.3)	0.161
PDE5i	31 (36.5)	70 (53.4)	10 (66.7)	**0.017**
sGC	2 (2.4)	2 (1.5)	2 (13.3)	**0.024**
ERA	63 (74.1)	90 (68.7)	12 (80.0)	0.517
Prostanoids	8 (9.4)	17 (12.9)	3 (20.0)	0.173
iv epoprostenol	3 (37.5)	4 (23.5)	1 (33.3)	0.757
sc treprostinil	0	3 (17.6)	2 (66.6)	**0.037**
inh iloprost	5 (62.5)	10 (58.8)	0	0.142
Selexipag	0	2 (1.5)	1 (6.6)	0.103
No PAH therapy	5 (5.8)	18 (13.7)	1 (6.6)	0.161
Monotherapy	58 (68.2)	55 (42.0)	4 (26.6)	<**0.0001**
PDE5i	12 (20.7)	12 (21.8)	1 (25.0)	0.973
sGC	1 (1.7)	1 (1.8)	1 (25.0)	**0.015**
ERA	43 (74.1)	39 (70.9)	2 (50.0)	0.572
Prostanoids	1 (1.7)	1 (1.8)	0	0.964
Double combination	19 (22.4)	46 (35.1)	6 (40.0)	0.101
PDE5i + ERA	15 (78.9)	40 (86.9)	6 (100.0)	0.409
PDE5i + Prostanoid	2 (10.5)	6 (13.0)	0	0.632

(continued)

Table 4. Continued

N = 231	Low risk	Intermediate risk	High risk	*p* Value*
ERA + Prostanoid	2 (10.5)	1 (2.1)	0	0.272
Triple combination	3 (3.5)	12 (9.1)	4 (26.6)	**0.009**

Note: Categorical variables are presented as frequency and percentage, n (%).
Continuous variables are presented as mean value ± standard deviation or median value with interquartile range.
*Statistical significance among low-, intermediate- and high-risk patients with pulmonary arterial hypertension: $p < 0.05$.
§$p < 0.05$ between low- and intermediate- risk patients for continuous variables.
$$p < 0.05$ between low- and high-risk patients for continuous variables.
#$p < 0.05$ between intermediate- and high-risk patients for continuous variables.
6-MWD: 6-minute walk distance; BMI: body mass index; bpm: beats per minute; CI: cardiac index; CO: cardiac output; ERA: endothelin receptor agonists; FC: functional class; HR: heart rate; inh: inhaled; iv: intravenous; mPAP: mean pulmonary artery pressure; mRAP: mean right atrial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; OAC: oral anticoagulant; PAH: pulmonary arterial hypertension; PAWP: pulmonary artery wedge pressure; PDE5i: phosphodiesterase type 5 inhibitors; PVR: pulmonary vascular resistance; RVEDD: right ventricular end-diastolic diameter; RVSP: right ventricular systolic pressure; sc: subcutaneous; sGC: guanylate cyclase stimulator; SvO_2; oxygen saturation in pulmonary artery; TAPSE: tricuspid annular plane systolic excursion; TR Vmax: maximal velocity of tricuspid regurgitation; WHO: World Health Organization; WU: wood units.

PAH-specific drugs. The majority of high-risk patients received a combination therapy (66.6%), while most low-risk patients were on monotherapy (68.2%), primarily with an ERA (74.1%). Furthermore, the need for oxygen therapy and diuretics was greater in high-risk patients when compared with low- and intermediate-risk ones.

Discussion

This is the first National Registry on PAH in Greece, supported by nine expert PH centers nationally, providing baseline information on demographics, epidemiology, clinical characteristics, and treatment management of the Greek patient population with PAH. The registry is among the most recent in Europe and the United States, as it was launched in January 2015. Although the number of patients included in the cohort is relatively small compared with other registries, most of the findings regarding epidemiology and clinical presentation are comparable with other cohorts (Table 5).[8,10,11,13,14,18,19] Our population in terms of demographic characteristics such as age, female predominance, and obesity prevalence, was similar to other registries.[8,10,11,13,14,18,19] Furthermore, hypertension, obesity, and diabetes mellitus were the most common comorbidities in PAH and especially in the IPAH/HPAH subgroup. This may be associated with late diagnosis of PAH—after the fifth decade of life in the majority of our patients and reflects the presence of a novel clinical entity of "atypical" PAH, highlighted also in other registries.[13,20] On the other hand, our cohort included a larger proportion of PAH-CHD (26%) and PAH-CTD (31%), compared with other registries, while only a minority due to drugs and toxins, human immunodeficiency virus, and portal hypertension (Table 5). This difference could be explained by the fact that most tertiary centers for CHD in Greece are participating in this registry, thus PAH is diagnosed early in the course of the disease. Moreover, the increased risk of developing PAH in the presence of systemic sclerosis and other CTDs, has raised awareness and resulted in the implementation of a close echo-based screening of these cases, which probably explains the larger number of reported PAH-CTD in our cohort.[21–23] However, in terms of other PAH etiologies the percentage is lower than in most other registries and is probably related to low overall physician awareness of PAH in these patients.[8,9,13,18,19,24]

Furthermore, in accordance with other PAH cohorts, dyspnea and fatigue were the most common symptoms at baseline. However, our population had more favorable clinical characteristics at diagnosis, since half of patients were in WHO II FC (Table 5). The 6-MWD distance was slightly better compared with other registries, while hemodynamics (lower mPAP and PVR, higher SVO_2%) were slightly more favorable in our population.[8,10,11,13–15,18,19] Similar to other registries, the majority of the PAH population was at intermediate 1-year mortality risk, according to the modified PAH risk assessment score.[13,16,17] This observation implies that PAH patients in our cohort may have underestimated their symptoms and their FC, quite common in the PAH-CHD cohort,[25] which could have led the physician to opt for monotherapy. It should be taken into consideration that echocardiography is widely available in Greece. Thus, the fact that most Greek patients have easy access to this, inexpensive in our country, first-line screening tool may be associated with earlier diagnosis in the course of the disease.

In terms of supportive therapy, diuretics were used by approximately half of patients with PAH. Oral anticoagulants were also frequently used in IPAH/HPAH subgroup, despite the fact that the recommendation for their administration in patients with IPAH has been downgraded to IIb according to the latest ESC Guidelines.[1]

Almost half of PAH patients received monotherapy at baseline assessment. ERAs and PDE5i, the former more frequently, were used as monotherapy. Within PAH group, ERAs were more frequently given as monotherapy in PAH-CHD subgroup, while PDE5i in PAH-CTD subgroup. These results are in agreement with previous reports demonstrating ERAs and PDE5i being the most widely used treatment-specific drugs.[9–11,13,14] ERA and PDE5i

Table 5. Comparative baseline demographic, clinical, hemodynamic, and treatment data between patients with PAH in Greece and other PAH Registries.

Registry Ref.	**HOPE**	**REVEAL**[13]	**COMPERA**[10]	**FRENCH**[19]	**SPANISH**[8]	**SWISS**[14]	**ENGLISH**[11]	**GIESSEN**[18]
Enrollment period	2015–2018	2006–2009	2007–2011	2002–2003	1998–2008	1998–2012	2001–2009	1993–2008
PAH population, *n*	231	2525	1278	674	866	517	482	685
PAH classification (%)								
IPAH	35.0	46.2	65.6	39.2	30.0	60.0	92.9	42.9
HPAH	2.0	2.7	N/A	3.9	N/A	N/A	5.4	N/A
DPAH	1.0	5.0	N/A	9.5	3.2	2.0	1.7	N/A
HIV-PAH	0	2.0	N/A	6.2	N/A	N/A	0	4.1
PAH-CTD	31.0	25.3	19.6	15.3	15.0	18.0	0	21.2
PAH-CHD	25.9	9.8	7.3	11.3	16.0	8.0	0	13.3
Po-PAH	3.0	5.0	3.9	10.4	7.0	5.0	0	7.4
Demographics			N=587					
Female (%)	64.5	79.5	60.3	65.3	71.0	60.0	69.9	65.0
Age (years)	51.8 ± 18.6	53.0 ± 14.0	71.0 (16.0)	50.0 ± 15.0	45.0 ± 17.0	57.0 ± 16.0	50.1 (17.1)	51.0 (16.0)
BMI (kg/m^2)	25.5 (7.7)	N/A	N/A	24.4 ± 5.5	N/A	26.0 ± 7.0	28.3 ± 6.3	N/A
Comorbidities (%)								
Arterial hypertension	25.5	40.2	N/A	N/A	N/A	N/A	5.3 (24/455)	N/A
Diabetes	13.0	12.0	N/A	N/A	N/A	N/A	14.3 (65/455)	N/A
Obesity	25.1	33.3	N/A	N/A	N/A	N/A		N/A
Smoking	4.3	N/A	N/A	N/A	N/A	N/A	14.4 (52/361)	N/A
WHO FC (%)								
II	55.0	N/A	9.0	24.0	31.0	24.0	15.5	19.0
III/IV	40.7	73.6 (1348/1831)	91.0	75.0	69.0	75.0	79.6	67.7
6-MWD (m)	373.4 ± 118.1	366.0 ± 126.0	293.0 (126.0)	329.0 ± 109.0	363.0 ± 120.0	362.0 ± 137.0	292.4 (123.0)	325.0 (126.0)
Right heart catheterization								
mRAP (mmHg)	8.8 ± 5.0	9.3 ± 5.6	8.0 (5.0)	8.0 ± 5.0	9.0 ± 5.0	9.0 ± 4.0	10.1 (6.0)	8.0 (6.0)
mPAP (mmHg)	47.1 ± 15.5	50.7 ± 13.6	44.0 (12.0)	55.0 ± 15.0	54.0 ± 16.0	48.0 ± 15.0	54.1 (13.9)	51.0 (16.0)
CI (mL/min/m^2)	2.6 ± 0.8	2.4 ± 0.8	2.2 (0.7)	2.5 ± 0.8	2.6 ± 0.9	2.5 ± 0.8	2.1 (0.7)	2.3 (0.8)
PVR (WU)	8.1 (6.4)	N/A	9.6 (5.5)	N/A	12.0 ± 6.0	9.4 ± 5.6	12.8 (6.3)	10.6 (9)
SVO_2 (%)	69.4 ± 8.1	62.9 ± 10.0	63.0 (8.0)	63.0 ± 9.0	N/A	63.0 ± 10.0	61.5 (9.5)	61.0 (10.0)
PAH-specific therapy (%)						*N* = 517	*N* = 479	*N* = 510
No therapy	10.4	3.5	0	N/A	N/A	28.0	0.6	11.4
Monotherapy	50.6	46.1	85.0	N/A	N/A	59.0	97.2	71.8
Combination therapy	38.9	50.4	15.0	N/A	N/A	13.0	2.2	16.8
PDE5i	48.1	49.0	62.4	N/A	N/A	22.0	29.2	N/A
ERAs	72.3	47.0	55.4	N/A	N/A	52.0	44.3	N/A
Prostanoids	12.1	40.5	2.7	N/A	N/A	14.0	18.8	N/A

Note: Categorical variables are presented as percentage.

Continuous variables are presented as mean value ± standard deviation or median value and interquartile range.

6-MWD: 6-minute walk distance; BMI: body mass index; CI: cardiac index; DPAH: pulmonary arterial hypertension induced by drugs and toxins; ERA: endothelin receptor agonists; FC: functional class; HIV-PAH: human immunodeficiency virus-pulmonary arterial hypertension; HPAH: hereditary pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; mPAP: mean pulmonary artery pressure; mRAP: mean right atrial pressure; N/A: not applicable; PAH: pulmonary arterial hypertension; PAH-CHD: pulmonary arterial hypertension associated with congenital heart disease; PAH-CTD: pulmonary arterial hypertension associated with connective tissue disease; PDE5i: phosphodiesterase type 5 inhibitors; Po-PAH: porto-pulmonary hypertension; PVR: pulmonary vascular resistance; SvO_2: oxygen saturation in pulmonary artery; WHO: World Health Organization; WU: Wood units.

combination was also the most widely used combination in PAH group, although the rate of dual therapy was lower than previously reported.[13] This is possibly related to the better WHO FC of the majority of our population, the large proportion of patients with Eisenmenger syndrome,[1] and the high prevalence of patients with PAH and comorbidities[6] that could explain why most patients received monotherapy. However, there were also registries that reported a much lower use of combination therapy at baseline compared with our cohort.[10,11,14,18] Furthermore, the use of prostanoids as monotherapy or combination therapy was lower in our cohort when compared with other

registries.[11,13,14] In general, treatment management was in line with the ESC/ERS treatment guidelines.[1,2] However, the satisfactory functional status (WHO I/II) of the majority of patients in our cohort, in contrast to other European registries, may partially explain the low percentage of prostanoid use in this population, albeit a more aggressive approach could also be considered.[26] Additionally, the intravenous route of administration along with the known side effects might have contributed to the low percentage of use of parenteral prostanoids as monotherapy or combination therapy in our cohort.

A limitation of this study is the relatively small sample size which does not yet permit the application of more sophisticated statistical methods that would provide reliable prognostic information. Additionally, in this paper, information regarding only the initial assessment is presented. Thus, data regarding the clinical course, survival, and evolution of treatment management over time are still pending.

In conclusion, this study indicates that the demographic, clinical, and management data of patients with PAH in Greece did not differ significantly when compared with other countries. However, the initial clinical assessment shows that although most PAH patients are of intermediate risk, their functional capacity is better than previously reported in similar populations. This may reflect an improvement in the timely identification of patients at risk for developing PAH and lead to early diagnosis of the disease; yet, adaptation of a contemporary aggressive targeted strategy should be encouraged.

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Ethical approval

The HOPE Registry received ethical approval from the Institutional Review Board of every participating center (AHEPA University Hospital, Thessaloniki; Mediterraneo Hospital, Athens; Attikon University General Hospital, Athens; Onassis Cardiac Surgery Center, Athens; Hippokration University General Hospital, Athens; Heraklion University Hospital, Crete; University Hospital of Ioannina; "G. Papanikolaou" Hospital, Thessaloniki; and University Hospital of Alexandroupolis) according to the Declaration of Helsinki, and all patients provided written informed consent for their inclusion in the study.

Authors' contribution

Alexandra Arvanitaki and Maria Boutsikou contributed equally to the design of this work, the acquisition, analysis, and interpretation of data, and drafted and revised the article for important intellectual content. Athanasios Manginas made a substantial contribution to the concept and design of this work and revised the article critically for important intellectual content. The rest of the authors contributed to the acquisition of patients' data and revised the article critically for important intellectual content.

Conflict of interest

Alexandra Arvanitaki and Maria Boutsikou were financially supported from the Hellenic Society for the Study of Pulmonary Hypertension. Anastasia Anthi reports receiving honoraria and consultancy fees from Actelion Pharmaceuticals Hellas, Bayer, ELPEN, GSK, MSD, Lilly, and United Therapeutics. Eftychia Demerouti is an advisory board member for Actelion Pharmaceuticals Hellas, MSD Hellas, and GlaxoSmithKline and an honorarium speaker for Actelion Pharmaceutical Hellas and MSD Hellas. George Giannakoulas reports receiving honoraria and consultancy fees from Actelion Pharmaceuticals Hellas,

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