UNIVERSITA' DEGLI STUDI DI GENOVA

DOTTORATO DI RICERCA XXXIV CICLO
EMATO ONCOLOGIA E MEDICINA INTERNA CLINICO-TRASLAZIONALE

Left heart disease phenotype in elderly patients with pulmonary arterial

hypertension: insights from the Italian PATRIARCA registry.

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Introduction

Pulmonary hypertension (PH) is a pathophysiological disorder that may complicate the majority of cardiovascular and respiratory diseases [1]. It can be classified in five groups according to hemodynamic profile and pathological findings.

According to the most recent European Society of Cardiology (ESC) guidelines, many conditions can cause pulmonary hypertension. In fact, pulmonary hypertension can be classified in 5 groups according to clinical presentation, physiopathology, emodinamic features and therapeutic possibilities. [1]. Such categories are Pulmonary Arterial Hypertension (PAH, Group 1), pulmonary hypertension due to left heart disease (Group 2), pulmonary hypertension due to lung diseases and/or hypoxia (Group 3), Chronic thromboembolic pulmonary hypertension (CTEPH, Group 4) and Pulmonary hypertension with unclear and/or multifactorial mechanisms (Group 5) [1].

As of today, only PAH and CTEPH have indication for specific therapy, therefore these categories represent the primary subject of interest and care to third level centres dedicated to pulmonary hypertension

PAH : elements of physiopathology and therapy

PAH is characterized by the presence of Pulmonary Vascular Resistance (PVR) >3 Wood Units (WU), in the absence of other causes of pre-capillary PH (such as PH due to lung diseases, CTEPH or other rare diseases), which can be ruled out during the diagnostic workup thanks to imaging methods and respiratory function assessment. The adjective "pre-capillary" reflects the defining element of PH physiopathology, which is the primary involvement of pulmonary small arteries and arterioles. In fact, PAH develops because of an imbalance between vasoconstrictor and vasodilator factors inside the pulmonary arterial circulation, resulting in prevalence of the former. In particular, there is a reduction of prostaglandin (PGI2) and nitric oxide (NO)

production made possible by NO synthase, while endothelin system increases its efficacy. [2] These processes lead to a remodelling of pulmonary arterial bed, with tunica media hypertrophy, intimal proliferation and fibrosis, aventitial thickening, in situ thrombosis and complex vascular lesions with focal myofibroblast and smooth muscle cells proliferation together with connective tissue matrix deposition (so called plexiform lesions). [2] These changes produce a pathologic elevation in PVR. The disease natural history then proceeds with right ventricle failure due to a chronic pressure overload, thus conditioning prognosis. Various PAH forms share this pathogenic sequence: idiopathic, heritable, drugs and toxic induced, associated with connective tissue diseases, HIV infection, portal hypertension, congenital heart diseases and schistosomiasis. PAH therapy gradually evolved throughout the last twenty years, increasing its complexity and moreover its efficacy. In fact, ESC guidelines affirm that PAH therapy does not consist of a mere drug prescription, but instead an elaborated strategy that must account for the single patient risk profile and response to different treatment lines. The physiopathological mechanisms leading to pulmonary vascular remodelling led to the development of three drug families that can act in synergy on the three pathways causing the aforementioned imbalance between vasodilation and vasoconstriction:

- NO pathway: to this day, two molecules were made available; type 5 phosphodiesterase (PDE-5i) inhibitors and guanilate cyclase (GC) stimulators. The first category prevents cyclic GMP degradation, that mediates intracellular NO effects, while the latter directly induce cyclic GMP production even in absence of NO. Sildenafil and tadalafil belong to the PDE-5i, while riociguat is the only GC stimulator approved for clinical use as of today. [3] [4] [5]

- Endothelin pathway: endothelin-1 acts as vasoconstrictor and mitogen through the bond with two different receptor isoforms located on pulmonary vascular smooth muscle cells, type A and type B. The latter are also present on endothelial cells, and their activation allows the release of vasodilating and cell proliferation

inhibition factors, such as NO and prostacyclin, which can compensate the negative effect of endothelin-1. However, type A receptors are much more predominant in vessels of PAH patients. Therefore, endothelin-1 receptor antagonism with bosentan, macitentan and ambrisentan represents the treatment strategy for PAH. [6] [7] [8]

- Prostacyclin pathway: prostacyclin is mainly produced by endothelial cells and determines a strong vasodilating effect on all vascular districts. It is the most powerful endogen platelet aggregation inhibitor, and has both cytoprotective and antiproliferatives effect. In PAH, there is a minor prostacyclin production, as well as its receptor expression. Thus, prostacyclin analogues (epoprostenol, iloprost e teprostinil,) and prostacyclin receptor agonists (selexipag) represent a valid therapeutic option in PAH. [9-12]

Regardless of the drug examined, most recent randomized clinical trials showed how an aggressive therapeutical approach might lead to outcomes that are more favourable. Therefore, current position is to prefer a combination therapy, reserving monotherapy for selected cases. [12,13]

CTEPH too is a pre-capillary form of PH, but it develops when thrombotic material persists in pulmonary circulation after an acute event, leading to chronicization and fibrosis. Through mechanisms still unclear, the presence of such clots gives birth to remodeling processes akin to those described in PAH, even in vessel in which thrombosis did not occur. This factor, joined with the mechanical flow obstruction, determines an increase of total PVR. CTEPH is quite rare, developing in 0.5-3.2% of patients survived to an acute pulmonary embolism. [14] Nevertheless, it could develop after acute events occurred without symptoms, therefore CTEPH should always be suspected at first evidence of PH. Pulmonary artery disobstruction through pulmonary thromboendoarterectomy with repeated circulatory arrest is the treatment of choice

for CTEPH, since potentially curative. [14] However, some patients are not eligible for this procedure because of extremely distal thrombotic lesions thus not surgically treatable, or because of the high risk linked to comorbidities. [15] Furthermore, CTEPH can persist in spite of surgical treatment or relapse after a temporary resolution. In these cases, percutaneous treatment is available as an alternative. [16,17] As far as medical therapy is concerned, to date riociguat is the only approved drug for inoperable CTEPH or persistent/relapsing form after pulmonary thromboendoarterectomy.[18,19]

Epidemiologic changes for PAH

While Pulmonary Arterial Hypertension (PAH, group 1 of the World Health Organisation classification) have been typically described among younger patients, as previously depicted in the 1980s US National Institutes of Health (NIH) registry where mean age of the 194 patients enrolled was 36 ± 15 years [20], the elderly population mostly show a post-capillary PH profile in the context of left heart disease (LHD, group 2) or a pre-capillary profile but in the presence of severe lung disease (group 3) or chronic thromboembolic pulmonary hypertension (CTEPH) [21,22].

Over the past years several PAH registries reported increasing age at PAH diagnosis. The Swiss Pulmonary Hypertension registry, which enrolled patients from 1998, showed an increase in the mean age of PAH patients from 53 ± 16 years between 2000 and 2004 to 60 ± 15 in the period 2009 – 2012 [23]. A not negligible quote of patients with a PAH diagnosis in the elderly is also reported in the French National registry, the US Registry to evaluate early and long-term pulmonary arterial disease management (REVEAL) and the European multicentre registry COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) [24-26].

These data partly reflect a change in disease phenotype, since it increasingly concerns people with subclinical yet haemodinamically significant forms of left ventricle diastolic dysfunction with consequential increase of right atrial filling pressures and backfire effect on pulmonary arterial pressure. (27) Moreover, this data highlight an increasing awareness of PAH together with a more detailed and effective screening towards both general population and categories at risk for developing PAH, such as patients with connective tissue diseases.

Despite these evidences, randomized controlled clinical trials that led to approval of drugs used for PAH did not involve elderly patients, as well as those with multiple comorbidities. Trials that ultimately allowed clinical use of ambrisentan e tadalafil combination [13], macitentan [8] and selexipag [12] recruited subjects with a mean age of 45-54 years old.

Compared to the younger population, elderly PAH patients have more comorbities such as ischemic heart disease, systemic hypertension, diabetes and chronic kidney disease (CKD) [28,29]. The presence of associated diseases can lead to difficulties in distinguishing between PAH and other forms of pulmonary hypertension, especially PH secondary to LHD.

Therefore, current guidelines do not examine the challenges in treating PAH and concomitant diseases, neither the potential prognostic impact of age and comorbidities. [30,31] Luckily, medical community shows awareness about their critical importance on daily clinical practice and their negative influence on the disease course. Nevertheless, clinical experience is only partially supported by literature. In the REVEAL registry study, among various comorbilities, just diabetes and chronic obstructive pulmonary disease (COPD) showed statistically significant association with higher mortality. [32] SPHAR Swedish registry identified CAD (coronary artery disease) and CKD (chronic kidney disease) as most common comorbidities among patients aged 70 or older, and linked with poor prognosis. [33

Recently, a pre-specified analysis of the AMBITION trial compared patients with and without a LHD phenotype according to clinical and haemodynamic parameters, applied as revised inclusion criteria by a protocol amendment [34]. Patients with a LHD profile were older (62.1 ± 10.2 vs 54.4 ± 14.6 years) with lower median distance performed at the six minute walking test (330.5 vs 363.7 meters), mean pulmonary artery pressure (mPAP, 42.2 ± 12.4 vs 48.7 ± 12.5) and pulmonary vascular resistance (512.1 ± 293.2 vs 824.9 ± 402.1 dyne*sec/cm^5). Nonetheless, they're response to treatment was lower than patients without LHD criteria and a greater quote of patients withdrew study medications [34].

Assumed the changing demographics of PAH patients and the higher frequency of left heart disease in older patients, we performed an analysis to evaluate the presence of a LHD phenotype

in a population of elderly patients with group 1 PH enrolled in the Italian multicentre PATRIARCA registry.

Methods

<u>Study population</u>

PATRIARCA (Registro dell'iPertensione ArTeriosa polmonaRe e ipertensIone polmonAre cRonica tromboemboliCa nell'Anziano) is a multicenter registry involving 11 PH centers in Northern Italy, aimed at gaining insights into the presentation and management of PAH and inoperable, persistent or relapsing chronic thromboembolic pulmonary hypertension (CTEPH) in elderly subjects. Those investigators who actively followed ≥20 PAH/CTEPH patients could join the registry, as an indicator of sufficient expertise in these diseases.

The study consists of 2 phases: one retrospective, which is concluded and has provided the data used for the present work, and another prospective that is about to start. The participating centers collected cross-sectional data on clinical, ECG, echocardiography, laboratory, and hemodynamic features, as well as on medical therapy, for all consenting consecutive patients with PAH or CTEPH and ≥70 year-old evaluated between December 1st, 2019 and September 15th, 2020. The earliest visit done during the study period was the reference, and information not collected at that time had to be the closest to the index date (e.g. if blood tests had been performed 1 and 8 weeks before the index visit, the former were recorded). Hemodynamic measurements at the time of the diagnosis were also requested, even if they were obtained before 70 years of age. Data were entered into an electronic clinical report form (eCRF) using the web-based application RedCap [35].

The registry was approved by the institutional ethics committees of the study centers (main approval 421/2018 CER Liguria).

For the purpose of this analysis, we considered the patients diagnosed with PAH, i.e. mPAP ≥25 mmHg and PAWP <15 mmHg, at 65 years of age or older. Furthermore, the following follow-up hemodynamic parameters need to be available: mean pulmonary artery pressure (mPAP), pulmonary artery wedge pressure (PAWP), cardiac output (CO), and pulmonary vascular resistance (PVR).

Definition of left heart disease phenotype

Included patients were grouped based on 2 definitions of LHD phenotype (**Table 1**).

First, LHD phenotype was identified like for the ex-PAS population of the AMBITION trial [34, as presence of either (i) ≥3 among diabetes, essential hypertension, body mass index (BMI) ≥30 Kg/m^2, or coronary artery disease (CAD) (clinical criteria) or (ii) PVR ≥3, but <3.75 WU or PVR ≥3.75 and <6.25 WU together with PAWP ≥13 and ≤15 mmHg (hemodynamic criteria). Second, we expanded the clinical criteria, classifying as LHD-likely also the patients who had permanent atrial fibrillation (AF) or echocardiographic parameters suggestive of LHD in addition to 2 among diabetes, hypertension, obesity, or CAD (**Table 1**).

Table 1. Criteria for left heart disease phenotype definition.

Main analysis
(i) Clinical criteria:
≥3 of among the following risk factors for LV diastolic dysfunction
- BMI ≥ 30 Kg/m^2
- essential hypertension
- diabetes mellitus
- significant CAD *
(ii) Hemodynamic criteria:
- PVR ≥3 and <3.75 WU
- or PVR ≥3.75 and <6.25 WU together with PAWP ≥13 and ≤15 mmHg
Secondary analysis
(i) Clinical criteria:
≥3 of among the following risk factors for LV diastolic dysfunction
- BMI ≥ 30 Kg/m^2
- essential hypertension
- diabetes mellitus
- significant CAD *
(ii) Expanded clinical criteria:
≥2 of the risk factors for LV diastolic dysfunction above + ≥1 among:
- permanent AF
- LV hypertrophy
- LVEF < 50%
- at least moderate mitral or aortic valve disease
- LA dilation
(iii) Hemodynamic criteria:
- PVR ≥3 and <3.75 WU
- or PVR ≥3.75 and <6.25 WU together with PAWP ≥13 and ≤15 mmHg

Clinical and hemodynamic criteria for left heart disease definition according to the main and secondary analysis.

* history of myocardial infarction and/or percutaneous coronary intervention, >50% stenosis in ≥1 vessel at coronary angiography, positive stress test, previous coronary artery bypass graft, or stable angina

LV, left ventricular; *BMI,* body mass index; *CAD,* coronary artery disease; *LVEF,* left ventricular ejection fraction; *LA,* left atrium; *PVR,* pulmonary vascular resistance; *PAWP,* pulmonary artery wedge pressure; *AF*, atrial fibrillation.

Statistical analysis

Normality was assessed with the Kolmogorov-Smirnov test. Continuous variables are presented as mean ± standard deviation (SD) or median [interquartile range, IQR, and were compared by 2-sided student t test or 2-sided Mann-Whitney test depending on the distribution. Categorical variables are reported as absolute count and percentages, and were compared by chi-squared test or Fisher exact test.

The correlates of the hemodynamic LHD profile were determined by means of a logistic regression model including the variables significantly different between patients with and without hemodynamics indicative of LHD.

Survival was assessed from the date of PAH diagnosis to the end of the study and evaluated using Kaplan-Meier estimates and log-rank testing.

P-values <0.05 were considered as statistically significant.

The analyses were performed with IBM SPSS Statistics version 25.0.

Results

One-hundred eighty ≥70 years-old patients with PAH or CTEPH were enrolled in the registry between December 1st 2019 and September 15th, 2020 (**Table 2**). After excluding those with CTEPH, diagnosed with PAH before 65 years of age, with post-capillary PH at the diagnostic right heart catheterization (RHC), and with incomplete hemodynamic information at follow-up, 69 subjects were included in the analysis (**Figure 1**).
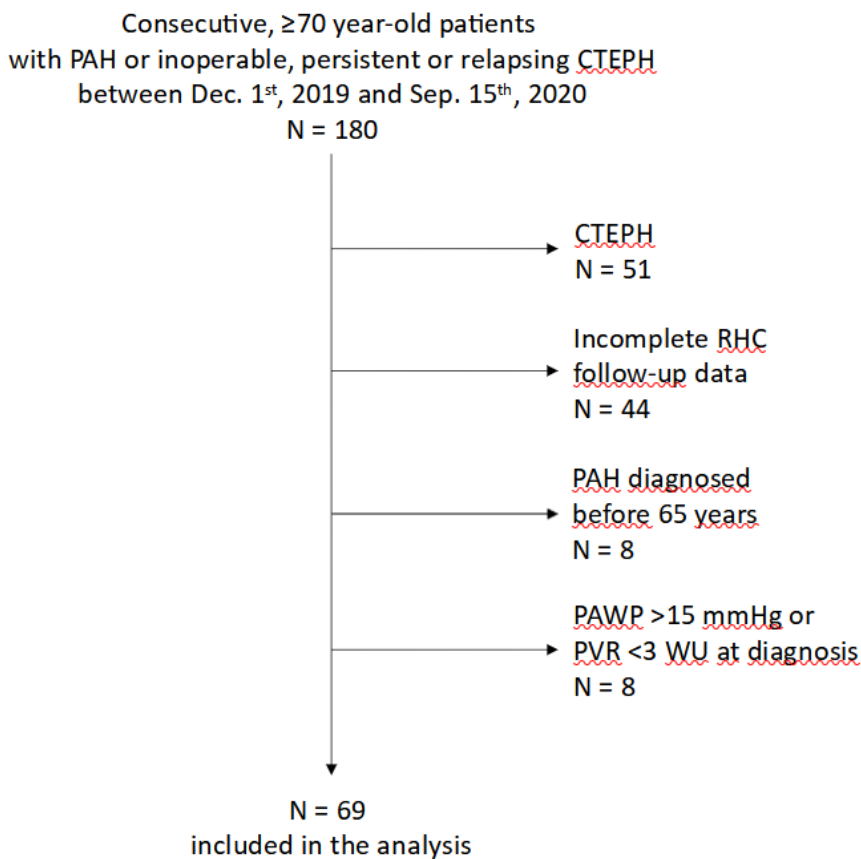
Figure 1 Patient enrollment in the PATRIARCA registry

Table 2. Patient enrollment among the Italian multicenter PATRIARCA registry.

Center	Enrolled patients (N=180)	Included in the analysis (N=69)
Cardiology, IRCCS Policlinico San Matteo, Pavia	56 (31)	23 (33)
Cardiology, IRCCS Policlinico San Martino, Genova	28 (16)	9 (13)
Cardiology, Ospedale San Gerardo, Monza	20 (11)	9 (13)
Cardiology, Ospedale di Bolzano	14 (8)	2 (3)
Cardiology, IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano	12 (7)	3 (4)
ASST Grande Ospedale Metropolitano Niguarda, Milano	12 (7)	8 (12)
Cardiology, Azienda sanitaria Universitaria Giuliano Isontina, Trieste	10 (6)	4 (6)
Cardiology, ASST degli Spedali Civili, Brescia	10 (6)	2 (3)
Cardiology, Ospedale di Circolo e Fondazione Macchi, Varese	9 (5)	4 (6)
Cardiology, ASST Papa Giovanni XXIII, Bergamo	5 (3)	3 (4)
Cardiology, Ospedale Maggiore della carità, Novara	4 (2)	2 (3)

Patient enrollment among the 11 centers participating in the Italian multicenter PATRIARCA registry between December 1st 2019 and September 15th 2020. Patient with a PAH diagnosis

after 65 years of age and with a complete haemodynamic evaluation were included in this analysis. Data are expressed as count (%).

These patients were mostly female (64%) with a mean age of 77±4 years (**Table 3**). The diagnosis of PAH had been made when they were 73±4 year-old: mPAP was 44±12 mmHg, PAWP was 10±3 mmHg, CO was 3.5±1.3 L/min, and PVR was 9.2±4.3 WU. Comorbidities were common: 45 (65%) had systemic hypertension, 17 (25%) CAD, 31 (45%) chronic obstructive pulmonary disease or an interstitial lung disease (not deemed the cause of PH by the investigators), and 26 (38%) chronic kidney disease (CKD). A the last RHC, which was performed 15 (4-33) months after reaching the diagnosis of PAH, mPAP, PAWP, CO, and PVR were 41±10 mmHg, 11±4 mmHg, 4.6±1.4 L/min, and 7.4±4.5 WU, respectively. Median right atrial pressure (RAP) was 7 (4-10) mmHg. Most subjects (63, 91%) were treated with PAH therapy and 52% were taking double oral combination therapy.

Table 3. Characteristics of the study population according to the main analysis criteria.

Characteristics	Overall (N=69)	No LHD profile (N=46)	LHD phenotype (N=23)	P
Demographics				
Age, y	77 ± 4	77 ± 4	77 ± 4	0.77
Female	44 (64)	29	15	0.86
Weight, Kg	64 ± 15	63 ± 14	69 ± 16	0.13
Height, cm	163 ± 9	162 ± 9	165 ± 8	0.20
BSA, m2	1.70 ± 0.22	1.67 ± 0.22	1.76 ± 0.22	0.11
BMI, Kg/m2	24 ± 5	24 ± 4	25 ± 5	0.27
Clinical and echocardiographic parameters				
WHO-FC I-II	32 (46)	21 (46)	11 (48)	0.80
Systemic hypertension	45 (65)	27 (59)	18 (78)	0.11
Diabetes	15 (22)	6 (13)	9 (39)	**0.01**
CAD	17 (25)	8 (17)	9 (39)	0.05
Permanent AF	3 (4)	2 (4)	1 (4)	1
Pulmonary disease	31 (45)	22 (48)	9 (39)	0.49
CKD	26 (38)	12 (26)	14 (61)	**0.003**
Previous/current cancer	8 (12)	6 (13)	2 (9)	0.60
SBP, mmHg	124 ± 15	124 ± 15	124 ± 15	0.98
DBP, mmHg	72 ± 9	73 ± 9	70 ± 9	0.22
SO2, %	95 [93; 97]	95 [93; 97]	95 [93; 97]	0.76
6MWD, meters	304 ± 199	315 ± 116	278 ± 127	0.35
Preserved LVEF	65 (94)	44 (96)	21 (91)	0.22
LVH	17 (25)	10 (22)	7 (30)	0.37
LA dilation	31 (45)	19 (41)	12 (52)	0.48
TAPSE, mm	20 ± 5	21 ± 4	19 ± 5	0.27
TRV, m/s	3.81 ± 0.76	3.91 ± 0.71	3.60 ± 0.82	0.12
TAPSE/TRV	5.6 ± 1.9	5.5 ± 1.9	5.8 ± 2.1	0.68
RVSP, mmHg	57 [42; 77]	62 [43; 80]	48 [38; 66]	0.15
RA dilation	53 (77)	34 (74)	19 (83)	0.38
Pericardial effusion	11 (16)	8 (17)	3 (13)	0.64
Most recent RHC				
RAP, mmHg	7 [4; 10]	6 [3; 9]	8 [5; 11]	0.06
mPAP, mmHg	41 ± 10	42 ± 11	38 ± 8	0.10
dPAP, mmHg	25 ± 9	27 ± 10	23 ± 6	0.13
sPAP, mmHg	70 ± 20	71 ± 21	66 ± 18	0.31
PAWP, mmHg	11 ± 4	10 ± 3	14 ± 5	**<0.001**
RAP/PAWP ratio	0.60 [0.46; 0.75]	0.60 [0.40; 0.75]	0.67 [0.46; 0.81]	0.61
PVR, WU	7.39 ± 4.53	8.30 ± 4.80	5.56 ± 3.31	**0.02**
Cardiac Output, L/min	4.59 ± 1.43	4.46 ± 1.55	4.85 ± 1.15	0.29
Cardiac index, L/min/m2	2.74 ± 0.81	2.67 ± 0.82	2.88 ± 0.79	0.30

Diagnosis to last RHC interval, months	15 [4; 33]	13 [4; 30]	18 [5; 38]	0.59
Treatment				
No PAH therapy	6 (9)	4 (9)	2 (9)	1
Bosentan	-	-	-	
Ambrisentan	17 (25)	12 (26)	5 (22)	0.69
Macitentan	32 (46)	21 (46)	11 (48)	0.74
ERA	49 (71)	33 (72)	16 (70)	0.85
Sildenafil	22 (32)	11 (24)	11 (48)	0.05
Tadalafil	25 (36)	18 (39)	7 (30)	0.48
Riociguat	3 (4)	3 (7)	0	0.21
PDE5i/GCs	50 (73)	32 (70)	18 (78)	0.45
Dual oral combination therapy	36 (52)	23 (50)	13 (57)	0.61
Selexipag	6 (9)	4 (9)	2 (9)	1
Treprostinil	-	-	-	
Epoprostenol i.v.	1 (1)	1 (2)	0	0.47
Inhaled iloprost	2 (3)	2 (4)	0	0.31
Beta blockers	9 (13)	5 (11)	4 (17)	0.45
RASi	23 (33)	10 (22)	13 (57)	**0.004**
MRA	32 (46)	20 (44)	12 (52)	0.44
Furosemide	57 (83)	38 (83)	19 (83)	1
Digoxin	6 (9)	5 (11)	1 (4)	0.37
Amiodarone	9 (13)	4 (9)	5 (22)	0.14
Warfarin	11 (16)	8 (17)	3 (13)	0.69
DOAC	11 (16)	6 (13)	5 (22)	0.31
SAPT	22 (32)	12 (26)	10 (44)	0.14
Statins	26 (38)	13 (28)	13 (57)	**0.02**
Ezetimibe	3 (4)	1 (2)	2 (9)	0.22
Glycemic treatment	12 (17)	4 (9)	8 (35)	**0.007**

Characteristics of patients with and without a left heart disease (LHD) phenotype according to the main analysis criteria. Data are expressed as n (%), mean ± SD or median [IQR], as appropriate.

BSA, body surface area; *BMI,* body mass index; *PAH,* pulmonary arterial hypertension; *WHO-FC,* World Health Organisation functional class; *CAD,* coronary artery disease; *AF,* atrial fibrillation; *CKD,* chronic kidney disease; *SBP,* systolic blood pressure; *DBP,* diastolic blood pressure; SO_2, oxygen saturation; *6MWD,* six minute walking distance; *LVEF*, left ventricular ejection fraction; *LVH,* left ventricular hypertrophy; *LA,* left atrium; *TAPSE,* tricuspid annular plane systolic excursion; *TRV,* tricuspid regurgitant velocity; *RVSP,* right ventricular systolic pressure; *RA,* right atrium; *RHC,* right heart catheterization; *RAP,* right atrial pressure; *mPAP,* *dPAP and sPAP* for mean, diastolic and systolic pulmonary artery pressure; *PAWP,* pulmonary
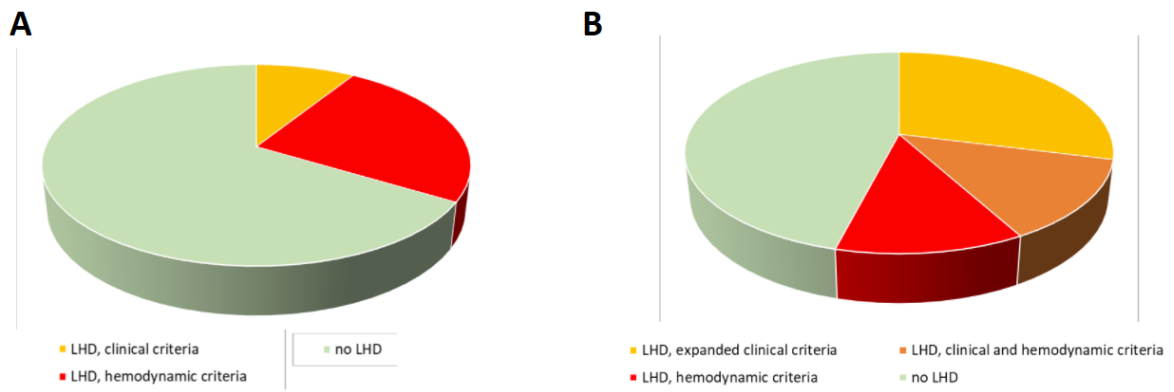
artery wedge pressure; *PVR,* pulmonary vascular resistance; *ERA,* endothelin receptor antagonist; *PDE5i,* phosphodiesterase type 5 inhibitor; *GCs,* guanylate cyclase stimulator; *RASi,* renin-angiotensin system inhibitors; *MRA,* mineralcorticoid receptor antagonist; *DOAC,* direct oral anticoagulant; *SAPT,* single antiplatelet therapy.

LHD phenotype analysis

According to the ex-PAS classification adopted for the AMBITION trial, 23 (33%) patients had a LHD phenotype: 6 based on clinical criteria and 17 based on hemodynamic criteria. Of note, none met both the clinical and hemodynamic criteria (**Figure 2A**).

The characteristics of subjects with and without LHD phenotype are summarized in **Table 3**. As expected, comorbidities were more frequent, PAWP was higher, and PVR was lower in the LHD phenotype group. There was also a trend for higher RAP. By contrast, no differences were found in functional class, 6 minute walking test, and echocardiographic parameters. The distribution of PAH drugs was comparable, while the use of renin-angiotensin inhibitors (RASi) and statins was greater in patients with LHD criteria.

The number of patients with a LHD phenotype rose to 37 (54%) when the expanded definition was employed: 20 met the modified clinical criteria, 8 the hemodynamic ones, and 9 both (**Figure 2B**). Their characteristics are outlined in **Table 4**. Overall, the contrasts between the LHD and no-LHD groups highlighted by applying the ex-PAS approach were confirmed when the expanded criteria were followed. As per definition, subjects with a profile suggestive for LHD showed higher rate of left ventricular hypertrophy, left atrial dilation and comorbities (diabetes and CKD). No substancial differences in hemodynamic profile were seen, except for a higher right atrial pressure and a not significant lower PVR. No differences in PAH therapy were identified, while they were more frequently treated with RASi.

A | **B**

- LHD, clinical criteria
- LHD, hemodynamic criteria
- no LHD

- LHD, expanded clinical criteria
- LHD, hemodynamic criteria
- LHD, clinical and hemodynamic criteria
- no LHD

Figure 2

Patients distribution according to main and secondary analysis LHD criteria.

Table 4. Baseline characteristics of the study population according to the secondary analysis.

Characteristic	Overall (N=69)	No LHD profile (N=32)	LHD phenotype (N=37)	P
Demographics				
Age at diagnosis, y	xx	76 ± 4	78 ± 3	0.11
Female	44 (64)	18 (56)	26 (70)	0.23
Weight, Kg	64 ± 15	62 ± 13	67 ± 16	0.16
Height, cm	163 ± 9	161 ± 9	164 ± 8	0.10
BSA, m^2	1.70 ± 0.22	1.65 ± 0.21	1.74 ± 0.23	0.14
BMI, Kg/m^2	24 ± 5	24 ± 4	25 ± 5	0.40
Clinical and echocardiographic parameters				
WHO-FC I-II	32 (46)	15 (47)	17 (46)	0.89
Systemic hypertension	45 (65)	17 (53)	28 (76)	0.05
Diabetes	15 (22)	2 (6)	13 (35)	**0.004**
CAD	17 (25)	6 (19)	11 (30)	0.29
Permanent AF	3 (4)	1 (3)	2 (5)	0.64
Pulmonary disease	31 (45)	17 (53)	14 (38)	0.20
CKD	26 (38)	5 (16)	21 (57)	**<0.001**
Previous/current cancer	8 (12)	5 (16)	3 (8)	0.33
SBP, mmHg	124 ± 15	125 ± 16	123 ± 14	0.68
DBP, mmHg	72 ± 9	74 ± 9	70 ± 9	0.11
SO$_2$, %	95 [93; 97]	94 [93; 96]	96 [94; 97]	0.31
6MWD, meters	304 ± 199	326 ± 131	279 ± 102	0.18
Preserved LVEF	65 (94)	31 (97)	34 (92)	0.63
LVH	17 (25)	3 (9)	14 (38)	**0.005**
LA dilation	31 (45)	7 (22)	24 (65)	**0.001**
TAPSE	20 ± 5	21 ± 5	20 ± 5	0.64
TRV, m/s	3.81 ± 0.76	3.87 ± 0.69	3.75 ± 0.82	0.53
TAPSE/TRV	5.6 ± 1.9	5.5 ± 1.9	5.7 ± 2.0	0.79
RVSP, mmHg	57 [42; 77]	65 [43; 77]	54 [40; 85]	0.50
RA dilation	53 (77)	24 (75)	29 (78)	0.29
Pericardial effusion	11 (16)	6 (19)	5 (14)	0.55
Most recent RHC				

RAP, mmHg	7 [4; 10]	5 [3; 8]	8 [5; 10]	**0.03**
mPAP, mmHg	41 ± 10	42 ± 12	40 ± 9	0.48
dPAP, mmHg	25 ± 9	27 ± 11	24 ± 7	0.16
sPAP, mmHg	70 ± 20	71 ± 21	68 ± 19	0.47
PAWP, mmHg	11 ± 4	10 ± 3	12 ± 5	0.64
RAP/PAWP ratio	0.60 [0.46; 0.75]	0.59 [0.39; 0.72]	0.64 [0.47; 0.81]	0.28
PVR, WU	7.39 ± 4.53	8.50 ± 5.26	6.42 ± 3.58	0.06
Cardiac Output, L/min	4.59 ± 1.43	4.39 ± 1.66	4.77 ± 1.19	0.28
Cardiac index, L/min/m^2	2.74 ± 0.81	2.63 ± 0.93	2.83 ± 0.70	0.32
Diagnosis to last RHC interval, months	15 [4; 33]	12 [4; 30]	18 [4; 38]	0.48
Treatment				
No PAH therapy	6 (9)	2 (6)	4 (11)	0.50
Bosentan	-	-	-	
Ambrisentan	17 (25)	7 (22)	10 (27)	0.62
Macitentan	32 (46)	17 (53)	15 (41)	0.35
ERA	49 (71)	24 (75)	25 (68)	0.50
Sildenafil	22 (32)	9 (28)	13 (35)	0.53
Tadalafil	25 (36)	10 (31)	15 (41)	0.42
Riociguat	3 (4)	3 (9)	0	0.06
PDE5i/GCs	50 (73)	22 (69)	28 (76)	0.52
Dual oral combination therapy	36 (52)	16 (50)	20 (54)	0.74
Selexipag	6 (9)	3 (9)	3 (8)	0.85
Treprostinil	-	-	-	
Epoprostenol i.v.	1 (1)	1 (3)	0	0.29
Inhaled iloprost	2 (3)	1 (3)	1 (3)	0.92
Beta blockers	9 (13)	3 (9)	6 (16)	0.40
RASi	23 (33)	6 (19)	17 (46)	**0.02**
MRA	32 (46)	14 (44)	18 (49)	0.69
Furosemide	57 (83)	24 (75)	33 (89)	0.12
Digoxin	6 (9)	3 (9)	3 (8)	0.85
Amiodarone	9 (13)	4 (13)	5 (14)	0.87
Warfarin	11 (16)	5 (16)	6 (16)	0.91

DOAC	11 (16)	5 (16)	6 (16)	0.91
SAPT	22 (32)	7 (22)	15 (41)	0.10
Statins	26 (38)	11 (34)	15 (41)	0.60
Ezetimibe	3 (4)	0	3 (8)	0.10
Glycemic treatment	12 (17)	1 (3)	11 (30)	**0.004**

Characteristics of patients with and without a left heart disease (LHD) phenotype according to the secondary analysis criteria. Data are expressed as n (%), mean ± SD or median [IQR], as appropriate.

LHD, left heart disease; *BSA,* body surface area; *BMI,* body mass index; *PAH,* pulmonary arterial hypertension; *WHO-FC,* World Health Organisation functional class; *CAD,* coronary artery disease; *AF,* atrial fibrillation; *CKD,* chronic kidney disease; *SBP,* systolic blood pressure; *DBP,* diastolic blood pressure; *SO$_2$,* oxygen saturation; *6MWD,* six minute walking distance; *LVEF*, left ventricular ejection fraction; *LVH,* left ventricular hypertrophy; *LA,* left atrium; *TAPSE,* tricuspid annular plane systolic excursion; *TRV,* tricuspid regurgitant velocity; *RVSP,* right ventricular systolic pressure; *RA,* right atrium; *RHC,* right heart catheterization; *RAP,* right atrial pressure; *mPAP, dPAP and sPAP* for mean, diastolic and systolic pulmonary artery pressure; *PAWP,* pulmonary artery wedge pressure; *PVR,* pulmonary vascular resistance; *ERA,* endothelin receptor antagonist; *PDE5i,* phosphodiesterase type 5 inhibitor; *GCs,* guanylate cyclase stimulator; *RASi,* renin-angiotensin system inhibitors; *MRA,* mineralcorticoid receptor antagonist; *DOAC,* direct oral anticoagulant; *SAPT,* single antiplatelet therapy.

Survival

Median follow-up from diagnosis was 4 [2-6] years for the whole cohort. At the end of the observation period, 13 (12%) patients were dead, with the estimated survival rates being 97%, 95%. and 91% at 2, 4, and 6 years, respectively, from diagnosis.

Four (13%) subjects with a LHD phenotype as per ex-PAS criteria and 9 (12%) without were dead at the study closure (P =0.87). When the expanded definition of LHD phenotype was used, the deaths were 9 (16%) and 4 (8%) in the LHD and no-LHD group, respectively (P =0.16).

Discussion

Demographics of patients with PH have changed over time, with an increasing number of elderly patients with a diagnosis of group 1 (PAH) and group 4 (CTEPH) pulmonary hypertension [21-28, 36-38]. This special population have higher prevalence of comorbidities and risk factors for left ventricular diastolic dysfunction compared with younger patients, which also usually have better clinical outcomes [28,29,39]. A correct diagnosis between PAH and PH secondary to left heart disease is mandatory given the possible deleterious effect of pulmonary vasodilators in the latter group [1, 40,41]. Although right heart catheterization is the gold standard for the diagnosis of PH, it can be insufficient to differentiate among pre- and post-capillary PH [1, 42,43]. Thus, it is recommended to identify patients with a LHD phenotype through multiple clinical, echocardiographic and hemodynamic features [1,44].

During the first months of enrolment in the AMBITION trial, a high prevalence of patients with risk factors for left heart disease were enrolled, leading to a modification in the inclusion criteria. Recently, McLaughlin et al. analyzed clinical differences and outcome among patients with a LHD phenotype included during this period (ex-primary analysis set) compared with subjects enrolled after the protocol amendment became effective (primary analysis set) [34]. The ex-primary analysis set cohort showed benefit from PAH treatment but less pronounced compared with the primary analysis set cohort. Nevertheless, they had a greater incidence of adverse events and study drug discontinuation [34].

In this study we sought to evaluate a real-world population of elderly patients with a diagnosis of PAH and to examine the characteristics and clinical outcome of subjects with a left heart disease phenotype. We enrolled a population of 69 patients with a median age at PAH diagnosis of 73 years, that is in line with recent literature. In the COMPERA registry the median age of incident idiopathic PAH was 71 years and up to 63% of patients were older than 65 years [8]. We found a high rate of comorbidities such as systemic hypertension (65%), diabetes (22%) and ischemic heart disease (25%), comparable with findings in the subgroup of patients with at

least 75 years enrolled in the Swedish SPAHR registry (66%, 30% and 26%, respectively) [29]. No specific PAH treatment was prescribed in 9% of subjects, as in the SPAHR registry, while a dual oral combination therapy was administered in 52% of the patients, a frequency higher than the one reported in the COMPERA (31.6% one year after diagnosis) and the Swedish registries (14% and 9% in the age groups 65-74 years and ≥75 years, respectively) [26,29]. This could be partly explained by the different enrolling periods and evolution in the management of PAH during the last years, favouring a sequential or upfront combination therapy to reach a low risk status profile [1, 45,46]. Nonetheless, the oral selective IP receptor agonist selexipag was use as triple oral combination treatment in 9% of the subjects, while no patient received subcutaneous treprostinil and the intravenous prostacyclin analog epoprostenol was administered only in one subject, confirming that elderly patients are treated less aggressively [47].

According to the criteria applied in the AMBITION trial, 33% of patients from our cohort had a LHD phenotype. This proportion increased to 54% when in the secondary analysis we included other parameters suggestive of LHD, such as the presence of LVH, left atrial dilation and permanent atrial fibrillation. It can be argued that many of these patients might have been misclassified as pre-capillary PH. Anyway, we included only patients with a definite pre-capillary PH at diagnostic right heart catheterization. Nevertheless, patients enrolled in PATRIARCA were treated in dedicated PH centres, after a diagnostic work-up in accordance with international guidelines, at last available RHC we found a median PAWP of 11 ± 4 mmHg, similar to that reported in the COMPERA (10 ± 3 mmHg) and REVEAL (9 ± 4 mmHg) registries [24,26]. No substantial differences in PAH specific treatment was underlined among patients with and without a LHD profile and overall mortality was comparable between the two groups. Albeit this analysis is not designed to investigate treatment effectiveness, we can highlight that in real-world elderly PAH patients are frequently treated with pulmonary vasodilators despite randomized clinical trials usually excluded this special population and the

presence of a LHD phenotype. The small sample size didn't allow to notice differences in overall mortality, but it is known that comorbidities such as ischemic heart disease and CKD are independently associated with survival in this subset [29].

We decided to modify clinical criteria from the analysis of McLaughlin et al. [34, introducing permanent atrial fibrillation and echocardiographic parameters as suggestive of LHD, because it is recommended to identify a LHD phenotype through a multiparametric approach [1, 44]. Anyway, it is not well defined which is the better way to detect a LHD profile that will not respond to standard PAH treatment and other parameters might improve this evaluation.

This study has several limitations. Firstly, it is limited by its retrospective observational nature, with possibility of selection bias, lack of standardization of registered variables and missing follow-up data. Anyhow, all patients were treated in dedicated PH centres in which diagnostic work-up, treatment prescription and follow up were conformed to the ESC/ERS international guidelines [1]. The sample size is limited to 69 patients, but we considered a rare disease such as PAH in a subset of specific population. Lastly, echocardiographic and hemodynamic parameters were obtained from the last available examination and not at diagnosis, with a possible influence from therapies prescribed meanwhile.

Conclusions

Although evidence from randomized clinical trials are limited, we report that in real world a substantial proportion of elderly PAH patients are treated with pulmonary vasodilators despite having elements suggestive for left heart disease and no difference in overall mortality was noticed. This highlight the importance to include these patients in future studies to evaluate the efficacy and safety profile of PAH specific treatment in this special population

References

1. Galiè, N. et al. Pulmonary Hypertension (Guidelines on Diagnosis and Treatment of). Eur Resp J. 2015, 46, p. 903-975.

2. Budhiraja, R., Tuder, R.M. e Hassoun, P.M. Endothelial dysfunction in pulmonary hypertension. Circulation. 2004, 109, p. 159-165.

3. Galiè, N. and the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005, 353, p. 2148-2157.

4. Galiè, N., et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation. 2009, 119, p. 2894-2903.

5. Langleben, D.Z., et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med. 2013, 369, p. 330-340.

6. Galiè, N., et al. Ambrisentan for the treatment of pulmonary arterial hypertension. Results of the ambrisentan in pulmonary arterial hypertension, randomized, doubleblind, placebo- controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation. 2008, 117, p. 3010- 3019.

7. Rubin, L.J., et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002, 346, p. 896-903.

8. Pulido, T., et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013, 369, p. 809-818.

9. Barst, R.J., et al. A comparison of continuous intravenous epoprostenol (prostacyclin). 1996, 334, p. 296-302.

10. Olschewski, H., et al. Inhaled iloprost in severe pulmonary hypertension. N Engl J Med. 2002, 347, p. 322–329.

11. Simonneau, G., et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension. A double-blind,

randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2002, 165, p. 800-804.

12. Sitbon, O., et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med. 2015, 373, p. 2522-2533.

13. Galiè, N., et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. New Eng J Med. 2015, 379(9), p. 834–844.

14. Ende-Verhaar, , Y.M., et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism: a contemporary view of the published literature. Eur Respir J. 2017, 49, p. 160-179.

15. Mahmud, E., et al. Chronic thromboembolic pulmonary hypertension: evolving therapeutic approaches for operable and inoperable disease. J Am Coll Cardiol. 2018, 71(21), p. 2468-2486.

16. Ogawa, A., et al. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: results of a multicenter registry. Circ Cardiovasc Qual Outcomes. 2017, 10, p. 004-029.

17. Inami, T., et al. Long-term outcomes after percutaneous transluminal pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Circulation. 2016, 134, p. 2030-2032.

18. Ghofrani, H.A., et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Eng J Med. 2013, 369, p. 319-329.

19. Simonneau, G., et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2). Eur Respir J. 2014, 45, p. 1293-1302.

20. D'Alonzo GE, Barst RJ, Ayres SM et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991 Sep 1;115(5):343-9. doi: 10.7326/0003-4819-115-5-343.

21. Pugh ME, Sivarajan L, Wang L et al. Causes of pulmonary hypertension in the elderly.Chest. 2014 Jul;146(1):159-166. doi: 10.1378/chest.13-1900.

22. Vistarini N, Morsolini M, Klersy C et al. Pulmonary endarterectomy in the elderly: safety, efficacy and risk factors. J Cardiovasc Med (Hagerstown). 2016 Feb;17(2):144-51. doi: 10.2459/JCM.0000000000000327.

23. Mueller-Mottet S, Stricker H, Domenighetti G et al. Long-term data from the Swiss pulmonary hypertension registry. Respiration. 2015;89(2):127-40. doi: 10.1159/000370125.

24. Humbert M, Sitbon O, Chaouat A et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006 May 1;173(9):1023-30. doi: 10.1164/rccm.200510-1668OC.

25. Badesch DB, Raskob GE, Elliott CG et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest. 2010 Feb;137(2):376-87. doi: 10.1378/chest.09-1140.

26. Hoeper MM, Huscher D, Ghofrani HA et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. Int J Cardiol. 2013 Sep 30;168(2):871-80. doi: 10.1016/j.ijcard.2012.10.026.

27. Opitz, C.F., et al. Pre-capillary, combined, and post-capillary pulmonary hypertension: a pathophysiological continuum. J Am Coll Cardiol. 2016, 68, p. 368-378.

28. Ling Y, Johnson MK, Kiely DG et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. Am J Respir Crit Care Med. 2012 Oct 15;186(8):790-6. doi: 10.1164/rccm.201203-0383OC.

29. Hjalmarsson C, Rådegran G, Kylhammar D et al. Impact of age and comorbidity on risk stratification in idiopathic pulmonary arterial hypertension. Eur Respir J. 2018 May 3;51(5):1702310. doi: 10.1183/13993003.02310-2017.

30. Benza, R.L., et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. Chest. 2012, 141, p. 354-362.

31. Raina, A. e Humbert, M. Risk assessment in pulmonary arterial hypertension. Eur Respir Rev. 2016, 25, p. 390-398.

32. Poms, A.D., et al. Comorbid conditions and outcomes in patients with pulmonary arterial hypertension: a REVEAL registry analysis. Chest. 2013, 144, p. 169-176.

33. Rådegran, G., Kylhammar, D. e al., et. Impact of age and comorbidity on risk stratification in idiopathic pulmonary arterial hypertension. Eur Respir J. 2018, 51, p. 170-231.

34. McLaughlin VV, Vachiery JL, Oudiz RJ et al. Patients with pulmonary arterial hypertension with and without cardiovascular risk factors: Results from the AMBITION trial. J Heart Lung Transplant. 2019 Dec;38(12):1286-1295. doi: 10.1016/j.healun.2019.09.010.

35. Harris PA, Taylor R, Thielke R et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009 Apr;42(2):377-81. doi: 10.1016/j.jbi.2008.08.010.

36. Rådegran G, Kjellström B, Ekmehag B et al. Characteristics and survival of adult Swedish PAH and CTEPH patients 2000-2014. Scand Cardiovasc J. 2016 Aug;50(4):243-50. doi: 10.1080/14017431.2016.1185532.

37. Frost AE, Badesch DB, Barst RJ et al. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US Contemporary Registries. Chest. 2011 Jan;139(1):128-37. doi: 10.1378/chest.10-0075.

38. McGoon MD, Benza RL, Escribano-Subias P et al. Pulmonary arterial hypertension: epidemiology and registries. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D51-9. doi: 10.1016/j.jacc.2013.10.023.

39. Rose JA, Cleveland JM, Rao Y et al. Effect of Age on Phenotype and Outcomes in Pulmonary Arterial Hypertension Trials. Chest. 2016 May;149(5):1234-44. doi: 10.1016/j.chest.2015.11.008.

40. Bermejo J, Yotti R, García-Orta R et al. Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: a multicenter, double-blind, randomized clinical trial. Eur Heart J. 2018 Apr 14;39(15):1255-1264. doi: 10.1093/eurheartj/ehx700.

41. Rosenkranz S, Gibbs JSR, Wachter R et al. Left ventricular heart failure and pulmonary hypertension. Eur Heart J. 2016 Mar 21;37(12):942-54. doi: 10.1093/eurheartj/ehv512.

42. Hoeper MM, Lam CSP, Vachiery JL et al. Pulmonary hypertension in heart failure with preserved ejection fraction: a plea for proper phenotyping and further research. Eur Heart J. 2017 Oct 7;38(38):2869-2873. doi: 10.1093/eurheartj/ehw597.

43. Halpern SD, Taichman DB. Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. Chest. 2009 Jul;136(1):37-43. doi: 10.1378/chest.08-2784.

44. Vachiéry JL, Tedford RJ, Rosenkranz S et al. Pulmonary hypertension due to left heart disease. Eur Respir J. 2019 Jan 24;53(1):1801897. doi: 10.1183/13993003.01897-2018.

45. Burks M, Stickel S, Galiè N. Pulmonary Arterial Hypertension: Combination Therapy in Practice. Am J Cardiovasc Drugs. 2018 Aug;18(4):249-257. doi: 10.1007/s40256-018-0272-5.

46. Sitbon O, Gaine S. Beyond a single pathway: combination therapy in pulmonary arterial hypertension. Eur Respir Rev. 2016 Dec;25(142):408-417. doi: 10.1183/16000617.0085-2016.

47. Campean IA, Lang IM. Treating pulmonary hypertension in the elderly. Expert Opin Pharmacother. 2020 Jul;21(10):1193-1200. doi: 10.1080/14656566.2020.1739270.