Risk Factor Profiles Achieved with Medical Therapy in Prevalent Patients with Pulmonary Arterial and Distal Chronic Thromboembolic Pulmonary Hypertension

Philipp Bartenstein Stéphanie Saxer Paula Appenzeller Mona Lichtblau
Esther I. Schwarz Silvia Ulrich

Clinic of Pulmonology, University Hospital Zurich, Zurich, Switzerland

Keywords

Pulmonary arterial hypertension · Chronic thromboembolic pulmonary hypertension · Combination therapy · Risk stratification · Therapeutic goals

Abstract

Background: The latest pulmonary hypertension (PH) guidelines define therapeutic goals in terms of symptoms, exercise capacity, and haemodynamics for patients with pulmonary arterial hypertension (PAH) and recommend advanced combined medical therapy. For inoperable or post-surgical residual distal chronic thromboembolic PH (CTEPH) medical treatment is similarly advised. **Objectives:** We analysed whether risk factor goals are achieved and combination therapy is used in prevalent patients with PAH or distal CTEPH. **Methods:** PAH or distal CTEPH patients who were seen at the University Hospital Zurich during the last year were analysed in terms of demography, clinical data, medication, and therapeutic goals. Achievement of therapeutic goals was defined as New York Heart Association (NYHA) class $\leq$ II, N-terminal pro-brain natriuretic peptide (NTpro-BNP) <300 ng/L, and 6-min walking distance (6MWD) >440 m. **Results:** A total of 108 PAH patients (age 59 ± 18 years, 62% female, 64% idiopathic, 36% associated) and 38

distal CTEPH patients (age 69 ± 14 years, 55% female) were included. They had been diagnosed on average 66 ± 48 months ($\pm$ SD) previously. The percentage of PAH/CTEPH patients with NYHA $\leq$ II was 52/53, respectively, the percentage of those with NTproBNP <300 ng/L was 61/52, and with 6MWD >440 m 63/50. Overall, 33/31% fulfilled 3 and 29/35% fulfilled 2 of these goals. Regarding therapy, 43% of PAH patients were on double and 10% on triple combination therapy, whereas 16% of distal CTEPH patients were on double and 3% on triple combination therapy. **Conclusions:** In this real-life cohort of prevalent patients with PAH or distal CTEPH, targeted drug therapy resulted in an achievement of $\geq 2/3$ predefined therapeutic goals in 2/3 of patients. Patients with PAH were more likely to receive combination therapy compared to CTEPH patients. © 2018 S. Karger AG, Basel

Introduction

The main symptom of precapillary pulmonary hypertension (PH) is progressive dyspnoea on exertion associated with reduced daily activity and impaired quality of life [1, 2]. In the absence of relevant lung disease, the main forms of precapillary PH are pulmonary arterial hy-

pertension (PAH) and chronic thromboembolic PH (CTEPH) [3]. Guidelines recommend regular assessment of the severity and prognosis of PH using multidimensional risk stratification including clinical, haemodynamic, and exercise data employing defined parameters with known prognostic significance [3]. Recent data have confirmed the prognostic value of these risk factors at baseline and have shown that achievement of goals including mere clinical data are of prognostic importance during initial follow-up [4–6]. Of interest, the prognosis of patients achieving these goals at follow-up on therapy was comparable to patients who already presented with a favourable risk factor profile. According to the French registry, follow-up assessments using brain natriuretic peptides (BNP) as a substitute for invasive pulmonary haemodynamics in addition to New York Heart Association (NYHA) functional class and 6-min walking distance (6MWD) accurately predicted transplant-free survival in patients with idiopathic, hereditary, or drug- and toxin-induced PAH [4].

During the last decades, several novel drugs were approved for PAH [3]. More than half of CTEPH patients can be treated and substantially ameliorated with pulmonary endarterectomy [7–9] and recently, significant functional improvements have been demonstrated with balloon pulmonary angioplasty in a further subgroup [10, 11]. The remaining patients with surgically inaccessible or post-interventional residual PH due to additional distal involvement (summarised as distal CTEPH) show similarities with PAH and are accordingly treated with drug therapy [12–15]. Combination drug therapy has been recommended in the latest guidelines for patients with PAH who do not achieve therapeutic goals in terms of symptoms, exercise capacity, and haemodynamics, and studies have shown an additional benefit of combination compared to a single drug therapy [16, 17]. The efficacy of combination therapy in distal CTEPH is less clear due to lack of studies. However, from a pathophysiological perspective, distal CTEPH might be expected to respond comparably to PAH [13] and thus an increasing number of PH centres also use combination therapy in patients with distal CTEPH [3, 18].

Studying real-life cohorts enhances the understanding of epidemiology and treatment outcomes and is less susceptible to selection bias. However, cohort studies usually provide less comprehensive data compared to prospective controlled trials and their findings have to be interpreted with caution due to lack of blinding and a comparative control group. Nevertheless, real-life data complement the knowledge gained in clinical trials. Over

the last 2 decades, prognostic data from different registries have been published [18–25]. Most analyses included only incident patients with PAH and analysed parameters at baseline or during a short-term follow-up [4–6, 26]. However, little is known about the achievement of predefined therapeutic goals in prevalent patients with PAH/distal CTEPH in real life and the long-term course on drug therapy. We thus reviewed all prevalent patients with PAH or distal CTEPH seen at least once between November 2015 and November 2016 at our institution and analysed to which extent the basic therapeutic goals (according to PH guidelines and recently published cohort data) are achieved on which drug regimens. We therefore focused on assessing NYHA functional class, exercise capacity measured by the 6MWD, and right ventricular function by measuring N-terminal pro-BNP (NTproBNP).

Methods

Patients with PAH or CTEPH treated in the PH centre of the University Hospital Zurich who gave written informed consent to be registered and followed up in an internal pseudonymised database were checked for eligibility. The study was approved by the local ethics committee of Zurich (Req-2016-00786) and registered on clinicaltrials.gov (NCT03198910).

PAH and CTEPH were diagnosed and classified according to the latest guidelines [12]. PAH subgroups with idiopathic/heritable PAH (IPAH) and associated with connective tissue disease, human immunodeficiency virus, portal hypertension, and congenital heart disease were eligible. As genetic testing for PAH is not reimbursed by Swiss health insurance companies, idiopathic and hereditary PAH were summarised as IPAH. Distal CTEPH was defined as either inoperable or persistent PH after pulmonary endarterectomy. All prevalent patients (diagnosed >12 months previously) with PAH/distal CTEPH who were seen at the PH centre of the University Hospital Zurich between November 2015 and November 2016 were analysed.

Patient characteristics (age, gender, BMI, PH group) and pulmonary haemodynamics assessed by diagnostic right heart catheterisation were retrieved at the time of diagnosis and the following data during regular follow-up after 3, 6, and 12 months and at the last prevalent visit: NYHA class, 6MWD, and NTproBNP. The following three thresholds of these outcome parameters were used to assess the achievement of treatment goals during routine follow-up: NYHA class ≤II, NTproBNP <300 ng/L, and 6MWD >440 m. These three parameters are, amongst others, associated with a 1-year mortality risk <5% [12]. Patients whose parameters were available at least at the time of diagnosis and the last prevalent visit were included (main group). For a more detailed insight, a subgroup which had at least 3 out of the 5 time points (diagnosis, after 3, 6, and 12 months, last prevalent visit) were analysed separately (comprehensive subgroup). The last prevalent visit was defined as the last visit the patient had in the evaluated period.

PH-targeted drug therapy included endothelin receptor antagonists (ERA), prostanoids, phosphodiesterase type 5 inhibitors (PDE-5-I), soluble guanylate cyclase stimulator (sGC), or high-dose calcium channel blockers in cases of vasoactive PAH.

Analyses were performed using SPSS Statistics version 23 (SPSS, Chicago, IL, USA). Data were summarised as means (standard deviation or percentages) and medians (quartiles) according to normal or non-normal distribution. Differences between groups were assessed by independent *t* tests or Mann-Whitney U tests according to normality distribution. Baseline and follow-up data (changes over time) were compared using analysis of variance (ANOVA), paired *t* tests, or Wilcoxon tests. Multiple regression was used to study factors influencing outcomes. A two-sided *p* value <0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 143 of 313 patients (105 PAH, 38 distal CTEPH) fulfilled the inclusion criteria and had data available at least at diagnosis and at the last prevalent visit. The flow of patients throughout the study is shown in Figure 1. Characteristics of patients with PAH and CTEPH are shown in Tables 1 and 2, respectively. Patients with PAH were younger than those with CTEPH without other demographic differences. Most patients with PAH were idiopathic (63%) or connective tissue disease-associated (20%); 77% of the patients with PAH were treated with ERA, 12% with prostanoids, 56% with PDE-5-I, and 10% with sGC. 44% were on double and 10% on triple combination therapy. The median follow-up time of PAH patients was 50 (29; 93) months (range 14–274 months). During follow-up, NYHA class significantly improved from 3 (2; 3) to 2 (2; 3) ($p < 0.05$); in particular, the number of patients in NYHA class I increased from 1 to 12%. 6MWD and NTproBNP remained unchanged.

Most patients with distal CTEPH were inoperable and treated with ERA (50%), prostanoids (3%), PDE-5-I (21%), and sGC stimulator (42%); 81% received a single drug, 16% were on a double, and 3% on a triple combination therapy. The median follow-up time of distal CTEPH was 40 (25; 103) months (range of 12–173 months). 6MWD and NTproBNP did not change significantly during follow-up. However, NYHA class significantly improved from 3 (2; 3) to 2 (2; 3) ($p < 0.05$). The percentage of patients with NYHA functional class I and II increased by 11 and 10%, respectively, from NYHA class III and IV.

Monotherapy versus Combination Therapy

Of patients with PAH, 48 were on a single drug (including 7 on high-dose calcium channel blockers due to

Fig. 1. Flowchart of patients throughout the study. PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy.

vasoactive PAH) and 57 were on combination therapy (Tables 1, 3). Age and BMI of patients in the single versus combination therapy groups did not differ at the time of diagnosis. Patients receiving monotherapy had a lower NTproBNP and mPAP and a higher cardiac index compared to those receiving combination therapy and tended to have a longer 6MWD and lower NYHA class. The change of NYHA functional class ($p = 0.070$), 6MWD ($p = 0.990$), and NTproBNP ($p = 0.208$) over time (first visit to last prevalent visit) did not differ between the two groups. Patients with combination therapy tended to be treated for a longer time than those with single therapy (58 [30; 110] vs. 46 [27; 82] months).

Only 7 of 38 patients with distal CTEPH received combination therapy (Tables 2, 3). At the time of diagnosis,

Table 1. Characteristics of 105 prevalent patients with PAH

	Diagnosis	<i>n</i>	Last pre- valent visit	<i>n</i>
Females	65 (62)	105		
Age, years	55 (38; 70)	105	59 (44; 75)*	105
BMI	26 (22; 29)	101	26 (22; 29)	92
Cardiac index, L/min/ m ²	2.7 (2.2; 3.2)	96		
mPAP, mm Hg	43 (32; 54)	102		
RAP, mm Hg	7 (5; 10)	99		
Follow-up, months			50 (29;93)	105
<i>PAH classification</i>				
Idiopathic/heritable	66 (63)			
Connective tissue dis- ease	21 (20)			
HIV infection	2 (2)			
Portal hypertension	3 (3)			
Congenital heart dis- ease	13 (12)			
<i>PAH therapy</i>				
ERA	81 (77)			
Prostanoid	13 (12)			
PDE-5-I	59 (56)			
sGC	11 (10)			
Monotherapy	48 (46)			
Double combination	46 (44)			
Triple combination	11 (10)			
<i>Follow-up parameters</i>				
NYHA functional class	3 (2; 3)	99	2 (2; 3)*	105
NYHA I	1 (1)		13 (12)	
NYHA II	34 (34)		42 (40)	
NYHA III	52 (53)		41 (39)	
NYHA IV	12 (12)		9 (9)	
6MWD, m	471 (363; 565)	90	480 (402; 565)	79
NTproBNP, ng/L	420 (159; 989)	83	217 (83; 847)	75

Data are shown as median (quartiles) or *n* (%). PAH, pulmonary arterial hypertension; BMI, body mass index; mPAP, mean pulmonary arterial pressure; RAP, right atrial pressure; HIV, human immunodeficiency virus; ERA, endothelin receptor antagonist; PDE-5-I, phosphodiesterase type 5 inhibitor; sGC, soluble guanylate cyclase stimulator; NYHA, New York Heart Association; 6MWD, 6-min walking distance; NTproBNP, N-terminal pro-brain natriuretic peptide. * $p < 0.001$ versus diagnosis.

these 7 patients had a significantly higher NTproBNP and mPAP compared to patients receiving monotherapy. CTEPH patients on combination therapy also tended to be younger and have a lower 6MWD and cardiac index than those treated with monotherapy. When comparing

Table 2. Characteristics of 38 prevalent patients with CTEPH

	Diagnosis	<i>n</i>	Last pre- valent visit	<i>n</i>
Females	21 (55)	38		
Age, years	67 (57; 73)	38	72 (60; 80)*	38
BMI	27 (23; 32)	38	27 (25; 32)	32
Cardiac index, L/min/m ²	2.7 (2.4; 3.0)	36		
mPAP, mm Hg	36 (32; 48)	37		
RAP, mm Hg	8 (4; 13)	35		
Follow-up, months			40 (25; 103)	38
<i>CTEPH classification</i>				
Inoperable	30 (79)			
Persistent PH after PEA	8 (21)			
<i>CTEPH therapy</i>				
ERA	19 (50)			
Prostanoid	1 (3)			
PDE-5-I	8 (21)			
sGC	16 (42)			
Monotherapy	31 (81)			
Double combination	6 (16)			
Triple combination	1 (3)			
<i>Follow-up parameters</i>				
NYHA functional class	3 (2;3)	38	2 (2;3)**	38
NYHA I	0 (0)		4 (11)	
NYHA II	12 (32)		16 (42)	
NYHA III	19 (50)		15 (39)	
NYHA IV	7 (18)		3 (8)	
6MWD, m	494 (334; 575)	33	480 (360;580)	31
NTproBNP, ng/L	490 (121; 1,596)	31	289 (146; 877)	29

Data are shown as median (quartiles) or *n* (%). CTEPH, chronic thromboembolic pulmonary hypertension; BMI, body mass index; mPAP, mean pulmonary arterial pressure; RAP, right atrial pressure; PEA, pulmonary endarterectomy; ERA, endothelin receptor antagonists; PDE-5-I, phosphodiesterase type 5 inhibitor; sGC, soluble guanylate cyclase stimulator; NYHA, New York Heart Association; 6MWD, 6-min walking distance; NTproBNP, N-terminal pro-brain natriuretic peptide. * $p < 0.001$ versus diagnosis; ** $p = 0.001$ versus diagnosis.

changes over time (first vs. last prevalent visit) in patients with CTEPH, the only significant difference between single and combination therapy was found in NTproBNP ($p = 0.040$), whereby combination therapy resulted in a larger reduction in NT-proBNP.

Achievement of Therapeutic Goals

At the time of diagnosis, 35% of PAH patients were already in NYHA class $\leq$ II, 43% had a NTproBNP <300

Table 3. Prevalent patients with PAH or distal CTEPH grouped according to their pulmonary hyper-tension-targeted therapy (monotherapy vs. combination therapy)

PAH	Monotherapy, <i>n</i> = 48 (46%)		Combination therapy, <i>n</i> = 57 (54%)	
	diagnosis	last prevalent visit	diagnosis	last prevalent visit
Age, years	55 (37; 71)	60 (43; 75)	55 (38; 70)	59 (46; 75)
BMI	26 (22; 30)	26 (21; 29)	25 (22; 29)	26 (22; 29)
NYHA functional class	3 (2; 3)	2 (2; 3)	3 (2; 3)	3 (2; 3) ^o
6MWD, m	483 (395; 585)	456 (424; 589)	455 (338; 533)	480 (348; 560)
NTproBNP, ng/L	196 (135; 612)	130 (63; 263)	730 (211; 1,741)*	379 (107; 1,073) ^o
Cardiac index, L/min/m ²	3.0 (2.4; 3.4)		2.4 (2.1; 3.0)*	
mPAP, mm Hg	34 (27; 44)		51 (40; 59)*	
Distal CTEPH	Monotherapy, <i>n</i> = 31 (82%)		Combination therapy, <i>n</i> = 7 (18%)	
	diagnosis	last prevalent visit	diagnosis	last prevalent visit
Age, years	68 (58; 73)	73 (63; 81)	61 (38; 64)	62 (44; 76)
BMI	28 (23; 32)	27 (25; 32)	27 (23; 38)	27 (21; 34)
NYHA functional class	3 (2; 3)	2 (2; 3)	3 (2; 3)	2 (2; 3)
6MWD, m	500 (368; 590)	490 (387; 597)	403 (278; 504)	368 (300; 435) ^o
NTproBNP, ng/L	274 (111; 1,334)	208 (124; 709)	2,004 (846; 2,921)*	1,454 (846; 2,921) ^o
Cardiac index, L/min/m ²	2.7 (2.4; 3.1)		2.3 (1.9; 2.7)	
mPAP, mm Hg	35 (29; 44)		48 (46; 54)*	

Data are shown as median (quartiles) or *n* (%). PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; NYHA, New York Heart Association; 6MWD, 6-min walking distance; NTproBNP, N-terminal pro-brain natriuretic peptide; mPAP, mean pulmonary arterial pressure. * *p* < 0.05 no/monotherapy at diagnosis versus combination therapy at diagnosis; ^o *p* < 0.05 no/monotherapy at last visit versus combination therapy at last visit.

ng/L, and 58% a 6MWD >440 m (Table 4); 13% fulfilled all three low-risk criteria, 34% two, 28% one, and 25% none. Up to the last prevalent visit, all three therapeutic goals were fulfilled by more than half of PAH patients and the number of patients that fulfilled three criteria considerably increased by 20% at the expense of fulfilling only two, one, or none of the goals (−5, −4, and −11%, respectively).

In patients with distal CTEPH, the distribution of the risk profile according to the predefined thresholds in NYHA class, 6MWD, and NTproBNP was similar to patients with PAH at diagnosis; 14% fulfilled all three criteria, 39% two, 18% one, and 29% none. Up to the last prevalent visit, fulfilling three, two, one, and no low-risk criteria changed by +17, −4, +1, and −14%, respectively.

Change in Risk Factor Profile over Time in Patients with More Complete Datasets

This prevalent subgroup of PAH with more comprehensive data available was seen in 2016 and on average diagnosed in 2014 (range from 2011 to 2015). At the time of diagnosis, 82% of this PAH subgroup received a single drug and 18% started directly with combination therapy. Over all time points, continuously more patients received combination therapy resulting in a 1:1 ratio of single versus combination therapy after a median follow-up time of 21 (17; 36) months. As shown in Table 5 and Figure 2, this PAH group significantly improved their NYHA class over all time points. The percentage of patients with NYHA class ≤II increased from 32 to 60%. The 6MWD stabilised around baseline value, with a peak of 536 m (420; 630) after 12 months. NTproBNP changed significantly after 3 and 6 months. After 12 months, NTproBNP was 157 ng/L (59; 463) at its lowest (Fig. 3).

Table 4. Therapeutic goals achieved in patients with PAH and distal CTEPH

	PAH				Distal CTEPH			
	diagnosis	<i>n</i>	last pre-valent visit	<i>n</i>	diagnosis	<i>n</i>	last pre-valent visit	<i>n</i>
NYHA ≤II	35 (35)	99	55 (52)	105	12 (32)	38	20 (53)	38
NTproBNP <300 ng/L	36 (43)	83	46 (61)	75	13 (42)	31	15 (52)	29
6MWD >440 m	52 (58)	90	50 (63)	79	21 (64)	33	18 (58)	31
All 3 criteria	10 (13)	76	21 (33)	63	4 (14)	28	8 (31)	26
2 criteria	26 (34)	76	18 (29)	63	11 (39)	28	9 (35)	26
1 criterion	21 (28)	76	15 (24)	63	5 (18)	28	5 (19)	26
No criterion	19 (25)	76	9 (14)	63	8 (29)	28	4 (15)	26

Data are shown as *n* (%). PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; NYHA, New York Heart Association; 6MWD, 6-min walking distance; NTproBNP, N-terminal pro-brain natriuretic peptide.

Table 5. Changes of risk factor profiles over time in PAH or distal CTEPH patients with comprehensive datasets at most predefined time points followed up closely in a tertiary care centre

	Diagnosis	<i>n</i>	3-month follow-up	<i>n</i>	6-month follow-up	<i>n</i>	12-month follow-up	<i>n</i>	Last prevalent visit	<i>n</i>	ANOVA, <i>p</i> value
<i>PAH</i>											
BMI	26 (23;29)	47	26 (23;29)	33	26 (24;31)	32	25 (23;30)	40	27 (24;30)	43	0.571
NYHA functional class	3 (2;3)	46	2.5 (2;3)*	36	2.5 (2;3)*	40	2 (2;3)*	44	2 (2;3)*	50	0.004
NYHA I	1 (2)		6 (17)		5 (13)		7 (16)		8 (16)		
NYHA II	14 (30)		12 (33)		15 (38)		17 (39)		22 (44)		
NYHA III	25 (54)		16 (44)		15 (38)		14 (32)		17 (34)		
NYHA IV	6 (13)		2 (6)		5 (13)		6 (14)		3 (6)		
6MWD, m	482 (369;578)	45	471 (373;560)	34	464 (388;561)	36	536 (420;630)	39	480 (418;572)	40	0.774
NTproBNP, ng/L	236 (135;861)	44	273 (119;470)*	27	243 (101;558)*	27	157 (59;463)	35	180 (73;359)	36	0.033
<i>CTEPH</i>											
BMI	28 (23;34)	20	28 (23;35)	16	29 (23;34)	15	25 (23;34)	14	28 (25;35)	16	0.849
NYHA functional class	3 (3;4)	20	3 (2;3)	16	3 (2;4)	16	2 (2;3)*	17	2.5 (2;3)*	20	0.004
NYHA I	0 (0)		0 (0)		0 (0)		3 (18)		3 (15)		
NYHA II	4 (20)		4 (25)		6 (38)		7 (41)		7 (35)		
NYHA III	10 (50)		10 (63)		6 (38)		6 (35)		8 (40)		
NYHA IV	6 (30)		2 (13)		4 (25)		1 (6)		2 (10)		
6MWD, m	438 (280;573)	18	464 (379;538)	14	444 (348;611)	13	470 (330;602)	17	470 (348;580)	15	0.211
NTproBNP, ng/L	745 (215;1544)	18	1,658 (137;2629)	11	755 (337;1601)	12	550 (95;1498)	15	320 (132;1,126)	13	0.363

Data are shown as median (quartiles) or *n* (%). PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; NYHA, New York Heart Association; 6MWD, 6-min walking distance; NTproBNP, N-terminal pro-brain natriuretic peptide; mPAP, mean pulmonary arterial pressure; ANOVA, analysis of variance. * *p* < 0.05 versus diagnosis.

In patients with distal CTEPH and comprehensive data available, the median year of diagnosis was 2014, with a range from 2012 to 2015 (Table 5; Fig. 2). No significant change in BMI and NTproBNP was observed after 3, 6, or 12 months or at the last prevalent visit. The NYHA class decreased significantly from baseline to 12 months and at the last prevalent visit, whereas BMI, NTproBNP, and 6MWD remained unchanged (Fig. 3).

Discussion

In this real-life cohort of prevalent patients with PAH and distal CTEPH, we show that NYHA class was sustainably improved and 6MWD and NTproBNP maintained for on average more than 3 years after diagnoses on drug therapy. These beneficial effects were achieved with a close clinical follow-up and timely initiation of combination therapy, which was started initially in 18% of PAH

Fig. 2. Change of New York Heart Association (NYHA) functional class over time in patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).

Fig. 3. a Change of 6-min walking distance (6MWD) over time in pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) with more complete datasets during follow-up over different time points. Shown as box plots (median; quartiles; ° outliers). **b** Change of N-terminal

brain natriuretic peptide (NTproBNP) with more complete datasets during follow-up over different time points in PAH and CTEPH. Shown as box plots (median; quartiles; ° outliers; * extreme outliers).

patients and increased to more than 50% after a median follow-up time of 21 months. Patients receiving combination therapy had higher NTproBNP and worse haemodynamics at diagnosis, indicating a more advanced disease state. This goal-oriented therapy in a real-life setting was not only associated with a higher number of patients being in favourable functional classes, but also an increased percentage of patients fulfilling the basic predefined therapeutic goals [3].

This study adds to the knowledge retrieved from other PH registries as it focuses on the clinical course and achievements of therapeutic goals of prevalent patients with PAH and distal CTEPH, which are known to behave differently compared to incident patients as included in most registries [8, 18, 25, 27–32]. This prevalent cohort of PAH/distal CTEPH provides real-life information on the effect of medical care and drug therapy on the progression of these chronic and formerly often rapidly fatal diseases. The amelioration of functional class and stabilisation of other risk factors along with an increasing number of patients fulfilling predefined therapeutic goals is reassuring that modern therapies help to improve the patient's condition in real life and indicates that the number of drugs prescribed nowadays reflects the severity of the disease [3, 33].

Epidemiology and Clinical Pathway

In the current observational cohort, the median age at the time of diagnosis was 55 years (38; 70) for patients with PAH and 67 years (57; 73) for patients with CTEPH, and is thus comparable to other national (Swiss, French, British, and American) and international cohorts [8, 18, 21, 25, 27, 29, 34]. While the NYHA class at the time of diagnosis was comparable to other registries, patients in our cohort had a better exercise capacity as assessed by the 6MWD, which was about 100 m longer [8, 18, 21, 27, 32]. One explanation could be the earlier detection of PH in recent years due to a higher awareness of physicians and other health care professionals indicating a better-preserved physical function. However, patients in the present cohort were diagnosed at a relatively higher age compared to historical cohorts but comparable to recent registry data [8, 18, 25, 27, 29]. Another explanation might be that in the present cohort, we assessed prevalent patients, which per se are a selection of patients with an overall better prognosis and thus have better functional parameters [22]. Thus, a comparison between baseline data from earlier published registries and our prevalent cohort can only be made with caution, due to the different inclusion criteria and the assessment period.

PAH patients in the present cohort were treated with PAH-targeted therapy. The majority of patients were diagnosed before the publication of the results of the ambition trial and latest guidelines [3, 16], which have shown a significantly lower risk of clinical failure events for initial combination therapy of ambrisentan and tadalafil compared to a single therapy with either one of these drugs. This study together with other recent results led to a paradigm shift in PAH therapy to early combination therapy [3, 35], although a goal-oriented strategy and initial combination therapy have never been directly compared in a randomised trial. In the present cohort of relatively low-risk prevalent patients, 82% initially started on monotherapy. The most frequently initiated drugs were ERAs, followed by PDE-5-I. These results correlate with previous data in Switzerland, but differ slightly from British or American cohorts, where PDE-5 inhibitors were used more often for initial treatment [27, 29]. The most frequent combination was ERA and PDE-5-I, as oral drugs were first combined before initiating a triple combination therapy including a parenteral prostanoid. Combination therapy was timely initiated in over half of the PAH patients even before clear clinical disease deterioration. In the present cohort, PAH patients who received combination therapy were in a clinically less favourable state with worse haemodynamics, functional class, and physical capacity as assessed by the 6MWD, and presumably a more advanced disease state, which again indicates that a goal-oriented therapeutic strategy was applied.

Patients with distal CTEPH were more often treated with a single drug over the entire observational period. Less than 1/5 of patients with distal CTEPH were treated with combination therapy, potentially related to the fact that patients with distal CTEPH in this cohort had less severe disease. Another reason might be that combination therapy has not been comprehensively studied in distal CTEPH [8, 14, 15, 36–39]; it also seems that this group behaves comparable to PAH [13]. In the International CTEPH registry [8], 20% of non-operable CTEPH patients received PDE-5 inhibitors, 38% ERAs, and 5% a prostanoid, which is comparable to our cohort; however, the present cohort revealed more patients on combination therapy (18% compared to 7.7%). This might be due to the fact that the CTEPH registry was published in 2011 whereas combination therapy has become more common in recent years only, despite the lack of evidence. Combination therapy, for example, was not allowed in the PAT-ENT or Benefit study, the only randomised controlled trials which were available during the treatment period of this cohort and which focused on medical therapy (rio-

ciguat or bosentan) in inoperable CTEPH [14, 37]. A recent randomised controlled trial assessing the efficacy of the ERA macitentan on distal CTEPH allowed inclusion of patients pretreated with PDE-5 inhibitors in the group of patients in functional class III, and could show that 46% of pretreated patients improved pulmonary vascular resistance after 16 weeks as the primary outcome, whereas the patients receiving mere macitentan did not (potentially due to their milder disease in functional class II) [40]. Despite these encouraging results, the evidence on combination therapy in distal CTEPH remains scarce and is mainly derived from registries and uncontrolled prospective trials only [15, 18, 23]. Therefore, the use of combination therapy in patients with CTEPH is still off-label and therefore not so widely used.

In the present cohort of PAH and distal CTEPH patients, the change of risk factor profiles did not significantly differ from diagnosis to the last prevalent visit between patients treated with single and combination therapy. We interpret this fact as an indication that combination therapy was started as a goal-oriented strategy in patients with a more advanced disease and therefore patients receiving combination therapy did not reach a better risk factor profile, but were potentially hindered in declining further.

Course of Risk Factor Profiles over the Observational Period

In this cohort of prevalent PAH patients, the average NYHA class improved significantly over time and the 6MWD and NYHA class stabilised, which is reassuring in this chronic disease with dismal prognosis without therapy [18, 41]. The same results were consistently found when analysing the course of these parameters under therapy only in PAH patients with more complete datasets who were closely followed up in our tertiary care centre (around half of the cohort). As in the overall cohort, this subgroup demonstrated an improved NYHA class over time under therapy, whereas the 6MWD remained stable (Tables 1, 5). NTproBNP is secreted by cardiac myocytes upon volume overload of the ventricle and has been shown to be a prognostic marker in PH and heart failure, and is commonly used to monitor the disease course [42–44]. In this cohort, we could show that starting from 1 year under therapy until the prevalent visit, NTproBNP decreased and remained normalised in a major proportion of PAH patients until the last visit of the observational period [45], which in addition to the stabilisation of exercise capacity and the improved functional class points towards haemodynamic stabilisation in these patients.

The improvement in NYHA class under medical therapy and stabilisation of the 6MWD and NTproBNP were also found in distal CTEPH, again indicating that these groups share response to therapy and pointing towards a common pathogenetic end pathway in these two disorders [13, 46, 47].

Therapeutic Goals

According to the latest PH guidelines, a comprehensive risk assessment is required to provide prognostic information [3]. An estimated 1-year mortality rate of <5% is considered as low risk and is therefore the aspired clinical status under treatment. NYHA class ≤II, NTproBNP <300 ng/L, and 6MWD >440 m are three therapeutic goals which are simple to measure and widely available during most routine follow-up visits. We thus focused on these three basic goals in the present study. At the time of diagnosis of this prevalent cohort, the number of fulfilled goals was already considerable. This might be attributed to an increasing awareness of PH during recent years in the primary care setting and reflects early diagnosis in the excellent, albeit very expensive, Swiss health care system. Under drug therapy and medical follow-up, the number of patients with PAH who fulfilled all three goals increased by 20%, and the number of patients who fulfilled no criterion decreased by 11% in this cohort under advanced medical therapy. The main improvement was found in the NYHA goal (+17%) and NTproBNP goal (+18%), whereas the 6MWD goal revealed an increase of +5%. This corresponds with the almost unchanged median 6MWD from baseline to last visit in this already relatively well-performing prevalent cohort. The goal achievements found in distal CTEPH were comparable to those in PAH.

Limitations

Due to the real-life cohort design of this study, the number of patients at each visit varied. Although all patients had data available at diagnosis and the last prevalent visit, only a subgroup had more complete data registered over consecutive visits. Therefore, the interpretation of the therapeutic goals in the course of the follow-up has to be cautiously interpreted.

This study presents information from a real-life cohort retrieving data from a tertiary care PH clinic, which however consists of a relatively limited number of patients that is not constant at the different follow-up time points. Risk factor profiles from these prevalent patients were not prospectively assessed within a clinical trial and there was no randomisation (e.g., of different treatment modalities

or single vs. combination therapy). Thus, these data are susceptible to selection bias and confounders and interpretation must account for this. Nevertheless, real-life data are important, as many patients in real life would not fulfil inclusion criteria for clinical trials due to comorbidities and other reasons.

Conclusion

In this real-life cohort of prevalent patients with PAH or distal CTEPH, a stabilisation or improvement of risk factor profiles and an increasing percentage of reached therapeutic goals was found in the course of the disease

under drug therapy. Patients with PAH are more likely to have a double combination therapy, whereas patients with CTEPH are mainly treated with a single drug. Whether more aggressive combination therapy would further improve goals in lower risk classes also remains to be determined.

Financial Disclosure and Conflicts of Interest

S.U. receives grants from the Swiss National Science Foundation, Zurich Lung, Actelion SA, and Orpha Swiss, all of which are not related to the present work. All other authors have no financial support and all have no conflicts of interest.

References

- Cenedese E, Speich R, Dorschner L, Ulrich S, Maggiorini M, Jenni R, Fischler M: Measurement of quality of life in pulmonary hypertension and its significance. *Eur Respir J* 2006;28: 808–815.
- Cima K, Twiss J, Speich R, McKenna SP, Grunig E, Kahler CM, Ehlken N, Treder U, Crawford SR, Huber LC, et al: The German adaptation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR). *Health Qual Life Outcomes* 2012;10:110.
- Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, et al: 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). *Eur Respir J* 2015;46:1855–1856.
- Boucly A, Weatherald J, Savale L, Jais X, Cottin V, Prevot G, Picard F, de Groote P, Jevnikar M, Bergot E, et al: Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J* 2017;50:1700889.
- Kylhammar D, Kjellstrom B, Hjalmarsson C, Jansson K, Nisell M, Soderberg S, Wikstrom G, Radegran G, SveFph, Spahr: A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J* 2017, Epub ahead of print.
- Hoepfer MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, Olsson KM, Meyer K, Vizza CD, Vonk-Noordegraaf A, et al: Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J* 2017;50:1700740.
- Kim NH, Delcroix M, Jenkins DP, Channick R, Darteville P, Jansa P, Lang I, Madani MM, Ogino H, Pengo V, et al: Chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D92–D99.
- Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, et al: Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation* 2011;124:1973–1981.
- Archibald CJ, Auger WR, Fedullo PF, Channick RN, Kerr KM, Jamieson SW, Kapelanski DP, Watt CN, Moser KM: Long-term outcome after pulmonary thromboendarterectomy. *Am J Respir Crit Care Med* 1999;160: 523–528.
- Olsson KM, Wiedenroth CB, Kamp JC, Breithacker A, Fuge J, Krombach GA, Haas M, Hamm C, Kramm T, Guth S, et al: Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience. *Eur Respir J* 2017;49:1602409.
- Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H, Matsubara H: Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv* 2012;5:748–755.
- Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, et al: 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Rev Esp Cardiol (Engl Ed)* 2016;69:177.
- Ulrich S, Fischler M, Speich R, Popov V, Maggiorini M: Chronic thromboembolic and pulmonary arterial hypertension share acute vasoactivity properties. *Chest* 2006;130:841–846.
- Ghofrani HA, D'Armini AM, Grimminger F, Hoepfer MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, et al: Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2013;369:319–329.
- Ulrich S, Speich R, Domenighetti G, Geiser T, Aubert JD, Rochat T, Huber L, Treder U, Fischler M: Bosentan therapy for chronic thromboembolic pulmonary hypertension. A national open label study assessing the effect of bosentan on haemodynamics, exercise capacity, quality of life, safety and tolerability in patients with chronic thromboembolic pulmonary hypertension (BOCTEPH-Study). *Swiss Med Wkly* 2007;137:573–580.
- Galie N, Barbera JA, Frost AE, Ghofrani HA, Hoepfer MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grunig E, et al: Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015;373:834–844.
- Sitbon O, Sattler C, Bertoletti L, Savale L, Cottin V, Jais X, De Groote P, Chaouat A, Chabannes C, Bergot E, et al: Initial dual oral combination therapy in pulmonary arterial hypertension. *Eur Respir J* 2016;47:1727–1736.
- Mueller-Mottet S, Stricker H, Domenighetti G, Azzola A, Geiser T, Schwerzmann M, Weilenmann D, Schoch O, Fellrath JM, Rochat T, et al: Long-term data from the Swiss pulmonary hypertension registry. *Respiration* 2015; 89:127–140.
- Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD: Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. *Circulation* 2012;125:113–122.

- 20 Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, et al: Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010;122:164–172.
- 21 Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, et al: Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006;173:1023–1030.
- 22 Humbert M, Sitbon O, Yaici A, Montani D, O’Callaghan DS, Jais X, Parent F, Savale L, Natali D, Gunther S, et al: Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010;36:549–555.
- 23 Fischler M, Speich R, Dorschner L, Nicod L, Domenighetti G, Tamm M, Rochat T, Aubert JD, Ulrich S, Swiss Society for Pulmonary Hypertension: Pulmonary hypertension in Switzerland: treatment and clinical course. *Swiss Med Wkly* 2008;138:371–378.
- 24 Hoeper MM, Huscher D, Ghofrani HA, Delcroix M, Distler O, Schweiger C, Grunig E, Staehler G, Rosenkranz S, Halank M, et al: Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. *Int J Cardiol* 2013;168:871–880.
- 25 Hurdman J, Condliffe R, Elliot CA, Davies C, Hill C, Wild JM, Capener D, Sephton P, Hamilton N, Armstrong IJ, et al: ASPIRE registry: assessing the spectrum of pulmonary hypertension identified at a referral centre. *Eur Respir J* 2012;39:945–955.
- 26 Nickel N, Golpon H, Greer M, Knudsen L, Olsson K, Westerkamp V, Welte T, Hoeper MM: The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2012;39:589–596.
- 27 Ling Y, Johnson MK, Kiely DG, Condliffe R, Elliot CA, Gibbs JS, Howard LS, Pepke-Zaba J, Sheares KK, Corris PA, et al: Changing demographics, epidemiology and survival of incident pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2012;186:790–796.
- 28 McGoon MD, Benza RL, Escribano-Subias P, Jiang X, Miller DP, Peacock AJ, Pepke-Zaba J, Pulido T, Rich S, Rosenkranz S, et al: Pulmonary arterial hypertension: epidemiology and registries. *J Am Coll Cardiol* 2013;62:D51–D59.
- 29 McGoon MD, Miller DP: REVEAL: a contemporary US pulmonary arterial hypertension registry. *Eur Respir Rev* 2012;21:8–18.
- 30 Muller-Mottet S, Hasler E, Opitz I, Weder W, Schuepbach R, Speich R, Ulrich S: Chronic thromboembolic pulmonary hypertension. *Cardiovasc Med* 2014;17:328–333.
- 31 Escribano-Subias P, Blanco I, Lopez-Meseguer M, Lopez-Guarch CJ, Roman A, Morales P, Castillo-Palma MJ, Segovia J, Gomez-Sanchez MA, Barbera JA, et al: Survival in pulmonary hypertension in Spain: insights from the Spanish registry. *Eur Respir J* 2012;40:596–603.
- 32 Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, et al: Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest* 2010;137:376–387.
- 33 Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J: Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J* 2005;26:858–863.
- 34 Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M: A USA-based registry for pulmonary arterial hypertension: 1982–2006. *Eur Respir J* 2007;30:1103–1110.
- 35 Pulido T, Adzerikho I, Channick RN, Delcroix M, Galie N, Ghofrani HA, Jansa P, Jing ZC, Le Brun FO, Mehta S, et al: Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013;369:809–818.
- 36 Hoeper MM, Kramm T, Wilkens H, Schulze C, Schafers HJ, Welte T, Mayer E: Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005;128:2363–2367.
- 37 Jais X, D’Armini AM, Jansa P, Torbicki A, Delcroix M, Ghofrani HA, Hoeper MM, Lang IM, Mayer E, Pepke-Zaba J, et al: Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFIT (bosentan effects in inoperable forms of chronic thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. *J Am Coll Cardiol* 2008;52:2127–2134.
- 38 Suntharalingam J, Treacy CM, Doughty NJ, Goldsmith K, Soon E, Toshner MR, Sheares KK, Hughes R, Morrell NW, Pepke-Zaba J: Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2008;134:229–236.
- 39 Simonneau G, D’Armini AM, Ghofrani HA, Grimminger F, Hoeper MM, Jansa P, Kim NH, Wang C, Wilkins MR, Fritsch A, et al: Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2). *Eur Respir J* 2015;45:1293–1302.
- 40 Ghofrani HA, Simonneau G, D’Armini AM, Fedullo P, Howard LS, Jais X, Jenkins DP, Jing ZC, Madani MM, Martin N, et al: Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. *Lancet Respir Med* 2017;5:785–794.
- 41 D’Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT et al: Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991;115:343–349.
- 42 Leuchte HH, Baumgartner RA, Nounou ME, Vogeser M, Neurohr C, Trautnitz M, Behr J: Brain natriuretic peptide is a prognostic parameter in chronic lung disease. *Am J Respir Crit Care Med* 2006;173:744–750.
- 43 Leuchte HH, El Nounou M, Tuerpe JC, Hartmann B, Baumgartner RA, Vogeser M, Muehling O, Behr J: N-terminal pro-brain natriuretic peptide and renal insufficiency as predictors of mortality in pulmonary hypertension. *Chest* 2007;131:402–409.
- 44 Warwick G, Thomas PS, Yates DH: Biomarkers in pulmonary hypertension. *Eur Respir J* 2008;32:503–512.
- 45 Raymond I, Groenning BA, Hildebrandt PR, Nilsson JC, Baumann M, Trawinski J, Pedersen F: The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population. *Heart* 2003;89:745–751.
- 46 Humbert M, Morrell NW, Archer SL, Stenmark KR, MacLean MR, Lang IM, Christman BW, Weir EK, Eickelberg O, Voelkel NF, et al: Cellular and molecular pathobiology of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;43:13S–24S.
- 47 Humbert M: Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: pathophysiology. *Eur Respir Rev* 2010;19:59–63.