CrossMark

Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension

A Pathophysiological Continuum

Christian F. Opitz, MD,[a,b] Marius M. Hoeper, MD,[c] J. Simon R. Gibbs, MD,[d] Harald Kaemmerer, MD, VMD,[e]
Joanna Pepke-Zaba, MD,[f] J. Gerry Coghlan, MD,[g] Laura Scelsi, MD,[h] Michele D'Alto, MD,[i] Karen M. Olsson, MD,[c]
Silvia Ulrich, MD,[j] Werner Scholtz, MD,[k] Uwe Schulz, MD,[l] Ekkehard Grünig, MD,[m] Carmine D. Vizza, MD,[n]
Gerd Staehler, MD,[o] Leonhard Bruch, MD,[p] Doerte Huscher, MSc, PhD,[q,r] David Pittrow, MD,[s]
Stephan Rosenkranz, MD[t,u]

ABSTRACT

BACKGROUND Pulmonary hypertension (PH) is hemodynamically classified as pre-capillary (as seen in idiopathic pulmonary arterial hypertension [IPAH]) or post-capillary (as seen in heart failure with preserved ejection fraction [HFpEF]). Overlaps between these conditions exist. Some patients present with risk factors for left heart disease but pre-capillary PH, whereas patients with HFpEF may have combined pre- and post-capillary PH.

OBJECTIVES This study sought to further characterize similarities and differences among patient populations with either PH-HFpEF or IPAH.

METHODS We used registry data to analyze clinical characteristics, hemodynamics, and treatment responses in patients with typical IPAH (<3 risk factors for left heart disease; n = 421), atypical IPAH (≥3 risk factors for left heart disease; n = 139), and PH-HFpEF (n = 226) receiving PH-targeted therapy.

RESULTS Compared with typical IPAH, patients with atypical IPAH and PH-HFpEF were older, had a higher body mass index, had more comorbidities, and had a lower 6-min walking distance, whereas mean pulmonary artery pressure (46.9 ± 13.3 mm Hg vs. 43.9 ± 10.7 mm Hg vs. 45.7 ± 9.4 mm Hg, respectively) and cardiac index (2.3 ± 0.8 l/min/m^2 vs. 2.2 ± 0.8 l/min/m^2 vs. 2.2 ± 0.7 l/min/m^2, respectively) were comparable among groups. After initiation of targeted PH therapies, all groups showed improvement in exercise capacity, functional class, and natriuretic peptides from baseline to 12 months, but treatment effects were less pronounced in patients with PH-HFpEF than typical IPAH; with atypical IPAH in between. Survival rates at 1, 3, and 5 years were almost identical for the 3 groups.

CONCLUSIONS Patients with atypical IPAH share features of both typical IPAH and PH-HFpEF, suggesting that there may be a continuum between these conditions. (J Am Coll Cardiol 2016;68:368–78) © 2016 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Heart failure with preserved ejection fraction (HFpEF) is frequently accompanied by pulmonary hypertension (PH), which is associated with a poor outcome. Recent studies have suggested that PH is found in 36% to 83% of patients with HFpEF (1–3) and that both elevated pulmonary artery pressure and right ventricular (RV) dysfunction are independent predictors of death in patients with HFpEF (1,4–6).

Hemodynamically, pre-capillary PH—characterized by a mean pulmonary arterial wedge pressure (PAWP) ≤15 mm Hg—is distinguished from post-capillary PH, as indicated by a PAWP >15 mm Hg (7–11). The classic example of a disease characterized by pre-capillary PH is idiopathic pulmonary arterial hypertension (IPAH), which is caused by an obliterative pulmonary vasculopathy affecting predominantly small pulmonary arterioles. In contrast, left heart disease, such as HFpEF, causes post-capillary PH due to backward transmission of elevated left-sided filling pressures into the pulmonary circulation. The latter group may present with isolated post-capillary PH or combined post-capillary PH with a pre-capillary component, as indicated by an elevated diastolic pressure gradient and/or an increased pulmonary vascular resistance (PVR) (8,11,12).

Despite these seemingly clear definitions, a growing number of patients with PH are identified in whom criteria from multiple PH categories exist simultaneously. For example, several registries have documented a change of phenotype in patients diagnosed with IPAH, associated with increasing age (13,14). A significant number of these patients have a comorbidity profile typically found in patients with HFpEF, such as arterial hypertension, obesity, diabetes, and atrial fibrillation (15). Recently, the terms typical and atypical PAH have been proposed to distinguish between these populations (16). The AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) trial excluded patients with 3 or more of these risk factors from the primary analysis set (17).

SEE PAGE 379

Although targeted therapies, including phosphodiesterase type 5 inhibitors (PDE5i), endothelin receptor antagonists (ERA), and prostacyclin analogues (PCA), are available for IPAH, evidence-based recommendations for the management of PH-HFpEF are lacking and current guidelines do not support the use of targeted PAH therapies in patients with PH-HFpEF (8,10,12). Additionally, patients with atypical IPAH have been underrepresented or excluded in clinical trials.

To further determine similarities and differences in demographics, comorbidities, hemodynamics,

ABBREVIATIONS AND ACRONYMS

ERA = endothelin receptor antagonist

HFpEF = heart failure with preserved ejection fraction

IPAH = idiopathic pulmonary arterial hypertension

PAPm = mean pulmonary artery pressure

PAWP = pulmonary arterial wedge pressure

PCA = prostacyclin analogue

PDE5i = phosphodiesterase type 5 inhibitor

PVR = pulmonary vascular resistance

TPG = mean transpulmonary pressure gradient

treatment responses, and outcomes of patients with typical or atypical IPAH and patients with PH-HFpEF, we analyzed data from COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension), a European-based PH registry that enrolls patients with all forms of PH who receive targeted therapy (13,18).

METHODS

An ongoing, investigator-initiated, noninterventional, prospective European-based registry, COMPERA is enrolling consecutive patients with all forms of PH receiving targeted therapies (NCT01347216). The present analysis included data recorded between January 2009 and April 2015 for incident patients (included into the COMPERA registry within 6 months of PH diagnosis) ages ≥18 years. The date of the first right heart catheterization confirming PH was defined as the date of diagnosis. Documentation included demographics (age, sex, body mass index [BMI], and comorbidities), type of PH according to the Nice classification, World Health Organization functional class (WHO-FC), 6-min walk distance (6MWD), hemodynamics, laboratory data, and detailed information about medications to treat PH. Data were collected at the time of diagnosis (baseline) and at 6-month intervals or whenever the patient has a pre-defined clinical event (death, transplantation, PH-related hospitalization, deterioration in WHO-FC, any unscheduled change in PAH therapy, or other serious adverse events). Out-of-range data or missing values were automatically queried during data entry, and independent onsite monitoring ensured source data verification. This study complies with the Declaration of Helsinki, the locally appointed ethics committees approved the research protocol, and informed consent was obtained from all subjects.

PATIENTS. IPAH was defined by mean pulmonary artery pressure (PAPm) ≥25 mm Hg, PAWP ≤15 mm Hg, and exclusion of other causes of PAH (Figure 1). Furthermore, patients with IPAH were subcategorized into typical (<3 risk factors for left heart disease) or atypical (≥3 risk factors for left heart disease) IPAH on the basis of the criteria used in the AMBITION trial. The pre-defined risk factors for left heart disease were arterial hypertension, coronary artery disease, diabetes, atrial fibrillation, and BMI >30 kg/m² at the time of diagnosis (17).

Inclusion criteria for the patients with PH-HFpEF were a diagnosis of combined post- and pre-capillary pulmonary hypertension (Cpc-PH) indicated by: 1) PAPm ≥25 mm Hg and mean PAWP >15 mm Hg; 2) preserved left ventricular ejection fraction (>45% by echocardiography); and 3) presence of echocardiographic signs of diastolic dysfunction of the left ventricle (corresponding to Nice Group 2.2) (8,19). Patients with incomplete data regarding their risk factor profiles were excluded from the analysis.

STATISTICAL ANALYSIS. Data are shown as mean ± SD or as median and interquartile range, respectively. For continuous data, group differences were compared using the Student *t* test in case of normal distribution or by the Mann-Whitney *U* test otherwise. Frequency differences were compared using the chi-square or Fisher exact test. Survival was evaluated with Kaplan-Meier analysis and log-rank test. Group-wise comparisons were performed with post hoc adjustment for 3 parallel tests. Predictors of treatment discontinuation were examined using logistic regression. With regard to follow-up data, the 3-month time-point allowed a time window of ±15 days and the 1-year time-point a window of ±3 months. SPSS Statistics version 19.0 (IBM Corp., Armonk, New York) was used for analysis.

RESULTS

Overall, 5,935 consecutive patients with PH were enrolled in the COMPERA registry between May 2007 and April 2015. Figure 1 shows the selection of patients for the present analysis. A total of 786 incident patients were eligible for the present analysis: 421 with typical IPAH, 139 with atypical IPAH, and 226 with PH-HFpEF. The mean duration of follow-up in all patients was 24.9 ± 20.1 months, and the median interval between follow-up documentations was 3.6 months.

Baseline characteristics were different between the 3 groups (Table 1). When compared with typical IPAH, patients with atypical IPAH as well as those with PH-HFpEF were significantly older, had a higher BMI, and had a lower 6MWD (all p < 0.001 vs. typical IPAH). Natriuretic peptide levels were higher in patients with PH-HFpEF when compared with typical, but not atypical, IPAH.

By definition, patients with typical IPAH had fewer comorbidities at the time of diagnosis. Although arterial hypertension was present in 43%, the other risk factors were found in <25% of these patients. In contrast, 99% of patients with atypical IPAH and 92% of those with PH-HFpEF had a history of arterial hypertension; all other risk factors were found more frequently in these groups (p < 0.001 vs. typical IPAH for all parameters).

HEMODYNAMICS. With respect to hemodynamic severity of PH, PAPm, cardiac index, and mixed venous oxygen saturation were comparable in all

FIGURE 1 Patient Selection

From the original COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) patients with pulmonary hypertension (PH), patients were enrolled with PH–heart failure with preserved ejection fraction (HFpEF), or typical or atypical idiopathic pulmonary arterial hypertension (IPAH) on the basis of the number of risk factors present at PH diagnosis: arterial hypertension, coronary artery disease, diabetes mellitus, atrial fibrillation, and body mass index >30 kg/m^2. PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure.

3 groups (Table 1). By definition, PAWP was higher in patients with PH-HFpEF, resulting in lower mean transpulmonary pressure gradient (TPG) and PVR compared with the other groups. Notably, right atrial pressure was considerably higher in patients with PH-HFpEF (13 ± 5 mm Hg) compared with typical IPAH (9 ± 5 mm Hg; p < 0.001) and atypical IPAH (9 ± 5 mm Hg; p < 0.001).

In the PH-HFpEF group, mean TPG was 26 ± 9 mm Hg, and the vast majority of these patients (201 of 226; 89%) had a TPG >12 mm Hg. Furthermore, mean PVR was elevated at 7.0 ± 3.4 Wood units (WU), indicating Cpc-PH (10).

TREATMENT CHARACTERISTICS. As per inclusion criteria, all patients in the COMPERA registry received at least 1 targeted PH therapy. However, the treatment patterns differed significantly between the 3 groups (Table 2): PDE5i were selected as first-line therapy in 77% of the patients with typical IPAH, in 81% with atypical IPAH, and in 94% with PH-HFpEF. In contrast, ERAs were used as first-line therapy in approximately one-third of patients with typical IPAH and one-fifth with atypical IPAH, but in only 7% of the patients with PH-HFpEF. The use of PCA as first-line treatment was <5% in all groups.

TABLE 1 Baseline Characteristics

	All Patients (N = 786)	Typical IPAH (n = 421)	Atypical IPAH (n = 139)	Typical vs. Atypical IPAH p Value	PH-HFpEF (n = 226)	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
Age, yrs	66.6 ± 15.0	61.5 ± 17.3	71.3 ± 9.2	<0.001	73.2 ± 8.3	<0.001	0.434
Female	467 (59.4)	250 (59.4)	77 (55.4%)	1.000	140 (61.9)	1.000	0.686
BMI, kg/m^2	28.1 (24.5-32.6)	26.0 (23.3-29.8)	32.2 (28.3-36.0)	<0.001	29.6 (25.7-34.0)	<0.001	0.002
WHO-FC				0.089		<0.001	0.315
I/II	91 (11.8)	71 (17.4)	12 (8.8)		8 (3.6)		
III	540 (70.3)	275 (67.6)	96 (70.6)		169 (75.1)		
IV	137 (17.8)	61 (15.0)	28 (20.6)		48 (21.3)		
6MWD, m	289.5 ± 121.8	319.0 ± 123.5	250.5 ± 104.2	<0.001	260.0 ± 115.0	<0.001	0.787
RAP, mm Hg	9.8 ± 5.4	8.5 ± 5.2	8.9 ± 4.8	0.615	12.9 ± 4.8	<0.001	<0.001
PAPm, mm Hg	46.0 ± 11.9	46.9 ± 13.3	43.9 ± 10.7	0.025	45.7 ± 9.4	0.437	0.326
PAWP, mm Hg	12.5 ± 6.0	9.3 ± 3.4	10.0 ± 3.6	0.186	19.9 ± 4.4	<0.001	<0.001
TPG, mm Hg	33.5 ± 13.1	37.6 ± 13.6	33.9 ± 11.1	0.006	25.8 ± 9.1	<0.001	<0.001
Cardiac index, l/min/m^2	2.2 ± 0.8	2.3 ± 0.8	2.2 ± 0.8	0.629	2.2 ± 0.7	0.653	0.988
PVR, Wood Units	9.6 ± 6.7	10.8 ± 6.0	9.8 ± 10.6	0.309	7.0 ± 3.4	<0.001	<0.001
SvO$_2$, %	62.2 ± 9.0	62.1 ± 9.9	62.7 ± 9.0	0.804	62.1 ± 6.9	0.999	0.863
BNP, pg/ml	269 (127-541)	287 (119-543)	200 (115-469)	1.000	310 (186-638)	0.963	0.312
NT-proBNP, pg/ml	1,738 (621-3,891)	1,435 (541-3,888)	1,683 (478-2,815)	1.000	2,196 (1,125-4,285)	0.021	0.066
Arterial hypertension	66.5	43.2	98.6	<0.001	91.9	<0.001	0.021
CAD	32.0	15.7	59.7	<0.001	46.4	<0.001	0.049
Diabetes mellitus	30.6	10.7	74.8	<0.001	41.2	<0.001	<0.001
AF	28.9	10.7	42.4	<0.001	54.4	<0.001	0.187
BMI >30 kg/m^2	37.6	23.5	65.2	<0.001	47.1	<0.001	0.002

Values are mean ± SD, n (%), median (interquartile range), or %.

6MWD = 6-min walking distance; AF = atrial fibrillation; BMI = body mass index; BNP = B-type natriuretic peptide; CAD = coronary artery disease; HFpEF = heart failure with preserved ejection fraction; IPAH = idiopathic pulmonary arterial hypertension; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAPm = mean pulmonary arterial pressure; PAWP = mean pulmonary artery wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SvO$_2$ = mixed venous oxygen saturation; TPG = transpulmonary gradient; WHO-FC = World Health Organization functional class.

TABLE 2 Targeted PH Therapies

	All Patients	Typical IPAH	Atypical IPAH	Typical vs. Atypical IPAH p Value	PH-HFpEF	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
PH treatment initiated within first 3 months							
n	786	421	139		226		
ERA	22.6	31.4	22.3	0.157	6.6	<0.001	<0.001
PDE5i	82.4	76.7	81.3	0.870	93.8	<0.001	0.001
PCA	1.7	2.6	0.7	0.931	0.4	0.197	1.000
2 or more PH drugs	11.7	17.8	7.9	0.013	2.7	<0.001	0.112
Anticoagulation	63.0	56.3	69.8	0.016	71.2	0.001	1.000
PH treatment at 1 year							
n	396	207	81		108		
ERA	36.4	48.3	35.8	0.195	13.9	<0.001	0.002
PDE5i	80.6	83.6	75.3	0.391	78.7	0.857	1.000
PCA	4.5	5.8	4.9	1.000	1.9	0.452	1.000
2 or more PH drugs	30.6	44.4	25.9	0.014	7.4	<0.001	0.003
Anticoagulation	67.5	62.8	71.6	0.513	73.4	0.184	1.000

Values are %, unless otherwise indicated.

ERA = endothelin receptor antagonist; PCA = prostacyclin analogue; PDE5i = phosphodiesterase type 5 inhibitor; other abbreviations as in **Table 1**.

During follow-up, the preference for PDE5i therapy in PH-HFpEF persisted (**Table 2**). At 1 year, 84% of the typical patients with IPAH received PDE5is, whereas 48% were treated with ERAs and 6% with PCAs. Patients with atypical IPAH showed similar preference patterns, but for patients with PH-HFpEF, there was significantly less use of ERAs (p < 0.001 vs. typical IPAH; p = 0.002 vs. atypical IPAH).

Combination therapy was initiated within 3 months after diagnosis in 18% of the patients with typical IPAH compared with only 8% of those with atypical IPAH and 3% of the patients with PH-HFpEF. At 1 year, combination therapy was used in 44% of the typical IPAH group, whereas the corresponding numbers for atypical IPAH and PH-HFpEF were 26% and 7%, respectively (**Table 2**).

As shown in **Table 3**, treatment discontinuation of PDE5i occurred significantly more often in patients with PH-HFpEF than with typical IPAH (18.4% vs. 8.8%; p = 0.005), and patients with atypical IPAH were in between at 13%. The main reasons for discontinuation in patients with PH-HFpEF were side effects in 5.3% and lack of efficacy in 10%, the latter being less frequently observed (<3%) in the other groups.

TABLE 3 Discontinuations of PH Therapies

	All Patients (N = 786)	Typical IPAH (n = 421)	Atypical IPAH (n = 139)	Typical vs. Atypical IPAH p Value	PH-HFpEF (n = 226)	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
PDE5i ever	696 (88.5)	359 (85.3)	120 (86.3)	1.000	217 (96.0)	<0.001	0.003
Patients with follow-up	618	306	106		206		
PDE5i discontinuations	79 (12.8)	27 (8.8)	14 (13.2)	0.578	38 (18.4)	0.005	0.795
Side effects	23 (3.7)	8 (2.6)	4 (3.8)	1.000	11 (5.3)	0.454	1.000
Efficacy failure	33 (5.3)	9 (2.9)	3 (2.8)	1.000	21 (10.2)	0.003	0.071
Other*	25 (4.0)	11 (3.6)	7 (6.6)	0.801	7 (3.4)	1.000	0.745
ERA ever	322 (41.0)	225 (53.4)	61 (43.9)	0.188	36 (15.9)	<0.001	<0.001
Patients with follow-up	281	190	56		35		
ERA discontinuations	56 (19.9)	28 (14.7)	13 (23.2)	0. 462	15 (42.9)	0.001	0.188
Side effects	36 (12.8)	18 (9.5)	10 (17.9)	0.286	8 (22.9)	0.117	1.000
Efficacy failure	9 (3.2)	4 (2.1)	1 (1.8)	1.000	4 (11.4)	0.066	0.210
Other†	11 (3.9)	6 (3.2)	2 (3.6)	1.000	3 (8.6)	0.447	1.000

Values are n (%) or n. *Including switch to riociguat. †Including withdrawal of sitaxentan.

Abbreviations as in **Tables 1 and 2**.

Within the small subgroup of patients with PH-HFpEF receiving an ERA, this treatment was discontinued in almost every second patient (43%; p = 0.001 vs. typical IPAH), either because of side effects (23%) or lack of improvement (11%). In patients with typical IPAH, side effects and lack of improvement were responsible for ERA discontinuation in 10% and 2%, respectively. Interestingly, patients with atypical IPAH again fell between these groups, with an ERA discontinuation rate of 23%.

Treatment discontinuations were associated with less severe hemodynamics. Patients with typical IPAH who discontinued pulmonary vasodilator therapy had lower values for PAPm (risk ratio [RR]: 0.965; 95% confidence interval [CI]: 0.933 to 0.998; p = 0.039) and right atrial pressure (RR: 0.885; 95% CI: 0.801 to 0.977; p = 0.016) compared with patients continuing this therapy. A similar pattern was observed in patients with PH-HFpEF. Patients who discontinued PDE5i therapy had lower PAPm (RR: 0.937; 95% CI: 0.897 to 0.979; p = 0.004) and TPG (RR: 0.928; 95% CI: 0.884 to 0.973; p = 0.002).

RESPONSE TO THERAPY. After PH therapies were initiated, WHO-FC, exercise capacity, and natriuretic

TABLE 4 Response to Targeted PH Therapy

	Typical IPAH	Atypical IPAH	Typical vs. Atypical IPAH p Value	PH-HFpEF	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
6MWD, m						
Baseline	320 (234 to 417)	250 (175 to 332)	<0.001	270 (165 to 345)	<0.001	1.000
12 months	414 (324 to 460)	310 (240 to 379)	<0.001	330 (194 to 380)	<0.001	1.000
Change from baseline in 6MWD, m						
Mean ± SD	52 ± 101	58 ± 84	1.000	33 ± 82	0.453	0.904
Median (IQR)	50 (1 to 00)	60 (10 to 75)		29 (−10 to 74)		
WHO-FC I/II						
Baseline	17.4	8.8	0.056	3.6	<0.001	0.164
12 months	39.5	26.2	0.208	23.0	0.026	1.000
Improvement of WHO-FC	34.5	36.9	1.000	36.8	1.000	1.000
Change from baseline in NT-proBNP/BNP, %	−42.6 (−77.1 to 17.4)	−35.9 (−69.9 to 13.8)	1.000	−13.7 (−40.6 to 32.2)	0.031	0.248

Values are median (interquartile range), mean ± SD, or %. Data shown on 6-min walking distance (6MWD) at baseline (on the basis of n = 324 for typical IPAH, n = 105 for atypical IPAH, and n = 184 for PH-HFpEF), at 12 months (on the basis of n = 126 for typical IPAH, n = 38 for atypical IPAH, and n = 46 for PH-HFpEF), and change from baseline (on the basis of n = 111 for typical IPAH, n = 29 for atypical IPAH, and n = 40 for PH-HFpEF); WHO-FC at baseline (on the basis of n = 407 for typical IPAH, n = 136 for atypical IPAH, and n = 225 for PH-HFpEF), at 12 months (on the basis of n = 177 for typical IPAH, n = 65 for atypical IPAH, and n = 87 for PH-HFpEF), and % improvement (on the basis of n = 174 for typical IPAH, n = 65 for atypical IPAH, and n = 87 for PH-HFpEF); and % changes from baseline to 12 months in plasma levels of natriuretic peptide serum levels (NT-proBNP or BNP, respectively; on the basis of n = 115 for typical IPAH, n = 47 for atypical IPAH, and n = 42 for PH-HFpEF).

Abbreviations as in **Table 1**.

FIGURE 2 5-Year Overall Survival

Years after diagnosis	"typical IPAH"	"atypical IPAH"	p_1	HFpEF	p_2	p_3
0	100%	100%		100%		
1	88.5%	89.1%		86.7%		
2	80.3%	73.4%	1.000	71.2%	0.384	1.000
3	68.0%	62.6%		61.7%		
4	62.4%	55.7%		49.8%		
5	50.2%	55.7%		44.8%		

"typical IPAH"
409   209   129   84   52   12

"atypical IPAH"
133   74   34   20   13   4

PH-HFpEF
222   119   79   39   19   9

There was no significant difference in survival among patients with PH who were studied. p_1 = p value for typical IPAH versus atypical IPAH; p_2 = p value for typical IPAH versus PH-HFpEF; p_3 = p value for atypical IPAH versus PH-HFpEF; other abbreviations as in **Figure 1**.

peptide levels improved from baseline to 12 months in all groups, but treatment effects were less pronounced in PH-HFpEF. In all 3 groups, WHO-FC improved in approximately one-third of the patients (**Table 4**). The percentage of patients in WHO-FC I or II at 12 months was 40% in the typical IPAH group, 26% in the atypical IPAH group (p = NS vs. typical IPAH), and 23% in the PH-HFpEF group (p = 0.026 vs. typical IPAH).

At 1 year, the mean 6MWD increased from baseline in all groups. Of note, 62% of patients with typical IPAH, 59% of patients with atypical PAH, and 43% of those with PH-HFpEF showed an improvement in 6MWD by >30 m.

Natriuretic peptide levels decreased in all groups; this was most pronounced in patients with typical IPAH (−43% from baseline) and to a lesser extent in atypical IPAH (−36% from baseline) and PH-HFpEF (−14% from baseline).

SURVIVAL. Within the first 5 years after initiation of targeted PH therapy, there was no difference in overall mortality among the 3 groups (**Figure 2**). However, patients with typical IPAH or atypical IPAH more often died from PH-related complications (56% and 58%, respectively) compared with patients with PH-HFpEF (32%; p = 0.026).

DISCUSSION

The current analysis compared disease characteristics, hemodynamics, treatment patterns, response to therapy, and mortality in patients with IPAH as well as in patients with PH due to HFpEF, all of whom received targeted PH therapy. Patients with IPAH were further subcategorized as typical and atypical, on the basis of the presence of risk factors for left heart disease. The risk profiles and demographic characteristics of patients with atypical IPAH resembled those of the PH-HFpEF group, whereas hemodynamics were comparable with typical IPAH. At the same time, severity of PH, as indicated by a high PAPm and a low cardiac index, was comparable in all 3 groups; the same was true for survival.

The selection of PH therapies and the evoked treatment response showed considerable differences among groups. Although treatment patterns in patients with typical IPAH were comparable with other cohorts (20), >90% of the patients with PH-HFpEF received first-line treatment with a PDE5i, whereas ERAs were rarely used. The therapeutic approach to atypical IPAH was in between these 2 conditions. The observed changes in WHO-FC, exercise capacity, and natriuretic peptide levels indicated some efficacy of

targeted therapies in all 3 populations, with the greatest improvements seen in patients with typical IPAH, the least improvements in patients with PH-HFpEF, and atypical IPAH again in between. With respect to side effects and tolerability of PH medications, differences between the 3 groups emerged. In patients with typical IPAH, side effect profile and drug tolerability matched data reported from clinical studies (17). In patients with PH-HFpEF, targeted therapies, particularly ERAs, were less well tolerated. Here, the drug discontinuation rate due to side effects or lack of efficacy reached 34% for ERA and 16% for PDE5i therapy. In atypical PAH, drug discontinuation rates were between those of typical IPAH and PH-HFpEF.

PH in association with left heart disease is arguably 1 of the most common forms of PH. Depending on methods and definitions used, the prevalence of PH in patients with HFpEF has been reported to be as high as 80% (1). Development of PH or RV dysfunction in patients with HF carries strong negative prognostic information (1,4,6). Despite the importance of PH in HFpEF, the underlying pathomechanisms are not entirely clear. Even less clear are the treatment options; current guidelines discourage the routine use of targeted PH therapy in patients with PH-HFpEF but rather emphasize the optimized treatment of the underlying diseases and comorbidities (10,12).

Our findings reinforced previous observations that there is a subpopulation among patients with HFpEF who have severe PH with a distinct pre-capillary component (15). Except for the elevated filling pressures and the resulting lower PVR, the hemodynamic profiles of these patients were similar to what was found in patients with IPAH. Given the fact that all patients included in our series had a preserved left ventricular systolic function, it is likely that the low cardiac output seen in the patients with PH-HFpEF resulted primarily from RV rather than left ventricular dysfunction.
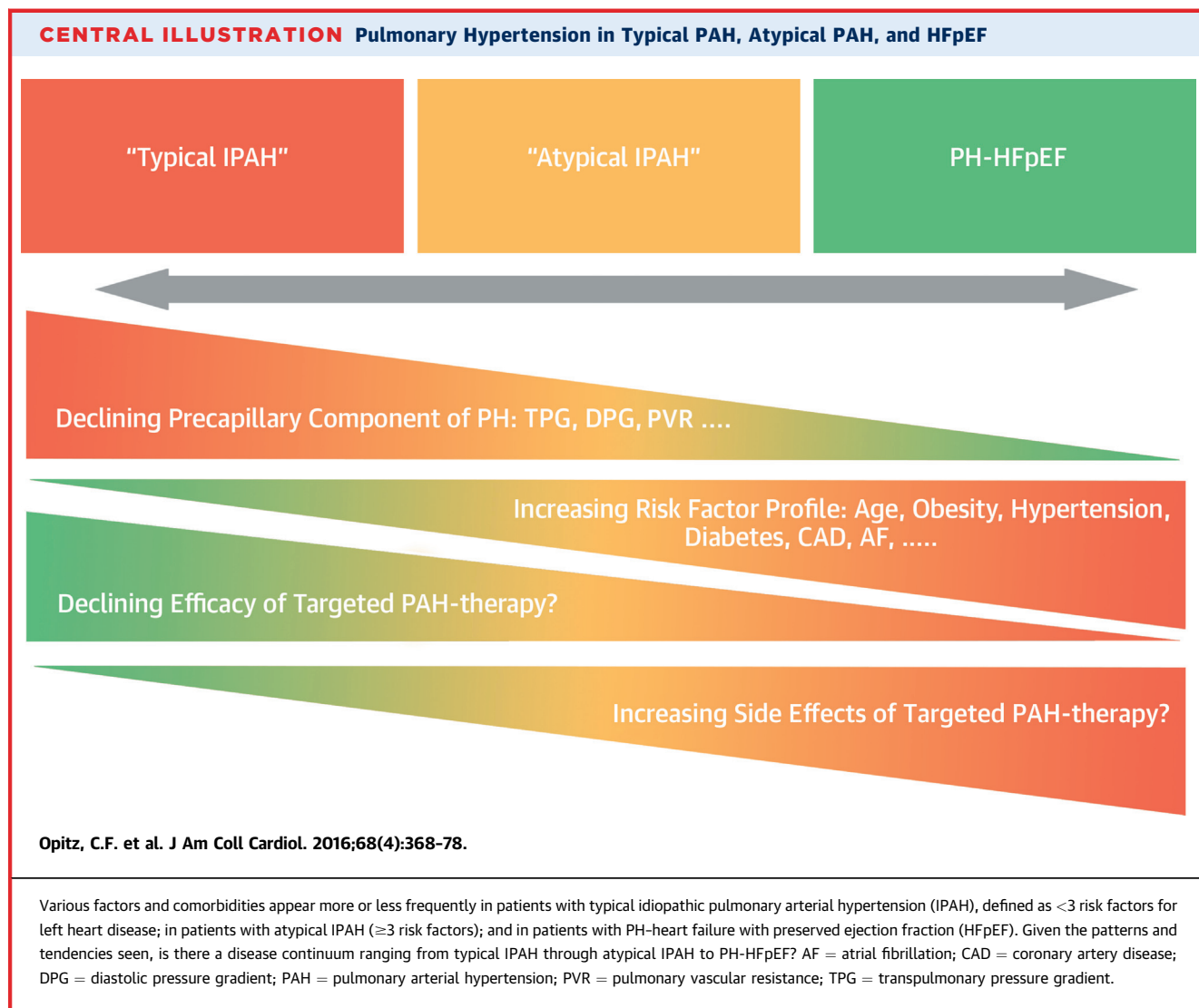
The presence of severe PH together with RV dysfunction was probably the rationale for the COMPERA investigators to prescribe drugs approved for PAH in patients with PH-HFpEF. According to the new European Society of Cardiology and European Respiratory Society guidelines, these patients may be categorized as having Cpc-PH (8,10). The strong preference for PDE5i as first-line therapy in PH-HFpEF may have resulted from previous studies of ERA and PDE5i in heart failure patients with reduced (21-24) and preserved ejection fraction (25). So far, almost all trials with ERA in patients with left heart disease failed to show clinical benefit and were associated with frequent side effects, predominantly fluid retention (26). The high discontinuation rate for ERA in our PH-HFpEF group was in line with these observations.

In contrast to ERA, there have been promising pre-clinical and clinical data for PDE5i in patients with PH-HFpEF, including a small positive randomized controlled trial (23,25). The largest study on the use of sildenafil in 216 patients with HFpEF, however, did not show improvement of exercise capacity or symptoms compared with placebo, but this study did not specifically include patients with PH-HFpEF (27). A recent single-center randomized clinical trial showed no efficacy of sildenafil in improving pulmonary hemodynamics or exercise capacity in 52 patients with HFpEF and predominantly post-capillary PH (28).

Our data indicated that PDE5i therapy was generally well-tolerated with comparable side effect profiles in patients with typical and atypical IPAH as well as in patients with PH-HFpEF. With respect to treatment efficacy, our results should be interpreted with particular caution. Improvements in 6MWD, WHO-FC, and natriuretic peptide levels were observed, although the changes were more pronounced with typical IPAH as compared with PH-HFpEF, whereas the responses in patients with atypical IPAH were in-between. Although efficacy failure led to treatment discontinuation in <3% of the patients with typical or atypical IPAH, this lack of improvement caused withdrawal of the PDE5i in 10% of the patients with PH-HFpEF. It is tempting to speculate that the declining contribution of a pre-capillary component of PH, as well as the increasing frequency of comorbidities from typical IPAH to atypical IPAH and PH-HFpEF, attenuated the treatment response of these patients with respect to PAH-targeted drugs. Charalampopoulos et al. (15) recently reported data supporting this concept. This would also explain the putative discrepancy between our patients with PH-HFpEF having a mean PVR of 7 WU and the previous reports mentioned earlier, which provided either no resistance data (2,27) or a median PVR of 2.6 WU (28).

The survival curves in the 3 patient populations studied herein were almost superimposable. In the ASPIRE (Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre) registry (20), patients with PH-HFpEF had a 3-year-survival rate >80%, compared with 62% in our series. In contrast to our patients, patients with PH-HFpEF in ASPIRE had lower PVR values and normal cardiac output. It is conceivable that our patients' more severe PH contributed to their higher mortality.

CENTRAL ILLUSTRATION Pulmonary Hypertension in Typical PAH, Atypical PAH, and HFpEF

Opitz, C.F. et al. J Am Coll Cardiol. 2016;68(4):368–78.

Various factors and comorbidities appear more or less frequently in patients with typical idiopathic pulmonary arterial hypertension (IPAH), defined as <3 risk factors for left heart disease; in patients with atypical IPAH (≥3 risk factors); and in patients with PH-heart failure with preserved ejection fraction (HFpEF). Given the patterns and tendencies seen, is there a disease continuum ranging from typical IPAH through atypical IPAH to PH-HFpEF? AF = atrial fibrillation; CAD = coronary artery disease; DPG = diastolic pressure gradient; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; TPG = transpulmonary pressure gradient.

This notion was supported by the fact that PH and right heart failure were listed as cause of death in 32% of the patients with PH-HFpEF in our series.

Our data supported the hypothesis that there may be a disease continuum ranging from typical IPAH through atypical IPAH to PH-HFpEF (**Central Illustration**). As in many other fields of medicine, clinical classifications were introduced to clarify complex biological systems, but often single cut-off values failed to separate disease entities, especially in multifactorial diseases and in aging patient populations (13). The hemodynamic separation of pre- from post-capillary PH by the PAWP threshold of 15 mm Hg might be such an example. On the basis of data presented here, it is most likely that a number of our patients have been labeled as IPAH despite the presence of several risk factors (as defined earlier)

predisposing for the development of post-capillary PH. In the AMBITION trial, this phenomenon was observed during the early enrollment period, which led to modification of the inclusion criteria preventing further enrollment of patients with 3 or more risk factors for left heart disease, that is, atypical IPAH (16,17). Interestingly, the analysis of the 2 groups ("original" vs. "restricted" inclusion criteria) supported our findings, as it described a similar shift in age and comorbidity profile with comparable hemodynamics. As in our study, patients with atypical IPAH in the AMBITION trial did respond to PH therapies, although the response was attenuated and the rate of treatment discontinuations was higher (17).

STUDY LIMITATIONS. Our study had both strengths and limitations. Strengths included the large sample size of prospectively enrolled patients with newly

diagnosed, incident PH; the relatively long observation period; the low number of patients who were lost to follow-up; the "real-life" setting; and the availability of hemodynamic data from right heart catheterization at the time of diagnosis. Limitations included the registry nature of the data source, which obviously does not reach the quality of a randomized clinical trial. Hence, any data on drug effects must be interpreted with great caution. However, the COMPERA registry enrolls consecutive patients on a prospective basis, and several control measures have been implemented to ensure high data quality, including independent on-site source data monitoring. Nevertheless, comorbidities were only documented as far as they are known to be associated with the development of left heart disease and/or PH. Medications other than PAH-approved drugs and anticoagulants were not documented. Complete follow-up data were not available for all parameters, and systematic echocardiographic or hemodynamic follow-up data were lacking. Further, we did not apply statistical measures to reduce confounding (such as propensity-score matching or multivariable risk-adjusted modeling), and thus, for all results and conclusions it must be considered that groups differed in many respects at baseline. Finally, the sample of patients with PH-HFpEF described herein represented a unique subset of patients with severe PH and HFpEF who were judged as candidates for targeted PH therapies by the expert COMPERA investigators on an individual basis. Therefore, our findings are not generalizable to all patients with PH-HFpEF and should not promote uncritical and potentially dangerous use of PAH drugs in this group of patients. In addition, the elevated right atrial pressure in the PH-HFpEF group might be an indicator that the therapeutic potential of optimized volume control (29) has not fully been utilized by the COMPERA investigators.

CONCLUSIONS

Our findings underscored the notion that there is a population of patients with risk factors for left heart disease presenting with pre-capillary PH that is characterized by disease features lying in between typical IPAH and PH-HFpEF. Our data, in line with recent reports from the AMBITION study (16,17) and others (15), indicated that these patients benefit from PH-targeted therapies, albeit to a lesser extent than patients with typical IPAH. In addition, our results also indicated potential benefits of PH-targeted therapies in patients with HFpEF and with combined pre- and post-capillary PH. As patients with atypical IPAH and PH-HFpEF are becoming more common, future studies should aim to identify the most appropriate treatment strategies for these patient populations.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Christian F. Opitz, Department of Cardiology, DRK Kliniken Berlin, Spandauer Damm 130, 14050 Berlin, Germany. E-mail: c.opitz@drk-kliniken-berlin.de.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with post-capillary pulmonary hypertension due to HFpEF, those with atypical idiopathic PAH associated with multiple risk factors for left-sided heart disease, and those with pre-capillary, idiopathic PAH span a pathophysiological continuum with different clinical characteristics and responses to therapy.

TRANSLATIONAL OUTLOOK: Future studies should assess the efficacy of pulmonary vasodilator therapies in patients with HFpEF and in those with combined forms of pre- and post-capillary PH.

REFERENCES

1. Lam CSP, Roger VL, Rodeheffer RJ, et al. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol 2009;53:1119–26.

2. Leung CC, Moondra V, Catherwood E, Andrus BW. Prevalence and risk factors of pulmonary hypertension in patients with elevated pulmonary venous pressure and preserved ejection fraction. Am J Cardiol 2010;106:284–6.

3. Shah AM, Claggett B, Sweitzer NK, et al. Cardiac structure and function and prognosis in heart failure with preserved ejection fraction: findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure

with an Aldosterone Antagonist (TOPCAT) trial. Circ Heart Fail 2014;7:740–51.

4. Mohammed SF, Hussain I, AbouEzzeddine OF, et al. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. Circulation 2014;130:2310–20.

5. Bursi F, McNallan SM, Redfield MM, et al. Pulmonary pressures and death in heart failure: a community study. J Am Coll Cardiol 2012;59:222–31.

6. Melenovsky V, Hwang S-J, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J 2014;35:3452–62.

7. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62: D34–41.

8. Vachiery JL, Adir Y, Barbera JA, et al. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol 2013;62:D100–8.

9. Hoeper MM, Bogaard H-J, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62:D42–50.

10. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016;37:67–119.

11. Rosenkranz S, Gibbs JSR, Wachter R, et al. Left ventricular heart failure and pulmonary hypertension. Eur Heart J 2016;37:942–54.

12. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493–537.

13. 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;168:871–80.

14. 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;186:790–6.

15. Charalampopoulos A, Howard LS, Tzoulaki I, et al. Response to pulmonary arterial hypertension drug therapies in patients with pulmonary arterial hypertension and cardiovascular risk factors. Pulm Circ 2014;4:669–78.

16. Mclaughlin V, Galie N, Barbera JA, et al. A comparison of characteristics and outcomes of patients with atypical and classical pulmonary arterial hypertension from the MAMBITION Trial. Presented at: American Thoracic Society International Conference; May 17, 2015: Denver, CO.

17. Galiè N, Barberà JA, Frost AE, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. N Engl J Med 2015;373:834–44.

18. Olsson KM, Delcroix M, Ghofrani HA, et al. Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). Circulation 2014;129:57–65.

19. Paulus WJ, Tschöpe C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539–50.

20. Hurdman J, Condliffe R, Elliot CA, et al. ASPIRE registry: assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. Eur Respir J 2012;39:945–55.

21. Lewis GD, Lachmann J, Camuso J, et al. Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. Circulation 2007;115:59–66.

22. Lewis GD, Systrom DM, Semigran MJ, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation 2007;116:1555–62.

23. Guazzi M, Vicenzi M, Arena R, Guazzi MD. PDE5 inhibition with sildenafil improves left ventricular diastolic function, cardiac geometry, and clinical status in patients with stable systolic heart failure: results of a 1-year, prospective, randomized, placebo-controlled study. Circ Heart Fail 2011;4:8–17.

24. Dumitrescu D, Seck C, Möhle L, et al. Therapeutic potential of sildenafil in patients with heart failure and reactive pulmonary hypertension. Int J Cardiol 2012;154:205–6.

25. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation 2011;124:164–74.

26. Packer M, McMurray J, Massie BM, et al. Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. J Card Fail 2005;11:12–20.

27. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2013;309:1268–77.

28. Hoendermis ES, Liu LCY, Hummel YM, et al. Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial. Eur Heart J 2015;36:2565–73.

29. Adamson PB, Abraham WT, Bourge RC, et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail 2014;7:935–44.

KEY WORDS heart failure with preserved ejection fraction, idiopathic pulmonary arterial hypertension