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RESEARCH ARTICLE

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Treatment pathways in Finnish patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH)

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Abstract

Treatment patterns of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) in Finland are unknown. Guidelines now recommend early escalation of treatment for PAH. We evaluated how well Finnish practice follows guidelines, and how treatment initiations and outcomes are related. The pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension patients in Finland cohort includes all PAH and CTEPH patients diagnosed between 2008 and 2020 in all Finnish university hospitals. Drug therapy was analysed in patients with medical/procedural history available, and changes in the 4-tier comparative, prospective registry of newly initiated therapies for pulmonary hypertension (COMPERA) 2.0 risk score were evaluated. PAH patients ($n = 268$) were initially treated with monotherapy (52%) or double therapy (24%). After year 2015, double therapy use increased to 39%. PAH treatment at 1 year after diagnosis included phosphodiesterase 5 inhibitors (71%), endothelin-receptor antagonist (48%), prostacyclin analogue (7%), calcium channel blocker (12%) and selexipag (1%). 35% achieved low risk at 1 year, increasing to 44% for patients diagnosed after 2015. Those remaining at intermediate-high (IH) or high risk (H) (28%) were not treated less aggressively than others but were older, had more comorbidities, and often history of smoking. CTEPH patients ($n = 189$) were treated with pulmonary endarterectomy (PEA) (27%), balloon pulmonary angioplasty (BPA) (11%) and medical therapy only (41%) within 1 year from diagnosis. 45% achieved low risk at 1 year. We present additional results on treatment of IH and H patients, patient characteristics preceding death, and treatment persistence. We found less treatment of PAH patients

with double or triple therapies and of CTEPH patients with PEA and BPA than expected but with good results. Patients not reaching low or intermediate COMPERA 2.0 were old and had comorbidities.

KEYWORDS
chronic thromboembolic pulmonary hypertension, pulmonary arterial hypertension, real-world evidence, treatment

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are clinically important classes of pulmonary hypertension (PH). PAH is characterized by pulmonary vasoconstriction and remodelling,[1] and CTEPH by obstruction of pulmonary arteries with fibrotic material and vascular remodelling.[2] The most common cause of death in PAH and CTEPH is right ventricular failure.[2]

Clinical studies and guidelines suggest a proactive approach to the PAH therapy, with initial double oral therapy unless patients have comorbidities and adding prostacyclins if patients have high risk of death.[2] Similarly, CTEPH patients should be evaluated for operability to pulmonary endarterectomy (PEA) and nonoperable patients to balloon pulmonary angioplasty (BPA) and medical therapy. Registries have shown limited adoption of these recommendations to clinical practice.[3]

Here, we studied how well the Finnish treatment patterns follow guidelines, whether treatment patterns can be explained by patient characteristics including comorbidities and how treatment initiation is related to outcomes.

METHODS

Study population

Patient data for the pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension patients in Finland (FINPAH) cohort was collected by electronic chart review at all five Finnish university hospitals (Helsinki, Turku, Tampere, Oulu, Kuopio) and thus includes the vast majority of Finnish PH patients.

Patients had to have a diagnosis of PAH (ICD-10 codes I27.0, I27.8, I27.9, Q21.8) or CTEPH (I27.2) or a prescription for a prostacyclin receptor agonist (PRA; selexipag) or a prostacyclin analogue (PCA; iloprost, treprostinil), an endothelin-receptor antagonist (ERA: bosentan, ambrisentan, sitaxentan, macitentan), a phosphodiesterase 5 inhibitor (PDE5: sildenafil, tadalafil) prescribed for PH, riociguat, or a calcium antagonist (calcium channel blocker, CCB: amlodipine, felodipine, nifedipine, diltiazem) for treatment of PH, or symptoms obviously indicating PH (with later verification of PAH or CTEPH), recorded at least once in 2008–2019. There weren't any clinical trials for PAH or CTEPH ongoing in Finland during the study period that could have influenced the drugs in use by these patients. Patients with history of lung transplant, and patients younger than 18 years at index date/study inclusion were excluded. Patients with diagnosis earlier than 2008 were excluded from the main analyses of treatments at diagnosis but included in the additional analyses to increase sample size. Of all PH patients, analysis was restricted to group 1 (PAH) and group 4 (CTEPH) patients. Patient baseline characteristics were presented earlier,[4] manuscript submitted.

Study design

Chart review was done by expert clinicians using electronic clinical research forms and spanned a wide range of variables, including demographics, comorbidities, clinical and laboratory data both at diagnosis and during follow-up, PAH medications and their dosing, hospitalizations, and interventions related to PAH or CTEPH. Clinical data was followed up until lung transplant, death, or December 31, 2020, whichever happened first. Mortality data until December 31, 2021 was obtained by linkage to the official Statistics Finland register, as well as causes of death until December 31, 2020 (these are only available with a delay). Six time-points were defined: diagnosis plus 3 months and 1, 2, 3, 4, and 5 years after diagnosis. Medical therapy at diagnosis was assessed at up to 3 months postdiagnosis to account for initial delays in treatment assignment. For PAH patients, the PAH-specific drug classes prescribed at each time point were extracted and the count of PAH-specific drug classes prescribed concurrently (i.e., monotherapy, double therapy, etc.) was evaluated. CTEPH patients were grouped on the basis of treatment with PEA and BPA. Patients that underwent both PEA and BPA were assigned to the PEA group. CTEPH patients without a

history of BPA were classified according to whether they received PAH-specific medical therapy.

The comparative, prospective registry of newly initiated therapies for pulmonary hypertension (COMPERA) 2.0 four-strata risk score, which is similar to the 4-strata risk-assessment tool in the 2022 european society of cardiology (ESC)/european respiratory society (ERS) guidelines for PH,[2,5] was calculated from the WHO functional class, 6-min walking distance, and brain natriuretic peptide (BNP) or N-terminal fragment of pro-BNP (NT-proBNP) using the observation of any of these closest to the target time point and last observations of other variables carried forward if necessary. If there was no observation of any of these variables within a time window of ±3 months around the target time point, the risk score was set to not available (NA).

Because of the Act on the Secondary Use of Health and Social Data in Finland, any observations concerning fewer than five (or three in special cases) study participants cannot be reported in general. Due to legal constraints, the data set is NA to individuals not mentioned in the research permit.

Analysis

Treatments and risk score distributions are presented descriptively, and no statistical testing was applied to the main analysis. Treatment use and risk score distribution at different time points were analysed as point prevalence, excluding dropouts due to death or end of follow-up. Where these are compared between populations, Pearson's chi-squared test was used. In sensitivity analysis, treatments at diagnosis and at 1 year postdiagnosis were evaluated separately for patients diagnosed in years 2008−2010, 2011−2013, 2014−2016, and 2017−2019. Using univariate Cox proportional hazards models, we analysed whether overall survival of PAH patients was predicted by the time of diagnosis (binary: before or after Sepember 30, 2015, when the European treatment guidelines[6] urging more aggressive first-line treatment were published) or by whether double therapy was started as the first PH medication.

Additional analyses investigated treatment at specific points in the patient disease history. First, in patients classified as intermediate-high (IH) or high (H) by

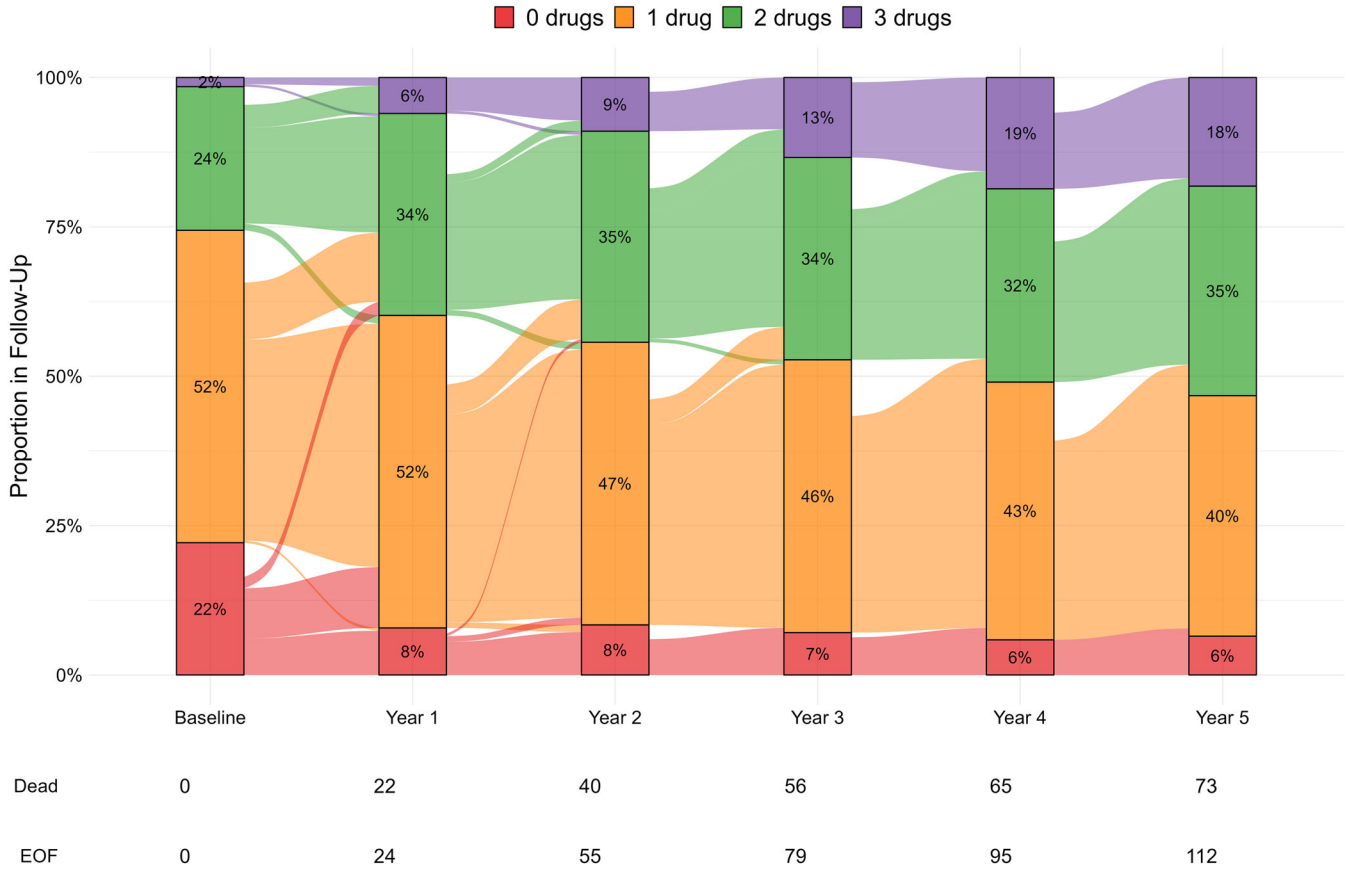

FIGURE 1 Proportion of PAH patients by medical therapy, at diagnosis and annually thereafter. *N* declines over time due to deaths and EOF. EOF, end of follow-up; PAH, pulmonary arterial hypertension.

COMPERA 2.0 at 1 year after diagnosis, we looked at patient characteristics, treatments and risk scores. The risk score recorded nearest to the 1-year time point was identified, and patients without observations relevant to the calculation of the risk score in a time window of ±3 months around the target date were excluded. The date of risk score was the index date for this analysis, and changes in treatment and risk score were evaluated over the following 6 months. Second, we additionally investigated treatments in use at specific time points; for these analyses, we used data on patients with medication data available and also included patients with a diagnosis before 2008. Here, we identified all patients with deaths recorded 2008-2020 and located the last recorded visit. Also, we extracted patient characteristics and treatment types at the time of being listed for a lung transplantation.

Finally, we aimed to estimate the prevalence and 1-year persistence of triple therapy with ERA, PDE5 and a PRA or PCA and the 1-year persistence of the drug classes constituting the first PH medication in patients starting medication between 0 and 90 days after diagnosis. These analyses included patients with a first diagnosis between 2008 and 2019. Persistence was estimated using the Kaplan-Meier method, with death or end of follow-up as censoring events. Drug changes within the same class were considered as persistent.

RESULTS

PAH patients ($N = 268$)

Figure 1 shows the evolution of drug treatment in the whole cohort during follow-up. Most patients (52%, $N = 262$) started with monotherapy and by year 5 ($N = 77$) the proportion of double and triple therapies increased to 35% and 18%, respectively. As expected, the most prescribed PAH treatment class (Figure 2) was PDE5 (up to 75%), followed by ERA (up to 61% of patients) or their combination (up to 27% of patients). Specific treatment was not registered for 6−8% patients.

Figure 3 shows the proportions of patients on mono-, double, and triple therapy across different time-points. After the release of new European guidelines on September 30, 2015, a change in initial treatment from monotherapy (dropping from 58% to 44%, $p = 0.047$) to double therapy (increasing from 14% to 39%, $p < 0.001$) is observed. Consistently, there was a trend for improved

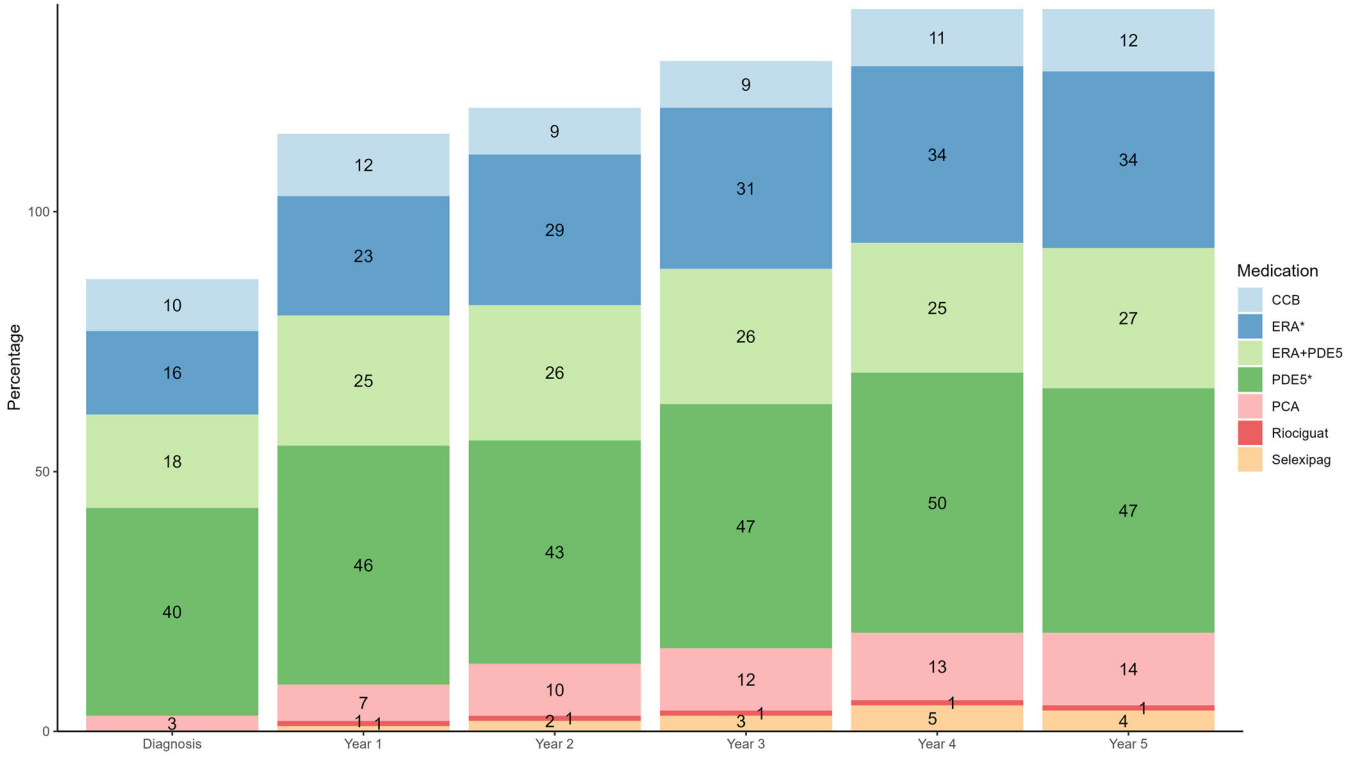

FIGURE 2 Proportion of PAH patients assigned to each drug class, over time. As patients can be assigned to combination therapies, the percentages do not add up to 100. *N* declines over time due to deaths and EOF. CCB, calcium channel blocker; EOF, end of follow-up; ERA, endothelin-receptor antagonist; ERA*, ERA but not PDE5; PAH, pulmonary arterial hypertension; PCA, prostacyclin analogue; PDE5, phosphodiesterase 5 inhibitor; PDE5*, PDE5 but not ERA.

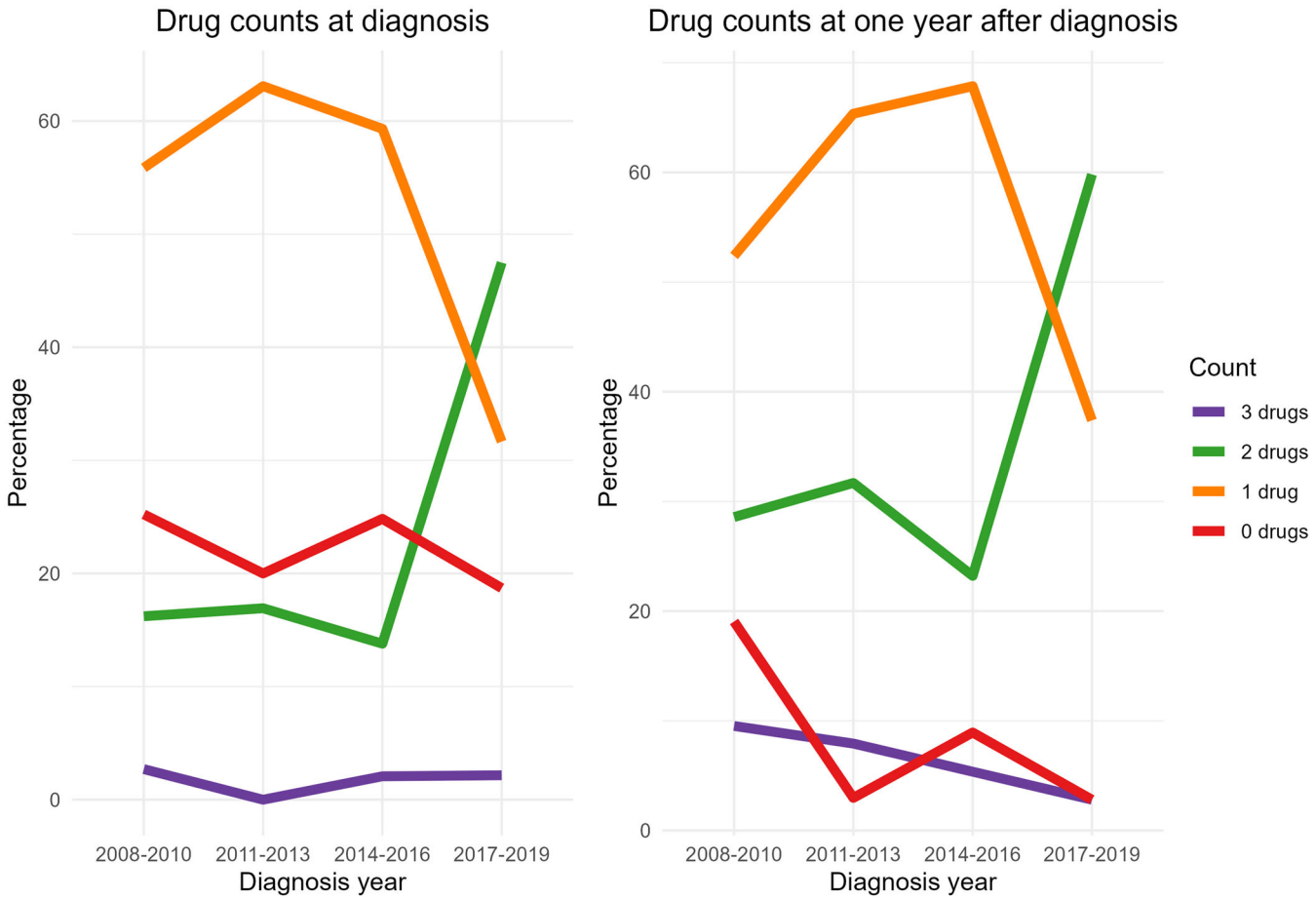

FIGURE 3 Proportion of PAH patients by medical therapy at diagnosis, by diagnosis period. PAH, pulmonary arterial hypertension.

survival of patients diagnosed after the release of the new guidelines in univariate analysis (hazard ratio [HR] 0.78, 95%-confidence interval (CI) 0.50−1.21, $p = 0.26$). Likewise, there was a trend for improved survival of patients treated with double therapy compared to other patients (HR 0.81, 95%-CI 0.51−1.27, $p = 0.35$).

COMPERA 2.0 four-level risk score distributions are presented in Figure 4. While 15% and 27% of patients presented as H or IH at diagnosis ($N = 255$), respectively, only 8% and 20% were still at H or IH 1 year later ($N = 172$). Figure 1 in the Supporting Information S1: Appendix shows how the risk score distribution has changed in patients diagnosed before or after the publication of the new European guideline on September 30, 2015. The proportion still in IH or H at 1 year dropped from 33% before 2015 ($N = 102$) to 21% after 2015 ($N = 70$). The patients remaining IH or H at 1 year ($N = 48$) had more often PAH associated with connective tissue diseases, the patients were older, had more often a history of smoking and lower diffusing capacity for carbon monoxide, atrial fibrillation, hypertension, diabetes and ischemic heart disease (Tables 1 and 2). Most of these patients were receiving monotherapy (46%, typically PDE5) or double therapy (42%, typically PDE5 + ERA) at the time of the IH/H observation. Treatment intensification was observed in few (<8%) patients. Six patients (13%) died within the next 6 months, six patients (13%) had improved COMPERA 2.0 4-strata risk score, and 3 (6%) had worse risk score. Listing for lung transplantation was recorded for 21 PAH patients (8%). At the time of listing, the patients were on average 48.1 (SD 8.4) years old and listing occurred on average 11.2 (SD 12.1) years since PAH diagnosis (median 8.2 years, IQR 2.3−12.6). 48% of these patients were using triple PAH therapy at the time of transplant listing.

Death records for 126 PAH patients could be analysed, and data for a last visit with a PH specialist was available for $N = 121$ patients. At their last visit (a mean 9.4 months before death), 40% were treated with PAH monotherapy (most commonly PDE5) and 30% received PAH double therapy (PDE5 + ERA was the most common combination). Triple therapy (mainly PDE5 + ERA + PCA) was less common (17%), and 12% were not receiving PAH medication (Supporting Information S1: Table 2). The cause of death was reported for 126 PAH

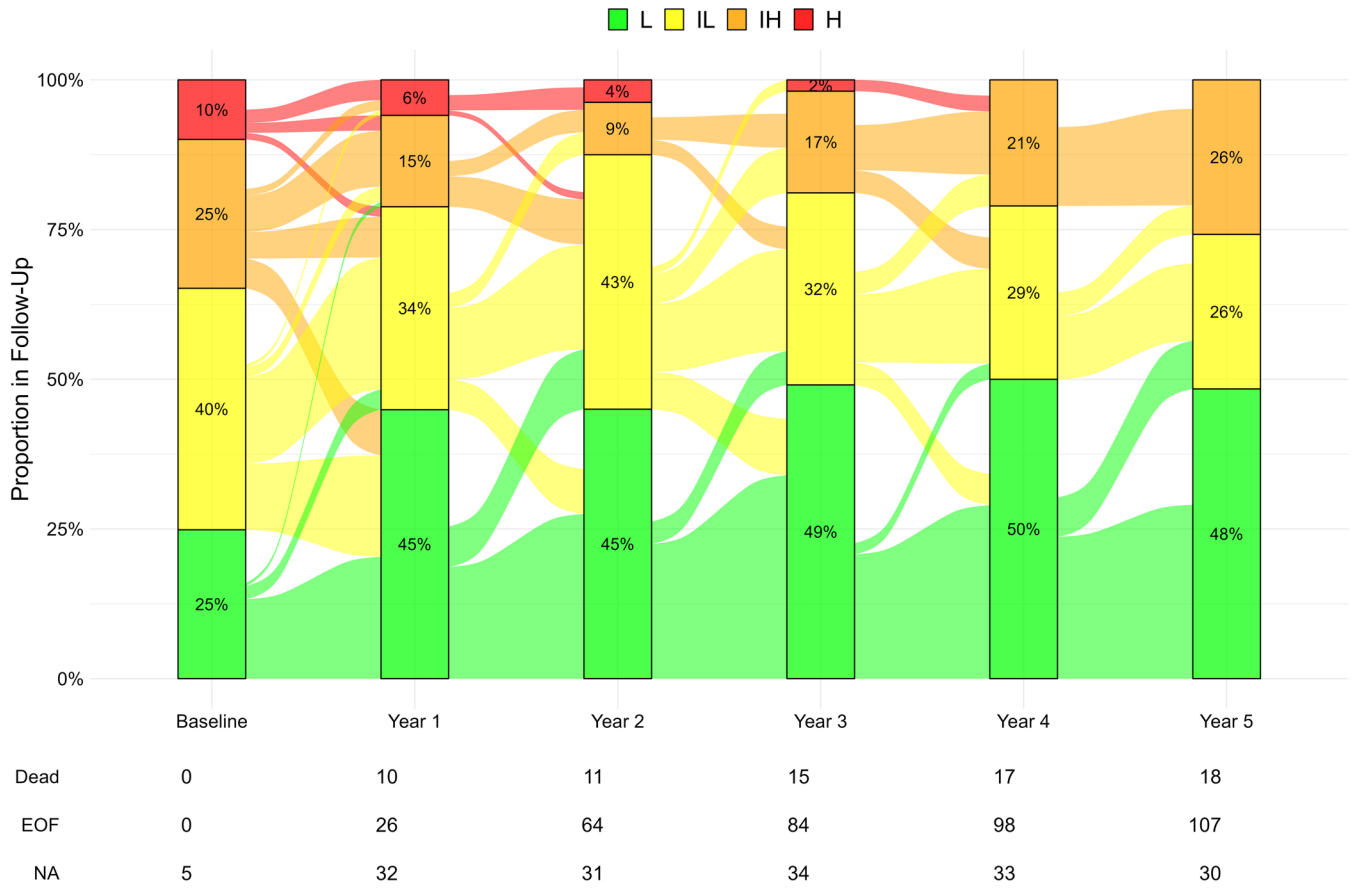

FIGURE 4 Proportion of PAH patients by COMPERA 2.0 4-strata risk score, at diagnosis and annually thereafter. *N* declines over time due to deaths and EOF. COMPERA, comparative, prospective registry of newly initiated therapies for pulmonary hypertension; EOF, end of follow-up; H, high; IH, intermediate-high, IL, intermediate-low; L, low, NA, not available.

patients. 81% of the deaths were related to PAH, most often with underlying cause of death primary PH (28%), congenital heart diseases (15%) and connective tissue diseases (10%). Non-PAH related causes included malignancies, coronary heart disease and liver cirrhosis. Less common causes cannot be reported due to the anonymization requirement.

CTEPH patients ($N = 189$)

Within 3 months after diagnosis, 46% of CTEPH patients ($N = 186$) were assigned medical therapy, 40% were untreated, 9% had BPA, and 6% PEA (Figure 5). One year after diagnosis ($N = 151$), 27% had been treated with PEA (23% treated with PAH-specific medication at 3 months after diagnosis), with 19% of operated patients receiving PAH-specific medical therapy after PEA. An additional 11% had undergone BPA, 41% were treated with PAH-specific medication (no surgery) and 21% had not received medical or surgical treatment for CTEPH by 1 year. Monotherapy was the most common form of medical therapy both at diagnosis and 1 year later, regardless of the year of diagnosis. Riociguat was used as part of the initial drug therapy ($N = 91$) in 20 patients (22%) and was in use in 25 patients (32%) at 1 year ($N = 79$).

While 10% and 25% of patients presented with H and IH COMPERA 2.0 risk at diagnosis ($N = 180$), respectively, 1 year after diagnosis ($N = 118$) only 6% and 10% of patients were at H or IH risk, respectively (Figure 6). Supporting Informatio S1: Figure 1 in the Supporting Informatio S1: Appendix shows that the risk score distribution at diagnosis and at 1 year has remained relatively unchanged before and after 2015. Of the patients remaining H or IH at 1 year ($N = 25$) few patients were treated with BPA or PEA, 56% with medical therapy and 20% had no therapy. The patients were on average older, more often female, had higher pulmonary vascular resistance (PVR) and lower cardiac index and more often diabetes and ischemic heart disease (Tables 1 and 2). Some treatment changes were observed in the next 6 months, but due to the anonymization requirements, it is impossible to report on

TABLE 1 Patient characteristics at diagnosis and characteristics of COMPERA 2.0 4-strata intermediate-high (IH) or high (H) patients 1 year after diagnosis.

Characteristic	PAH cohort at diagnosis ($N = 268$)	PAH patients with IH/H at 1 year after diagnosis ($n = 48$[a])	CTEPH cohort at diagnosis ($N = 189$)	CTEPH patients with IH/H at 1 year after diagnosis ($n = 25$[a])
PAH Subclass			-	-
- IPAH	106 (40%)	23 (48%)		
- HPAH	10 (4%)	0		
- APAH Connective Disease	76 (28%)	17 (35%)		
- APAH Congenital Heart Disease	39 (15%)	0		
- APAH Portal Hypertension	7 (3%)	0		
- APAH HIV	<5 (<2%)	0		
- PVOD or PCH	12 (5%)	<5 (<9%)		
- Drugs or Toxins	7 (3%)	0		
- Unspecified	<11 (<4%)	<5 (<9%)		
Age, mean (SD)	57.4 (16.3)	67.2 (11.3)	63.0 (13.4)	70.9 (11.9)
Female sex, *N* (proportion)	195 (72.8%)	35 (73%)	93 (49.2%)	16 (64%)
BMI, kg/m^2, mean (SD)	27.5 (6.2)	28.9 (7.5)	28.8 (6.7)	28.2 (4.8)
Smoking (Current or previous)	42.7%	58%	43.5%	32%
Time from first symptoms to diagnosis, years,				
Median (IQR)	1.0 (0.6–2.1)	1.0 (0.7–2.3)	1.0 (0.6–1.8)	0.9 (0.5–2.0)
NYHA FC				
I	5.2%	0.0%	0.0%	<21.7%
II	26.2%	<3.5%[b]	33.3%	<21.7%
III	56.0%	>77.1%	55.0%	<21.7%
IV	12.5%	19.8%	11.7%	78.3%
Clinical right heart insufficiency	52 (22%)	15 (35%)	27 (17%)	5 (23%)
Blood pressure, mmHg				
- systolic, mean (SD)	130 (24)	128 (20)	131 (18)	126 (29)
- diastolic, mean (SD)	79 (13)	75 (11)	81 (12)	76 (12)
Heart rate (1/min), mean (SD)	77 (14)	73 (12)	75 (14)	71 (11)
O_2 saturation, %, mean (SD)	93.8 (4.7)	93 (5.0)	92.0 (11.2)	92 (4.7)
NT-proBNP, ng/L,				
mean (SD)	2389 (3091)	4174 (8449)	1916 (3359)	2589 (2259)
median (IQR)	1493 (520–3124)	1800 (716–3280)	829 (255–2043)	1973 (1332–3054)
BNP, ng/L, mean (SD)	428.1 (428.0)	406 (333)	212.4 (281.4)	733 (210)

(Continues)

TABLE 1 (Continued)

Characteristic	PAH cohort at diagnosis ($N = 268$)	PAH patients with IH/H at 1 year after diagnosis ($n = 48$[a])	CTEPH cohort at diagnosis ($N = 189$)	CTEPH patients with IH/H at 1 year after diagnosis ($n = 25$[a])
Creatinine, μmol/L, mean (SD)	90.4 (71.8)	106 (55)	88.9 (26.1)	100 (40)
6-min walking distance, m, mean (SD)	347.9 (151.6)	247 (121)	371.1 (143.4)	274 (94)
Right heart catheterization recorded, *N* (proportion)	255 (95.1%)	<5 (<9%)	177 (93.7%)	<5 (<20%)
mPAP (mmHg), mean (SD)	46.7 (11.4)	42.0 (1.4)	44.6 (10.1)	46.5 (8.7)
PCWP (mmHg), mean (SD)	10.8 (4.8)	7.9 (0.9)	9.9 (4.8)	13.3 (5.3)
CI (l/min), mean (SD)	2.4 (0.8)	2.2 (0.0)	2.4 (0.9)	1.8 (0.1)
PVR (WU), mean (SD)	9.1 (4.3)	7.9 (0.9)	8.3 (4.0)	10.7 (2.3)
RA/CVP (mmHg), mean (SD)	9.1 (10.1)	14.5 (2.1)	7,2 (4.0)	14.5 (7.8)
DLCOc %, mean (SD)	53.5 (19.3)	45.3 (16.0)	71.5 (16.6)	n.r.
ECHO:				
TAPSE, mm, mean (SD)	17.5 (5.0)	17.0 (4.8)	19.3 (5.0)	16.8 (4.4)
Pericardial fluid *N*, %	33 (18%)	5 (14%)	10 (8%)	<5 (<20%)
LV eccentric *N*, %	115 (78%)	17 (77%)	76 (75%)	<5 (<20%)
Normal (>50%) respiratory variation in IVC *N*, %	98 (67%)	18 (58%)	68 (71%)	11 (65%)

Abbreviations: BNP, brain natriuretic peptide; CI, cardiac index; COMPERA, comparative, prospective registry of newly initiated therapies for pulmonary hypertension; DLCOc, diffusing capacity of the lungs for carbon monoxide, adjusted for hemoglobin; ECHO, echocardiography; EKG, electrocardiogram; IVC, inferior vena cava; mPAP, mean pulmonary arterial pressure; n.r., not reported; NT-proBNP, N-terminal prohormone of BNP; NYHA FC, New York Heart Association Functional Class; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RBBB, right bundle-branch block; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.

[a]Data for some patients was missing for employment, smoking status, and the clinical examinations;

[b]Exact numbers not reported to protect anonymity.

any particular changes. Fewer than three patients died. The Compera 2.0 4-strata risk score improved in around 30% of patients and worsened in fewer than three patients.

Neither listings for lung transplant nor lung transplants were recorded for the CTEPH patients. Data for a last visit with a PH specialist was available for most patients. At a mean 12.1 months before death, most patients (29%) received monotherapy (most commonly PDE5), 18% received double therapy (most commonly PDE5 + ERA), 20% received no PAH medication, and for 32%, no information on medication was available.

The cause of death could be obtained for 56 CTEPH patients. Sixty-three percent of the deaths were CTEPH-related, most often with underlying cause of death pulmonary embolism (23, 41%) and PH. Among the most common non-CTEPH related causes were malignancies, cerebrovascular diseases, and coronary heart disease. Less common causes could not be reported due to the anonymization requirement.

Treatment persistence

Persistence to the initial PAH treatment could be analysed in 306 patients (62%) of the FINPAH cohort. In these patients, the first treatment included a PDE5 (68%), ERA (30%), CCB (9%), riociguat (9%), and selexipag or PCA (3%; persistence was not estimated due to small sample size). Persistence at 1 year from treatment start was highest for ERA (91.5%), followed by riociguat (87.8%), PDE5 (86.4%), and CCB (84.1%), see Supporting Information S1: Figure 3. Of the ERA drugs, treatment persistence at 1 year was highest for macitentan (95.7%), followed by ambrisentan (81.3%) and bosentan (76.5%), see Supporting Information S1: Figure 4.

TABLE 2 Comorbidities of patients at diagnosis and for the subset of patients with IH or H COMPERA 2.0 4-strata risk score at 1 year after diagnosis.

Diagnosis, *N* (proportion)	PAH cohort at diagnosis (*N* = 268)	PAH patients with IH/H at 1 year after diagnosis (*n* = 48)	CTEPH cohort at diagnosis (*N* = 189)	CTEPH patients with IH/H at 1 year after diagnosis (n = 25)
Major cardiovascular comorbidities				
3 or more CV comorbidities	23 (9%)	8 (17%)	15 (8%)	6 (24%)
Treated hypertension	101 (38%)	27 (56%)	95 (50%)	13 (52%)
Diabetes	52 (19%)	14 (29%)	26 (14%)	6 (24%)
Stroke	7 (3%)	<5 (<10%)	9 (5%)	<5 (<20%)
Ischemic heart disease	34 (13%)	11 (23%)	22 (12%)	5 (20%)
Atrial fibrillation or flutter	56 (21%)	16 (33%)	18 (10%)	6 (24%)
Chronic kidney disease	14 (5%)	<5 (<10%)	6 (3%)	<5 (<20%)
Lung disease	78 (29%)	20 (42%)	54 (29%)	6 (24%)
Asthma	34 (13%)	<5 (<10%)	38 (20%)	5 (20%)
Parenchymal	17 (6%)	5 (10%)	<5 (<3%)	0
COPD or emphysema	13 (5%)	<5 (<10%)	17 (9%)	0
Other	26 (10%)	9 (19%)	8 (4%)	<5 (<20%)
Rheumatic diseases	90 (34%)	20 (42%)	10 (5%)	<5 (<20%)
Scleroderma or CREST	54 (20%)	13 (27%)	0	0
Sjögren	13 (5%)	5 (10%)	<5 (<3%)	<5 (<20%)
Rheumatoid arthritis	6 (2%)	<5 (<10%)	7 (4%)	<5 (<20%)
Other (including MCTD)	22 (8%)	<5 (<10%)	<5 (<3%)	0
Sleep apnea	23 (9%)	8 (17%)	17 (9%)	0 (0%)
Valvular disease (moderate or severe)	36 (13%)	<5 (<10%)	14 (7%)	<5 (<20%)
Tricuspid regurgitation	24 (9%)	<5 (<10%)	8 (4%)	<5 (<20%)
Other	12 (4%)	<5 (<10%)	6 (3%)	0

Abbreviations: COMPERA, comparative, prospective registry of newly initiated therapies for pulmonary hypertension; COPD, chronic obstructive pulmonary disease; CREST, limited cutaneous form of systemic sclerosis; H, high risk; IH, intermediate-high; MCTD, mixed cutaneous tissue disease.

Forty-one patients (8%) used triple therapy at any time. Their median age at start of triple therapy was 60 (interquartile range 46–69), and the PH types were IPAH (15, 37%), APAH connective tissue disorders (11, 27%), other Group I PAH subclasses (9, 22%), and other types of PH including CTEPH (6, 15%). Triple therapy was started at median 25.8 months since diagnosis (IQR 7.8–43.7). The most common drugs used for triple therapy, among the ERA drugs, were macitentan (20 patients, 49%), bosentan (11, 27%) and ambrisentan (10, 24%). Sildenafil (36, 88%) was more commonly used than tadalafil (5, 12%). Iloprost was the most likely initial PRA/PCA (21, 51%), followed by selexipag (12, 29%) and parenteral treprostinil (8, 20%). At 1 year from initiation of triple therapy, persistence was 87.5%. By 1 year, four patients (10%) had died or received lung transplants, 3 (7%) were lost to follow-up, and 5 (12%) had discontinued PRA/PCA medication. Of the 29 patients still using PRA/

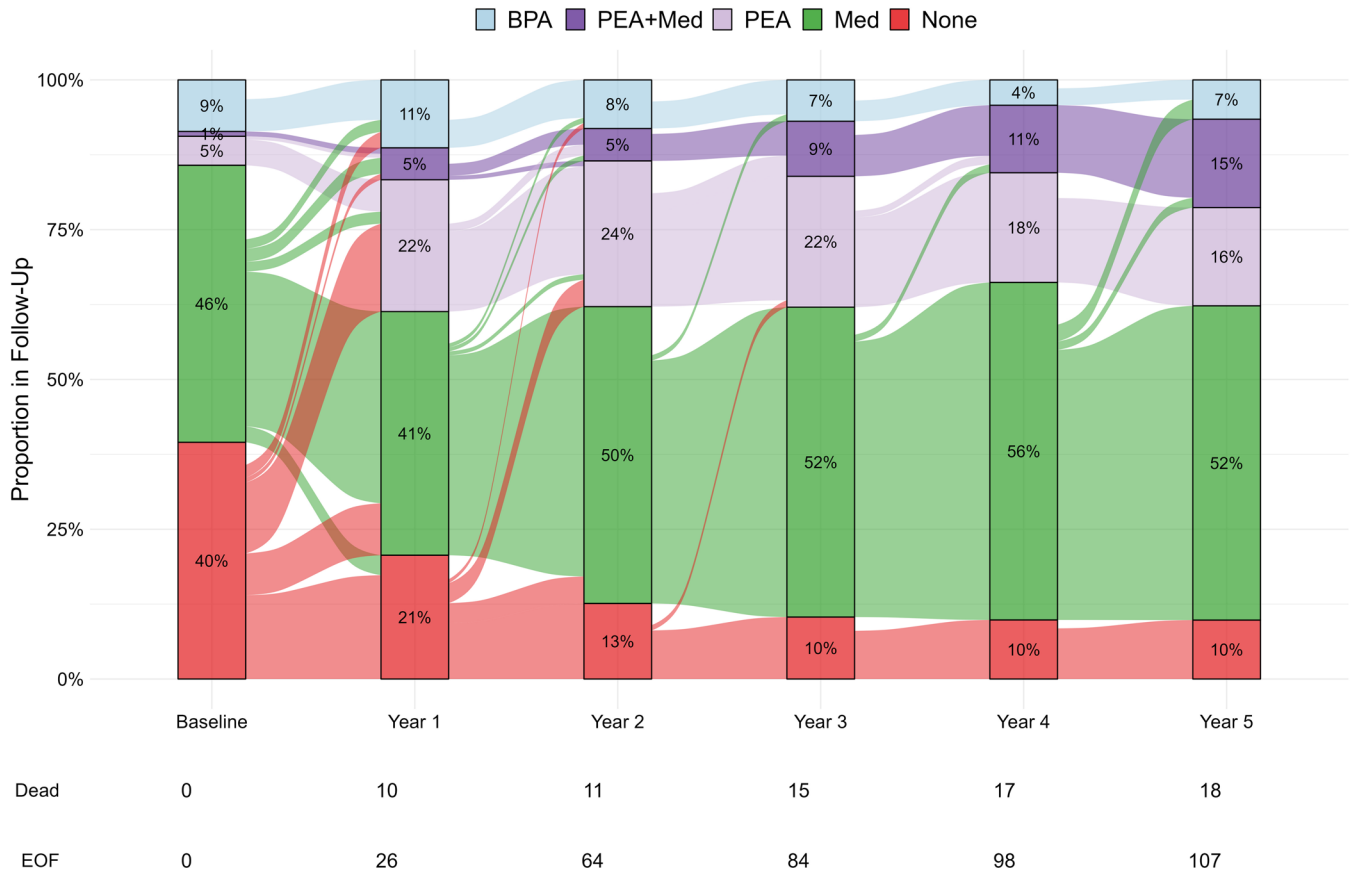

FIGURE 5 Proportion of CTEPH patients by surgical and medical therapy, at diagnosis and annually thereafter. *N* declines over time due to deaths and EOF. BPA, History of balloon pulmonary angioplasty; EOF, end of follow-up; Med, ongoing PH medication, None, no PH-specific treatment or surgery; PEA, History of PEA, no PH medication; PEA + Med, History of pulmonary endarterectomy (PEA), ongoing PH medication.

PCA at 1 year, 12 (41%) used iloprost, 8 (28%) used selexipag, and 9 (31%) used parenteral treprostinil.

DISCUSSION

This is the first systematic and comprehensive description of treatments used in the PAH and CTEPH patient populations in Finland.

In PAH, most patients started with monotherapy, but the use of double therapy increased from 16% to 47% during the recruitment period. This is in line with the release of PAH guidelines in 2015 and similar to the results of the Swedish pulmonary artery hypertension and chronic thromboembolic pulmonary hypertension registry (SPAHR).[3] During follow-up, the proportion of double and triple therapies increased, and this was associated with increasing the proportion of patients in low and intermediate-low risk up to 78% in the newer patients at 2 years. Patient risk at least at baseline was lower than for example, in SPAHR,[7] COMPERA,[8] and the French[9] registries.

However, a significant proportion of patients remained IH or H after 1 year. Their PAH-treatment was not escalated as only 6% of PAH patients remaining IH or H started selexipag or prostacyclins within a year.[10] This could, however, at least partly be explained by the patients being older and having comorbidities, but they had similar hemodynamics to the whole cohort. Consistently, in SPAHR[11] and COMPERA[12] registries, old/comorbid PAH patients had little or no improvement in risk status. Whether conservative treatment of this population is justified is not known as comorbid patients improved hemodynamics with double therapy,[12] and sequential triple therapy improved outcome.[13] Consistently, parenteral prostacyclins improved risk category in 6 months.[10] The use of triple therapy increased steadily during follow-up in up to 18% of patients at 5 years and in similar proportion of patients before death. Unexpectedly, triple therapy was concentrated in patients listed for lung transplantation (48%). Although the proportion of patients using triple therapy appears to be low, it is in the same range as reported in SPAHR.[3]

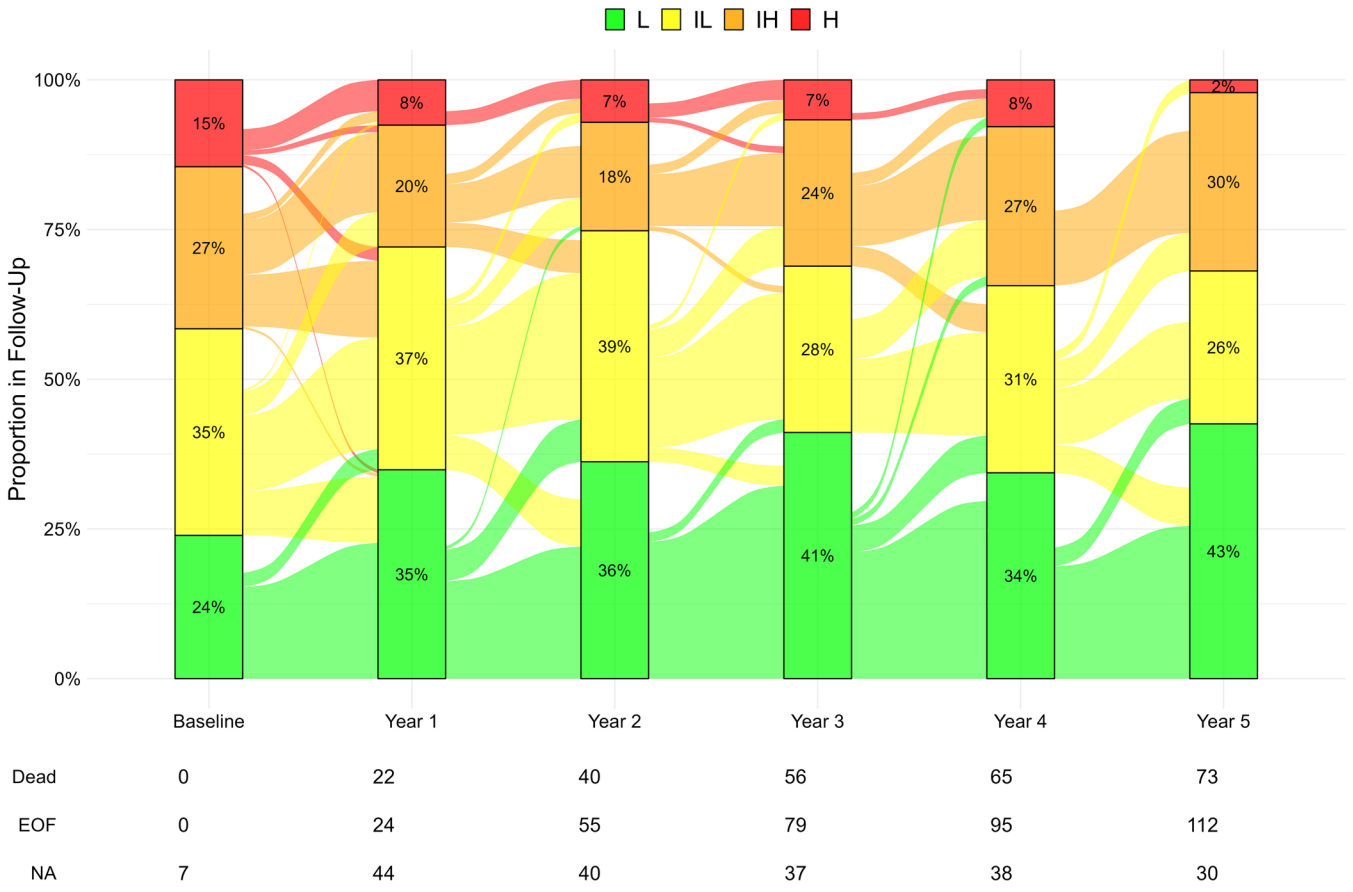

FIGURE 6 Proportion of CTEPH patients by COMPERA 2.0 4-strata risk score, at diagnosis and annually thereafter. Flows from/to NA, Dead or EOF states not shown. *N* declines over time due to deaths and EOF. COMPERA, comparative, prospective registry of newly initiated therapies for pulmonary hypertension; EOF, end of follow-up; H, high; IH, intermediate-high; IL, intermediate-low; L, low; NA, not available.

The causes of death are of interest as PAH patients diagnosed today are different from the early registries.[14] Still, in our cohort 81% of deaths were related to the disease. The proportion of right heart failure could not be reliably discriminated as in a great proportion of patients only the underlying cause without the immediate cause of death was reported. This is consistent with a previous report by Tonelli et al.[15] in which 44% of PAH patients died of right heart failure, and in another 44% death was PAH-related. In addition, in a more recent pilot study in 61% death was due to PAH and in 25% PAH-related.[16]

In CTEPH, operability of PEA (and BPA) is of major importance and the roles of risk assessment and medical therapy are less established. In our cohort, only 30% of patients underwent PEA surgery, which is close to that in SPAHR.[17] Although guidelines do not recommend the use of medical therapy before PEA,[2] in this cohort 24% of patients were pretreated with PAH-specific drugs. This is in line with pretreatment of 28% in a European registry[18] and 26% in international CTEPH registry,[19] but significantly less than 63% in SPAHR (mono 46%, double 17%).[17] After PEA residual PH is common and 19% of PEA-treated patients were treated with PAH-specific drugs at 1 year and 48% at 5 years. However, this was significantly less as compared to that of 59% in SPAHR at 1 year (75% mono) and 91% at 5 years (67% mono). The PEA group had superior survival compared to non-operated patients (manuscript submitted) and 38% of PEA patients improved COMPERA 2.0 risk at 1 year.[10]

Medical therapy for CTEPH at baseline and at 1 year was mostly monotherapy but increased to double therapy for about 30% of patients (about 40% of treated) at the last visit. This is consistent with limited trial evidence for drug efficacy in CTEPH[20,21] and is in line with drug therapy used in SPAHR[17] and in international CTEPH registries.[18,22,23] Of our patients treated with medical therapy, only 17% improved COMPERA 2.0 risk.[10]

BPA was first carried out in Finland in 2017. It was recently included in the CTEPH treatment in the ESC/ERS PH guidelines.[2] In this cohort, <5 patients were treated with BPA before PEA, 7 patients were treated

with BPA after PEA and 34 nonoperated patients underwent BPA. 79% of the BPA patients also received medical therapy (48% before, 74% after). 58% of non-PEA patients improved risk after BPA.[10] This is consistent with other registries showing improved symptoms, exercise capacity and hemodynamics after BPA.[24]

The cause of death of CTEPH patients was CTEPH-related only in 63% of patients. This is similar to findings from International CTEPH registry[22] and pilot study from Japan.[16] Cancer is a major contributor of both thrombophilia leading to the development of CTEPH and death. The rate of cancer varies from 5%[25] up to 60% of patients.[16]

While not a prospective quality register, this retrospective chart review should have a near-complete coverage of the target patient populations in Finland. Accuracy and completeness of data is limited by its recording and extraction from the hospital data systems.

The univariate analyses of HRs associated with time of diagnosis and use of double medication in PAH patients should not be read to indicate causal relationships, as this is a small observational data set, and no attempt was made to adjust for confounders or predictors of treatment choice.

Finally, the time point for analysis (e.g., treatment at 1 year and before death, treatment effect at 6 months) were chosen retrospectively and did not necessarily reflect the schedule of clinical visits, which probably impacted data quality.

Taken together, we found less treatment of PAH patients with double or triple therapies and of CTEPH patients with PEA and BPA than expected but results were in line with other registries and in PAH improved with time. PAH and CTEPH patients not reaching low or intermediate COMPERA 2.0 were old and had comorbidities.

AUTHOR CONTRIBUTIONS

Study management and supervision: Airi Puhakka and Erkki Soini. *Conceptualization*: Markku Pentikäinen, Airi Puhakka, and Erkki Soini. *Design*: All. *Data acquisition and management*: Markku Pentikäinen, Piia Simonen, Pauliina Leskelä, Terttu Harju, Pertti Jääskeläinen, Christian Asseburg, and Minna Oksanen. Analysis: Airi Puhakka, Markku Pentikäinen, Piia Simonen, Minna Oksanen, and Christian Asseburg. *Interpretation*: Airi Puhakka, Markku Pentikäinen, Piia Simonen, and Erkki Soini. *Manuscript drafting*: Christian Asseburg, Airi Puhakka, Markku Pentikäinen, Piia Simonen, Minna Oksanen, and Erkki Soini. *Revisions and final approval*: All.

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CONFLICTS OF INTEREST STATEMENT

Financial relationships in the last 24 months. Markku Pentikäinen: AOP Health, AstraZeneca, Bayer, Boehringer-Ingelheim, GE Healthcare, Janssen, MSD, Orion Pharma. Piia Simonen: Janssen. Pauliina Leskelä: Abbott, Janssen, Medtronic. Terttu Harju: Janssen, Nordic Infucare. Pertti Jääskeläinen: Janssen. Christina Wennerström: Janssen. Airi Puhakka: Bittium, Idorsia, Janssen, Johnson and Johnson. The remaining authors declare no conflicts of interest.

ETHICS STATEMENT

The study follows the Act on the Secondary Use of Health and Social Data (552/2019), with Finnish Social and Health Data Permit Authority (Findata) permit number THL/3614/14.02.00/2020. The study was retrospective and non-interventional, so patient consent was not required. Ethical approval was obtained from Helsinki University Hospital (HUS/2179/2020).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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