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ORIGINAL ARTICLE

Phenotype and outcomes according to loop diuretic use in pulmonary arterial hypertension

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Abstract

Aims The use of loop diuretics in pulmonary arterial hypertension (PAH) is less frequent compared with heart failure. The clinical and prognostic characteristics of PAH patients according to loop diuretic use remain unexplored. In this study, we retrospectively analysed the characteristics and survival of PAH patients requiring different doses of loop diuretics.

Methods and results Patients diagnosed with PAH between 2001 and 2022 at seven European centres for the management of PAH. According to the median equivalent dose of furosemide in the overall cohort, patients were divided into two subgroups: no/low-dose loop diuretic and high-dose loop diuretic. Primary outcome was 5 year all-cause mortality. Among the 397 patients included, 227 (57%) were treated with loop diuretics. Median daily furosemide equivalent dose was 25 mg, and accordingly patients were divided in no/low dose (i.e. ≤25 mg, *n* = 257, 65%) vs. high dose (i.e. >25 mg, *n* = 140, 35%). Patients in the high-dose group were older, more likely to have comorbidities, and had a more severe disease according to the ESC/ERS risk category. Crude 5 year survival was significantly shorter in patients in the high-dose group, but after adjustment for age, sex, and risk category, high loop diuretic dose was not significantly associated with the primary outcome.

Conclusions Use of high dose of loop diuretics in PAH is associated with a higher burden of comorbidities, more severe disease, and worse survival. However, in PAH, the need of high loop diuretic dose is a marker of disease severity and not an independent prognostic factor.

Keywords Diuretics; Pulmonary hypertension; Congestion; Prognosis; Comorbidities

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Introduction

Pulmonary arterial hypertension (PAH) is a rare disease characterized by an unfavourable remodelling of the pulmonary vessels, leading to ventricular-arterial uncoupling and, finally, right ventricle (RV) failure. Specific vasodilators are the mainstay drug therapy of this condition, in order to unload the RV improving patient's prognosis.[1]

Among medical treatments, diuretics play a key role in decreasing congestion when RV failure occurs, since increased right sided filling pressures determine venous congestion and progressive worsening of renal function, activating a

vicious circle, which perpetuates right heart failure (HF). Loop diuretics, alone or in combination with other classes, are administered depending on the patient status and cautiously in order to prevent excessive volume depletion that may led to further decline in cardiac output (CO), symptomatic hypotension or renal injury.[2]

In left heart disease (LHD), loop diuretics are largely used and in some observational studies, higher doses have been associated with worse prognosis.[3–5] However, it remains unclear whether the association with prognosis was primarily related to the more severe disease (prognostic marker) or to a harmful effect of high diuretic doses (prognostic factor). In the PAH population instead, little is known about the prevalence of loop diuretic therapy and its possible association with prognosis.[6]

This study aimed to explore the use of loop diuretics in the PAH population and to evaluate the possible association of high diuretic dose with prognosis.

Methods

Study population and design

We retrospectively analysed patients from the FOCUS-PAH Registry with available information on loop diuretic therapy, enrolled between 4 April 2001 and 22 December 2022. As previously described, the FOCUS-PAH is an ongoing registry recruiting patients $\geq$ 18 years old with a diagnosis of group 1 pulmonary hypertension (PH) at seven tertiary care centres (Trieste University Hospital, Trieste, Italy; Hammersmith Hospital, London, United Kingdom; IRCCS *Ospedale Policlinico San Martino*, Genova, Italy; University Hospital Spedali Civili of Brescia, Brescia, Italy; *Fondazione Monasterio*, Pisa, Italy; Niguarda Hospital, Milan, Italy; Udine University Hospital, Udine, Italy).[7]

PAH was diagnosed according to current European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines and included idiopathic, heritable, and drug-induced PAH, or PAH associated with connective tissue diseases (CTD), congenital heart diseases (CHD), human immunodeficiency virus (HIV), or portal hypertension. All patients underwent right heart catheterization (RHC) at baseline to confirm pre-capillary PH, defined as mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg, pulmonary artery wedge pressure (PAWP) $<$ 15 mmHg, and pulmonary vascular resistance (PVR) $>$ 3 Wood units for patients diagnosed up to the release of new guidelines in 2022 and as mPAP $>$ 20 mm Hg, PAWP $<$ 15 mm Hg, and PVR $>$ 2 Wood units for patients diagnosed afterwards.[1,8] The following comorbidities were collected: systemic hypertension (sHTN), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), connective tissue disease (CTD), chronic kidney disease (CKD), and history of atrial fibrillation (AF). CKD was defined as evidence of kidney structure or function abnormalities for at least 3 months, following KDIGO criteria.[9]

Complete diagnostic work-up was performed and patients with PH group 2 to 5 were excluded. Baseline risk was estimated according to the 2022 ESC/ERS 'three strata' risk estimation tool, which grades several variables on a scale from 1 to 3 (1 = low, 2 = intermediate, 3 = high). The tool was applied when at least three variables were available. Variables included signs of right HF, progression rate of symptoms and clinical manifestation, syncope, World Health Organization functional class (WHO-FC), meters covered during the 6 min walking test (6MWT), cardiopulmonary exercise test parameters such as peak VO_2 and VE/VCO_2 slope, brain natriuretic peptide (BNP) and n-terminal proBNP levels; echocardiographic parameters such as right atrium (RA) area, tricuspid annular plane systolic excursion, and systolic pulmonary artery pressure ratio (TAPSE/sPAP); evidence of pericardial effusion and parameters from baseline RHC such as mean right atrial pressure (mRAP), cardiac index, stroke volume index, and venous oxygen saturation[1] (SVO_2). Magnetic resonance imaging data were available only in a minority of the cases and therefore were not included. The overall risk category was determined by computing the mean of the risk grades from available variables for each patient and rounding to the nearest integer.

Right ventricular dysfunction was defined by the identification of at least one echocardiographic parameter of altered ventricular function, namely fractional area change $<$ 35% or TAPSE $<$ 18 mm.[1]

Specific therapies included phosphodiesterase-5 inhibitors (PDE5i), endothelin receptor antagonists (ERA), riociguat, and prostacyclin analogues according to the recommendations existing at the time of patient evaluation. Data were completely anonymized. The institutional ethics board approved the study.

The population was divided into high-dose and no/low-dose groups according to the median oral loop diuretic dose at baseline in the overall study population. Loop diuretic dose for non-furosemide loop diuretics was calculated as furosemide-equivalent dose: 40 mg of furosemide is considered equal to 1 mg of bumetanide or 10 mg of torasemide.

The PAH-LHD phenotype at presentation according to the AMBITION criteria was also classified.[10]

The primary endpoint of the study was 5 year all-cause mortality. Furthermore, the composite of all-cause mortality, lung transplantation, and the initiation of parenteral prostanoid therapy was assessed as secondary endpoint.

Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation (*SD*) or median and inter-quartile range (IQR), as

appropriate, for continuous variables, and counts and percentage for categorical variables.

Cross-sectional comparisons between no/low and high diuretic dose groups were made using the ANOVA test for continuous variables or the non-parametric Mann–Whitney *U* test when necessary. The χ^2 or Fisher exact tests were calculated for discrete variables.

Multivariable logistic regression analysis was fitted to identify the predictors of high-dose use of loop diuretics. Additional sensitivity analysis was repeated considering eGFR $<$60 mL/min/1.73 m^2 instead of history of CKD as a marker of kidney failure.

Kaplan–Meier curves for 5 year survival were estimated and compared across the two subgroups using the log-rank test. Univariable Cox regression models were performed to evaluate the association between patients' characteristics and the primary outcome and multivariable Cox regression models were conducted to evaluate the association between the two groups and the primary outcome, adjusted for demographic variables (age and sex) and for the risk category assessed by the 2022 ESC/ERS 'three strata' risk estimation tool. An additional sensitivity analysis was performed by dividing patients according to loop diuretic use (i.e. any dose) vs. non-use. A *P* value $<$0.05 was considered as statistically significant. IBM SPSS statistics, Version 29.0.0.0 (241) and Stata version 17 (Stata Corp., College Station, TX, USA) were used for statistical analysis and illustrations. Authors fully accessed and took responsibility for the data and agreed to the manuscript as written.

Results

Study population

Among 411 patients included in the Registry during the study period, 397 (97%) had available information on loop diuretic use and were included in the analysis. In total, loop diuretics were prescribed in 227 patients (57%), 207 (91%) received furosemide, and 20 (9%) received bumetanide while no patients received torasemide. One hundred seventy patients (43%) received no loop diuretic.

The main features of the population are shown in *Table 1*. Median age was 59 years (IQR 48–73), most patients were female (264, 67%), 151 patients (38%) had idiopathic PAH. WHO-FC was II or III in 320 (83%) patients. RV systolic dysfunction was present in 232 patients (63%).

Only five patients (1%) had received a diagnosis of PAH according to 2022 ESC/ERS guidelines criteria therefore having mild haemodynamic PH signs (mPAP 20–24 mmHg).

The estimated three-classes ESC/ERS risk was intermediate in 295 patients (75%). Upfront combination therapy or therapy with parenteral prostanoids was prescribed in 39% of cases.

Median daily dose of furosemide in the overall cohort was 25 mg (IQR 0–40 mg). Patients in the no/low-dose group (i.e. $\leq$25 mg) were 257 (65%), with a median daily dose of furosemide of 0 mg (IQR 0–20 mg) whereas 140 (35%) were in the high-dose group (i.e. $>$25 mg), with a median daily dose of 50 mg (IQR 40–100 mg). Those in the high-dose group were older and with a higher prevalence of comorbidities, including sHTN, obesity, type 2 DM, non-severe COPD, and AF (*Figure 1*). The prevalence of CKD was numerically higher in the high-dose group, and accordingly, eGFR was lower in the high vs. no/low-dose group (eGFR 73 ± 28 vs. 82 ± 29 mL/min/1.73 m^2, *P* = 0.002).

Moreover, they had more severe symptoms, higher natriuretic peptides, and lower functional capacity (6MWT 252, IQR 130–331, vs. 347, IQR 243–436 m, $P < 0.001$). RV function and right ventricular-arterial coupling were more impaired in the high-dose group, and left atrium (LA) was more dilated. The haemodynamic profile was also worse in the high-dose group, as testified by higher mRAP and lower cardiac index, in spite of similar values of both mPAP and PVR compared with the no/low-dose group.

Consistently, patients in the high-dose group presented with higher ESC/ERS estimated risk, but the proportion of patients on single or combination therapy was similar.

Finally, patients categorized as PAH-LHD were 88 (22%) divided in 31 (22%) in the high-dose group and 57 (22%) in the no/low-dose group, with no significant difference between the two groups (*P* = 0.993).

Predictors of high-dose loop diuretics use

Results from the univariable logistic regression analysis are shown in *Supporting information*, *Table S1*. After adjustment for other demographic, clinical and comorbidity confounders, age at diagnosis [odds ratio (OR) 1.03, 95% confidence interval (CI) 1.01–1.04, *P* = 0.003], obesity (OR 2.03, 95% CI 1.17–3.52, *P* = 0.011), DM (OR 2.20, 95% CI 1.18–4.09, *P* = 0.013), AF (OR 2.37, 95% CI 1.25–4.49, *P* = 0.008) and higher ESC/ERS risk category (OR 6.73, 95% CI 3.29–13.74, $P < 0.001$) were associated with higher likelihood of being on higher dose of loop diuretics (*Table 2*).

Results were consistent when we considered eGFR $<$60 mL/min/1.73 m^2 instead of history of CKD as a marker of kidney failure (*Table S2*).

Survival and disease progression according to loop diuretic use

During a median follow-up of 3.9 years (IQR 2.3–6.3 years), 106 patients (27%) died. Five-year all-cause mortality was

Table 1 Characteristics of the study population and divided according to loop diuretic dose

	All patients (n = 397)	High dose (n = 140, 35%)	No/low dose (n = 257, 65%)	P
Demographic				
Age (years)	59 (48,73)	65 (53, 76)	57 (46, 71)	<0.001
Sex female (%)	264 (67)	93 (66)	171 (67)	0.98
PAH group (%)				0.41
1.1 Idiopathic	151 (38)	59 (42)	92 (36)	
1.2 Heritable	14 (4)	2 (1)	12 (5)	
1.3 Drug and toxin induced	9 (2)	4 (3)	5 (2)	
1.4 Associated with other conditions	222 (56)	75 (54)	147 (57)	
Comorbidities				
sHTN (%)	160 (40)	54 (46)	95 (37)	0.066
IHD (%)	53 (13)	23 (16)	30 (12)	0.18
AF (%)	60 (15)	37 (26)	23 (9)	<0.001
Obesity (BMI ≥ 30 kg/m^2) (%)	89 (23)	41 (30)	48 (19)	0.014
Type 2 DM (%)	70 (18)	39 (28)	31 (12)	<0.001
CKD (%)	81 (20)	35 (25)	46 (18)	0.093
COPD (%)	77 (19)	36 (26)	41 (16)	0.019
Clinical variables				
Symptoms-diagnosis time (month)	20 ± 2	23 ± 3	19 ± 2	0.204
HF presentation (%)	208 (52)	102 (73)	106 (41)	<0.001
Syncope presentation (%)	7 (2)	2 (1)	5 (2)	0.71
WHO class (%)				<0.001
I	24 (6)	4 (3)	20 (8)	
II	137 (36)	34 (25)	103 (41)	
III	183 (47)	84 (62)	99 (40)	
IV	42 (11)	14 (10)	28 (11)	
III–IV	225 (58)	98 (72)	127 (51)	<0.001
Systolic blood pressure, mmHg	123 ± 18	122 ± 18	142 ± 18	0.192
Heart rate, bpm	80 ± 15	83 ± 15	79 ± 15	0.016
6MWT, m	312 (199, 411)	252 (130, 331)	347 (243, 436)	<0.001
Laboratory tests				
eGFR, mL/min/1.73 m^2	79 ± 28	73 ± 28	82 ± 29	0.002
eGFR, <60 mL/min/1.73 m^2	94 (25)	40 (30)	54 (23)	0.138
Haemoglobin, g/dL	13,7 ± 2,2	13,6 ± 2,4	13,7 ± 2,1	0.796
BNP, pg/mL	242 (88, 591)	492 (216, 911)	167 (66, 383)	<0.001
Echocardiography				
RA area, cm^2	24 ± 7	28 ± 7	22 ± 7	<0.001
LA area, cm^2	19 ± 7	21 ± 7	18 ± 6	<0.001
RV dysfunction, (%)	232 (63)	95 (73)	137 (58)	0.006
LVEF, %	59 ± 6	58 ± 6	59 ± 7	0.204
TAPSE, mm	17 ± 5	16 ± 5	18 ± 5	0.006
PAPs, mmHg	73 ± 23	76 ± 21	71 ± 24	0.018
TAPSE/PAPs	0,027 ± 0,014	0,024 ± 0,013	0,029 ± 0,015	0.001
Pericardial effusion (%)	100 (27)	46 (34)	54 (23)	0.016
E/E' ratio	8,5 ± 4,2	9,3 ± 5,1	8,1 ± 3,7	0.064
IVC dilatation (%)	115 (34)	58 (47)	57 (26)	<0.001
IVC hypocollassability (%)	121 (35)	58 (46)	63 (28)	<0.001
Right heart catheterization				
mRAP, mmHg	8 ± 5	10 ± 5	7 ± 4	<0.001
sPAP, mmHg	72 (58,88)	75 (61, 89)	72 (55, 88)	0.15
dPAP, mmHg	29 (22,37)	30 (24, 37)	29 (21, 36)	0.17
mPAP, mmHg	46 ± 10	46 ± 12	45 ± 14	0.326
PAWP, mmHg	10 ± 4	11 ± 4	9 ± 4	0.019
PVR, WU	11,9 ± 5,6	10,2 ± 2,2	12,8 ± 3,1	0.548
CI, L/min/m^2	2,4 ± 0,8	2,3 ± 0,7	2,54 ± 0,8	0.034
PAH-LHD phenotype	88 (22)	31 (22)	57 (22)	0.993
Therapy at discharge				
Single (%)	179 (45)	68 (49)	111 (43)	0.303
Dual (%)	143 (36)	54 (39)	89 (35)	0.43
Triple or epo (%)	12 (3)	5 (4)	7 (3)	0.637
Risk class—ESC/ERS risk tool				<0.001
Low	57 (15)	7 (5)	50 (20)	
Intermediate	295 (75)	114 (81)	181 (71)	
High	42 (11)	19 (14)	23 (9)	

6MWT, 6 min walking test; AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; dPAP, diastolic PAP; eGFR, estimated glomerular filtration rate; ESC/ERS, European Society of Cardiology/European Respiratory Society; IHD, ischaemic heart disease; LA, left atrium; LVEF, left ventricle ejection fraction; mPAP, medium PAP; mRAP, medium RA pressure; NT-proBNP, n-terminal pro BNP; PAH, pulmonary arterial hypertension; PAH-LHD, pulmonary arterial hypertension–left heart disease phenotype; PAWP, pulmonary Artery Wedge Pressure, PVR, pulmonary vascular resistance, CI, cardiac index; RA, right atrium; RV, right ventricle; sHTN, systemic hypertension; sPAP, systolic pulmonary arterial pressure; TAPSE, Tricuspid annular plane systolic excursion; WHO, World Health Organization.

Figure 1 Distribution of comorbidities according to loop diuretic dose. AF, atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease.

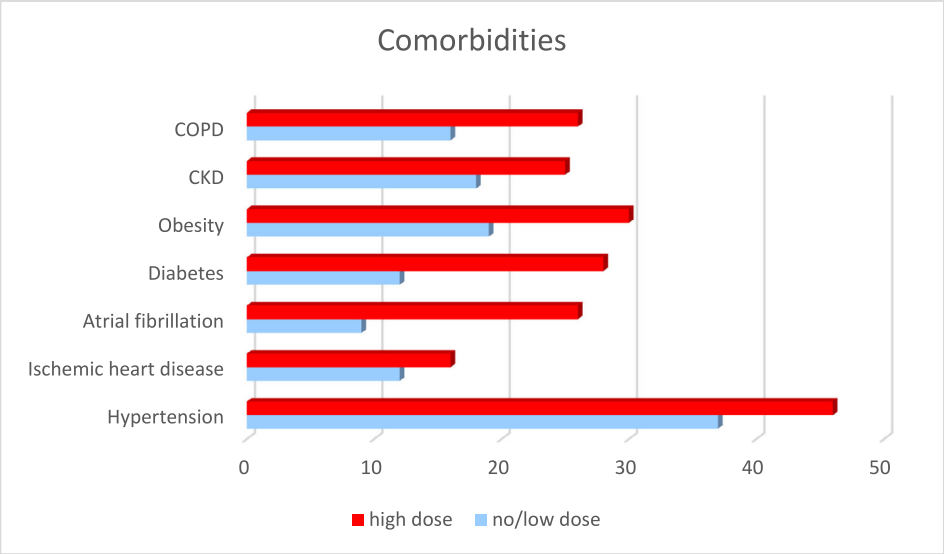


Table 2 Multivariable analysis on predictors of high-dose loop diuretics use

	OR	95% CI	*P*
Age	1.03	1.01–1.04	0.003
Male sex	0.74	0.44–1.26	0.261
Obesity	2.03	1.17–3.5	0.011
sHTN	0.85	0.50–1.44	0.548
AF	2.37	1.25–4.49	0.008
Type 2 DM	2.20	1.18–4.09	0.013
COPD	1.43	0.80–2.53	0.226
CTD	0.69	0.39–1.22	0.198
CKD	0.91	0.49–1.68	0.771
ESC/ERS risk category	6.73	3.29–13.74	<0.001

AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; DM, diabetes mellitus; ESC/ERS, European Society of Cardiology/European Respiratory Society; OR, odds ratio, sHTN, systemic hypertension.

21% (82 patients). As shown in *Figure 2*, crude 5 year survival was significantly lower in patients in the high-dose group (log-rank $P = 0.003$). However, after adjustment for age, sex and ESC/ERS risk category, high loop diuretic dose was not independently associated with higher 5 year mortality risk [hazard ratio (HR) 1.19, 95% CI 0.75–1.88, $P = 0.462$].

Consistent results were obtained by dividing the patients according to the absence or presence of loop diuretic use (HR for 5 year mortality 0.96, 95% CI 0.59–1.55, $P = 0.872$; *Figure S1*).

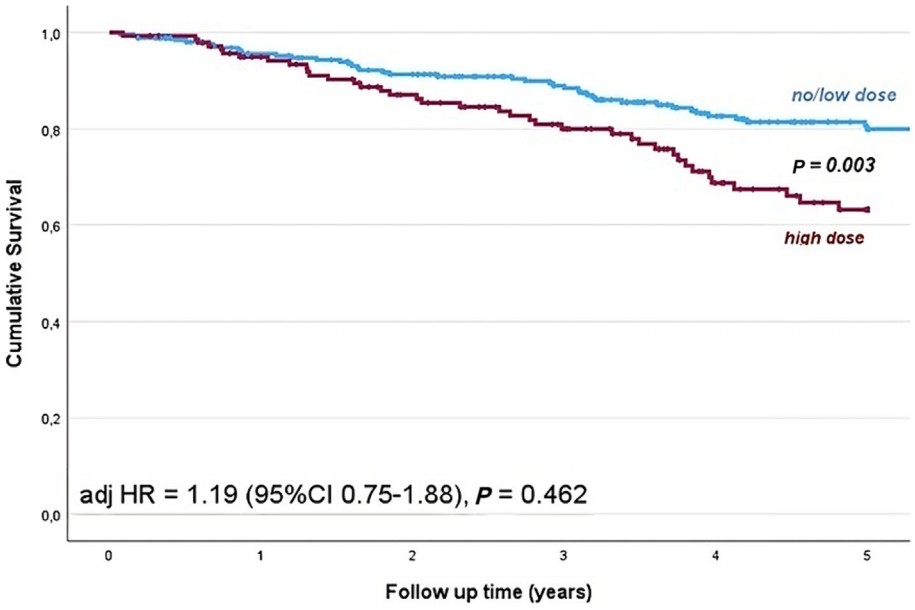
Furthermore, the lack of association for higher doses of loop diuretics was also demonstrated for the secondary composite endpoint of 5 year all-cause mortality, lung transplantation, and progression to parenteral prostanoids, after adjustment for age, sex, and ESC/ERS risk category (HR 1.28, 95% CI 0.86–1.91, $P = 0.226$; *Table S3*).

Discussion

Right HF is the most concerning consequence of worsening RV afterload due to the pulmonary vascular disease. This usually causes widespread fluid retention, decreased renal blood flow, and activation of the neuro-hormonal system. Furthermore, venous congestion progressively impairs renal function leading to a vicious cycle perpetuating systemic congestion.

In the recent PH ESC/ERS guidelines the recommendations on the use of diuretics have remained unchanged and are based on symptoms and signs of congestion. However, information on the general use of diuretics in PAH are scarce and data on prognostic implications practically absent.[11] In our study we described for the first time in a multicentre, real-world, cohort of patients with PAH the use of loop diuretics and the prognostic correlates associated with their use. The key findings are that (i) loop diuretics in PAH patients are frequently used but mostly at low doses, (ii) factors associated with the use of high diuretic dose are related not only with the severity of the disease but also with the higher prevalence of comorbidities, (iii) crude 5 year mortality in patients treated with high loop diuretics dose was higher. However, after adjusting for demographic and clinical factors, the use of high dose of loop diuretics was not associated with a worse prognosis.

Figure 2 Five-year survival in patients in the no/low vs. high loop diuretic dose group. Adj HR, adjusted hazard ratio.



Diuretic therapy in PAH population

As previously reported, diuretic therapy is common among patients with PAH, although in former studies detailed information on dosages and modalities were unavailable.[12]

Reports from the larger worldwide registries on PAH, for instance, did not provide information on diuretic use, despite the very precise characterization of clinical, biochemical and haemodynamic variables in PAH patients.[13,14] In poorly selected cohorts, with no discrimination regarding PH aetiology, the use of diuretics was close to 70%.[15] In our study, more than half of the included patients was treated with loop diuretics at baseline. Importantly, it must be noted that the overall dose was mostly low, as attested by the median dose of 25 mg. This is not surprising because in PAH the degree of congestion is generally less severe compared with patients with left-sided HF.

The link between diuretic therapy, comorbidities, and disease severity

In PAH, as well as in other forms of HF, diuretics are primarily prescribed for congestion relief, which reflects high right sided filling pressures and ventricular-arterial uncoupling. Accordingly, higher loop diuretics doses are expected in patients with more severe PAH.

However, with the changing demographic of the PAH population, the burden of comorbidities among PAH patients is increasing, and this might act as a confounder in the definition of symptoms severity and in grading congestion.[7,16–21] For instance, in obese patients or in patients with risk factors for LHD, the assessment of symptoms and of clinical congestion can be harder, leading to overprescription of loop diuretics. In our cohort, patients on higher dose of diuretics had worse functional status and more comorbidities whereas the proportion of patients exhibiting a LHD phenotype was similar across the two cohorts receiving different diuretic regimens.

Haemodynamic and echocardiographic data in the high-dose group were consistent with a worse RV function and higher LV filling pressures, most likely found in patients with more comorbidities. With the identification of the predictors of high loop diuretic dose use in the adjusted analysis, we have confirmed that not only the severity of the disease and the grade of congestion guide the decision of clinicians on the use and dosing of diuretics, but also the comorbidity profile, with age, obesity, AF and type 2 DM being associated with higher likelihood of using high dose of loop diuretics.

Although the estimated risk observed in patients taking high dose of diuretics was higher, there were no differences in the treatment with pulmonary vasodilators. This observation might be explained by a less aggressive approach in patients with more comorbidities despite the higher risk and warrants further investigations to eventually overcome treatment inertia. In left-side HF, for instance, use of higher diuretics doses limited the uptitration of evidence-based therapies.[22] Therefore, it is important to prioritize disease-specific treatments over relying solely on diuretics for symptom relief, as diuretics may not significantly impact on disease progression or RV remodelling.

Diuretic therapy and outcome in PAH

Comorbidities correlate with lower survival and less favourable response to specific therapies, but diuretics were not specifically included among confounders.[23]

A more advanced disease and its increased severity are reasonable explanations for the higher crude mortality observed in patients treated with higher dose of diuretics. However, in left HF, the complex relationship between high diuretic dose, more severe HF, and direct negative prognostic effect of diuretics has been investigated and only partially resolved.[3,24] Diuretics can impair patient's outcome through different mechanisms. Beyond the severity of the disease, inappropriately high doses of diuretics can cause electrolyte abnormalities, hypovolaemia, and hypotension, induce additional neurohormonal activation or promote further deterioration in kidney function.[3,22,25]

In our study population, after adjusting for measures of disease severity, that is the ESC/ERS risk stratification tool, in addition to age and sex, the association between the use of high dose of loop diuretics and mortality was neutral, supporting the hypothesis of no causality between more intense diuretic use and prognosis.

Supporting diuretic use as a marker of comorbidity rather than disease severity, similar findings emerged from stratifying patients by loop diuretic use instead of by dose.

Furthermore, neutrality was achieved even when looking at a combined endpoint of 5 year all-cause mortality, lung transplant, and progression to parenteral prostanoids.

Limitations

As with all observational studies, our research faces the inherent bias of its retrospective design; therefore, causal relationship can be only hypothesized.

The study population was enrolled in tertiary care centres for PAH management; thus, imposing a selection bias.

Novel ESC/ERS 2022 criteria for PAH definition have been only recently incorporated in clinical practice; therefore, very few patients are included with mild PAH (i.e. mPAP between 20 and 25 mmHg).[1] We cannot exclude changes in therapeutic strategies across the study period as patients were retrospectively enrolled since 2001. We only considered baseline assessment and trends in diuretic use and implications on outcome warrant further investigations.

Although most of our cohort was diagnosed using the 2015 ESC guidelines criteria, we applied the 2022 recommended three-strata model for risk stratification, incorporating all available data, including haemodynamics, as it has been shown to more accurately predict 1 year mortality risk.[8,26–28]

Unfortunately, signs of venous congestion were not systematically available; however, natriuretic peptides and particularly, invasive RAP can be interpreted as solid markers of venous congestion.

Finally, the decision to separate no/low- vs. high-dose groups with a cut-off of 25 mg was arbitrary as no previous studies specifically explored this issue. We assumed as a reasonable value the median furosemide-equivalent dose observed in our population.

Conclusions

In this real-world, multicentre, registry-based study, 57% of PAH patients at baseline were treated with loop diuretics.

The use of high dose of loop diuretics characterizes patients with higher burden of comorbidities and more severe disease. However, the worse crude survival observed in patients treated with higher loop diuretics dose was not confirmed after adjustment for confounders suggesting that their use in PAH represents a marker of disease severity rather than an independent prognostic factor.

Conflict of interest

D. S. has been an advisory board member for Merck, Novo Nordisk, Acceleron, Janssen, and Novartis and has received speaker fees from Novartis, none related to the present study. P. A. has received speaker and/or advisor fees from Janssen, MSD, and Gossamer Bio generally related to the topic of pulmonary arterial hypertension, and speaker and/or advisor fees from AstraZeneca, Novartis, Boehringer Ingelheim, Bayer, Vifor, and Daiichi-Sankyo outside the scopes of the present work. F. L. G. has received speaker and/or advisor fees from Janssen and MSD related to the topic of pulmonary arterial hypertension but not to the scope of this paper.

Supporting information

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

Table S1. Univariable analysis on predictors of high dose loop diuretics use.

Table S2. Multivariable analysis on predictors of high dose loop diuretics use using eGFR <60 mL/min as kidney failure marker.

Table S3. Higher LD doses and composite outcome of 5-year all-cause mortality, lung transplantation, and progression to parenteral prostanoids.

Figure S1. 5-year survival in patients in the no vs. high loop diuretic dose group.

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