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Medication adherence and clinical outcome in patients with pulmonary arterial hypertension or distal chronic thromboembolic pulmonary hypertension

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ABSTRACT

Introduction In pulmonary arterial hypertension (PAH) and distal chronic thromboembolic pulmonary hypertension (CTEPH), the consistent use of disease-specific therapies is crucial. We aimed to investigate medication adherence to oral disease-specific medication and the impact on clinical outcome among patients with PAH or CTEPH to identify potential patient-related reasons for treatment incompliance.

Study design and methods This prospective study focused on medication adherence using a multimeasure approach, including specialty pharmacy order data to calculate medication possession ratio (MPR) and self-reporting via questionnaire among patients with PAH or CTEPH. Adherence rates of ≥80% were considered adherent. Simplified four-strata risk categories according to the 2022 European Respiratory Society/European Society of Cardiology pulmonary hypertension (PH) guidelines were determined.

Results We included 93 patients (66% women, 75% PAH, 25% CTEPH, 57±17 years), all on PH-targeted oral medication between 2013 and 2023. Overall, a number of 73 patients (78%) were classified as adherent. The mean MPR was 98±19% and the mean value of questionnaire responses was 89±10%. At the end of the observation period, adherent patients improved their risk category, while non-adherent patients did not. Factors associated with adherence were older age (OR=1.03, 95% CI=1.01 to 1.07) and being classified in a higher risk category (OR=2.13; 95% CI=1.11 to 4.64). Patients with adverse drug reactions were 75% more likely to be non-adherent to medication (OR=0.25; 95% CI=0.08 to 0.77).

Conclusion In this collective, mean MPR and self-reported adherence were overall high, with 78% of patients classified as adherent. Adherent patients improved clinical outcomes contrary to non-adherent patients. Insufficient adherence and potential contributing factors should be regularly considered, especially in patients without improvement after starting disease-specific therapy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pulmonary arterial hypertension (PAH) and distal chronic thromboembolic pulmonary hypertension (CTEPH) are chronic diseases and fatal if untreated. Continuous medication intake is essential for symptom relief, quality of life and disease stabilisation. Yet adherence levels and reasons for non-adherence within this patient population are not well understood.

WHAT THIS STUDY ADDS

⇒ Medication adherence in this cohort was 78%, with improved clinical outcomes and risk score associated with adherence. Factors associated with non-adherence included younger age, less disease severity and adverse drug reactions.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Strict medication adherence is key for symptom reduction, improved clinical outcomes and enhanced quality of life. Understanding adherence levels and reasons for non-adherence is essential for enhancing medication intake and improving clinical outcome and risk score.

INTRODUCTION

According to the guidelines of the European Society of Cardiology and the European Respiratory Society (ESC/ERS),[1] haemodynamic parameters obtained through right heart catheterisation (RHC), including a mean pulmonary artery pressure >20 mmHg, pulmonary artery wedge pressure ≤15 mmHg and pulmonary vascular resistance >2 Wood units, are used as diagnostic thresholds for precapillary pulmonary hypertension (PH). Due to variations in pathophysiological mechanisms and consequently the overall clinical presentation, PH can be classified into five major groups, each of which is managed

differently.[2] Pulmonary arterial hypertension (PAH), categorised as group 1 and chronic thromboembolic pulmonary hypertension (CTEPH), a substantial part of group 4, represent forms of pre-capillary PH. Both PAH as well as CTEPH typically follow a progressive course, ultimately leading to right heart failure and death.[3 4] In selected patients with CTEPH, surgical pulmonary endarterectomy (PEA) is the treatment of choice.[3] However, in distal CTEPH defined as inoperable or residual PH after PEA,[3] and for patients with PAH[5] oral PH-targeted medications provide significant benefits.[6] Specific PH-targeted medications including phosphodiesterase type-5 inhibitors (PDE5i), endothelin receptor antagonists (ERA), prostacyclin receptor agonists (PRA), soluble guanylate cyclase stimulators (sGCs) and calcium channel blockers (CCB) complemented by supportive measures[7 8] are essential to alleviate symptoms and improve lifetime in PAH and CTEPH.[1]

For risk stratification during clinical follow-up investigations and guidance in therapeutic decision-making, a four-strata risk model is recommended,[1] which includes solely non-invasive clinical information such as WHO functional class (WHO-FC), NT-pro brain natriuretic peptide (NT-proBNP) and 6-minute walk distance (6MWD).[9 10] The four-strata risk stratification divides into four groups to assess disease severity and estimate 1-year mortality. Studies have demonstrated that PH-targeted therapies improve exercise capacity and parameters such as WHO-FC or 6MWD[11] and extend time to potential clinical deterioration.[12] To keep mortality low and enhance clinical conditions in the severe disease of PH the consistent use of disease-specific therapies is crucial.[13] From various other chronic diseases it is well known that non-adherence is not only associated with clinical deterioration, hospitalisation and premature death but also with higher costs of care and diminished quality of life.[14–17] The WHO's report from 2003[15] indicated an adherence rate of merely 50% among patients with various chronic diseases, posing a significant hurdle for public health initiatives.

The limited existing data on medication adherence in patients with PAH or CTEPH indicated suboptimal results[18–21] and studies associating adherence with clinical outcomes are sparse. Our objective was to evaluate the adherence to PH-targeted oral medications among patients diagnosed with PAH or CTEPH. Medication adherence, evaluated through the order history of the specialty pharmacy MediService AG (Zuchwil, Switzerland) and self-reported data by questionnaire, was compared with clinical outcomes observed during follow-up examinations. Moreover, our objective was to identify potential reasons for the lack of treatment adherence.

MATERIALS AND METHODS

Study design and population

The aim of this prospective study was to assess the medication adherence of disease-specific oral PH therapies within the Zurich PH cohort among patients with PAH or distal CTEPH and contextualising the results within clinical parameters. For this purpose, pharmacy claims data from 2013 to 2023 were used and complemented by questionnaire. All patients provided written informed consent.

Patients were included if they were diagnosed with PAH or CTEPH according to ESC/ERS Guidelines[1] and were aged ≥18 years. Exclusion criteria encompassed patients belonging to other PH groups or those who never received disease-specific oral PH therapy. Additionally, patients were excluded if adherence could not be determined due to only short duration of PH-targeted therapy intake, defined as less than 3 months, or if pharmacy data was unavailable and the questionnaire was not returned. All patients obtained PH-targeted drugs according to current ESC/ERS Guidelines[1] in line with patients' preference and overall clinical picture.

Patient and public involvement

Patients were not involved in the design and conduct of this research.

Study measures

Adherence

Medication adherence was assessed for disease-specific oral PH-therapies including CCB (amlodipine, nifedipine), ERA (ambrisentan, bosentan, macitentan), PDE5i (sildenafil, tadalafil), PRA (selexipag) and sGCs (riociguat). The evaluation was conducted using a multimeasure approach, as recommended in prior studies[22 23] using the medication possession ratio (MPR) and self-reported medication intake via questionnaire.

MPR involves comparing the proportion of days for which medication was dispensed to the proportion of days medication was required according to prescription, based on specialty pharmacy data.[23] For calculation, the formula was adjusted and applied as described below for each drug separately. Treatment changes or interruptions were taken into account and included in the calculation by determining mean daily dosages. The maximal adherence value for each drug was 100%.

$$mMPR\,(\%) = \left(\frac{(noforderedpackages) * (dosageperpackage/meandailydosage)}{((lastorderdate) - (firstorderdate)) + (dosageperpackage/meandailydosage)}\right) * 100$$

Abbreviations: mMPR=mean medication possession ratio.

All patients alive, who were still on oral PH-targeted treatment, were sent a questionnaire via regular mail. This questionnaire was designed to identify cases of insufficient adherence, even if patients displayed adherence according to the MPR method. Additionally, the questionnaire was used to assess adherence among patients who were not customers of the specialty pharmacy,

MediService AG (Zuchwil, Switzerland). It comprised 10 statements each of which had to be rated using a 4-point Likert scale, with options including 'strongly disagree', 'disagree', 'agree' and 'strongly agree'. To evaluate adherence, an average score of chosen answers was calculated. A higher average score indicated greater medication adherence. Consistent with current literature,[22] a cut-off value of ≥80% was applied to classify patients as adherent, based on either MPR or responses from the questionnaire. Conversely, patients were considered non-adherent if they achieved a value lower than 80% for just one drug assessed using the MPR method or for the overall score on the questionnaire.

Clinical outcomes

Clinical outcomes were assessed at three distinct time points during clinically indicated assessments at the PH-Centre, University Hospital Zurich, Switzerland: before initiating specific PH-medication (baseline, t_1), at first follow-up (6 months after treatment initiation, t_2) and at the latest documented follow-up (t_3). For patients with CTEPH and residual PH following PEA, baseline (t_1) was established at the restart of oral PH-specific therapy, typically at the first RHC after PEA, when residual PH was diagnosed. To conduct clinical assessments, a simplified four-strata risk score was used, as recommended by recent guidelines[1 9 10] comprising the non-invasive parameters WHO-FC, NT-proBNP and 6MWD.

Outcomes

The primary outcome of the study was the proportion of patients classified as adherent within our cohort and the changes in the four-strata risk categories during clinically indicated follow-up consultations. The secondary outcome aimed to identify potential reasons for the lack of treatment adherence.

Data analysis and statistics

Data are presented as mean±SD or number (percentage). Only fully completed questionnaires were included in the analysis. Patients were categorised into adherence groups, with those achieving a value <80% considered non-adherent based on either the MPR method or questionnaire data. Before conducting statistical analyses by using RStudio V.2023.12.1+402, data was checked for completeness and units whereby missing values were not replaced. For all statistical analyses a p value <0.05 was considered statistically significant.

At baseline, differences in clinical parameters between groups were compared using t-tests for independent samples. Medication data were compared using Pearson's χ^2 test and Fisher's exact test. To detect significant change between different time points, analysis of variance and the Friedman test were performed as appropriate. Changes in clinical parameters over time within each group were assessed using t-tests for dependent samples.

A logistic regression model was created to predict adherence. For evaluation of explanatory variables associated with adherence, preceding univariate logistic regression was conducted. By using forward selection and backward elimination, values were included in multivariate logistic regression analysis. Therefore, ORs with 95% CIs were calculated.

RESULTS

Study population

Of 125 patients, 93 patients with 61 (66%) being women with a mean age of 57±17 years at baseline, qualified for the study (online supplemental figure S1). Among these patients, 23 (25%) were diagnosed with CTEPH (6 after PEA) while 70 (75%) were diagnosed with PAH. 22 (24%) patients had deceased during the time of the study. Each patient received specific oral PH treatment according to guidelines.[1] A majority of 70 (75%) patients were prescribed ERA. PDE5i, sGCs, PDA and CCB were further prescribed within our cohort. Combination therapy (54%) was somewhat more frequently prescribed than monotherapy (46%). Additionally, 9 (10%) patients received intravenous or subcutaneous PH-targeted treatment on top of oral PH-medication. At baseline measures, a total of 27 (29%) patients were classified as low risk. A vast majority of patients were categorised as intermediate-low risk (39%), while approximately one-third of all patients were collectively classified into the intermediate-high (26%) or high (6%) risk category. The overall patient flow is illustrated in online supplemental figure S1 and baseline characteristics are presented in table 1.

Medication adherence

Out of the total, 79/93 (85%) patients were customers of the specialty pharmacy MediService while 14 (15%) patients obtained their medication at regular pharmacies (online supplemental table S1). A questionnaire was sent to the 68 (73%) patients who were still alive and still on PH-therapy. 58 returned it completed, resulting in an 85% response rate (online supplemental figure S2). Using the MPR method, 87% (69 out of 79 patients using the specialty pharmacy) of patients demonstrated adherence with a cut-off value of ≥80%. According to the questionnaire responses, 78% (45 out of 58 questionnaires) of patients were adherent. Patients were classified as non-adherent if they scored <80% according to either assessment method. The overall adherence rate, combining both assessment methods, was 78% (73/93). Overall, the average for MPR was 98±19% and the average value of the questionnaire responses was 89±10% (table 2). By comparing the questionnaire results with the MPR method, the questionnaire achieved a sensitivity of 50%, specificity of 84.21%, positive predictive value of 33.33% and negative predictive value of 91.43%.

Of importance, in Switzerland, all residents are required to have mandatory health insurance that provides comprehensive coverage, including medications. Patients pay an

Table 1 Baseline characteristics and difference between groups stratified by adherence

	Overall cohort (n=93)	Adherent (n=73)	Non-adherent (n=20)	P value
Female, n (%)	61 (66)	48 (66)	13 (65)	0.950
Deceased, n (%)	22 (24)	20 (27)	2 (10)	0.107
Age, years	57±17	59±17	49±16	0.032*
Height, cm	167±11	166±10	171±11	0.101
Weight, kg	74±18	73±15	81±27	0.186
Body mass index, kg/m^2	26.5±5.6	26.15±4.4	27.7±8.8	0.441
Body surface area, m^2	1.84±0.2	1.82±0.2	1.93±0.3	0.170
PH groups				
Group 1 - pulmonary arterial hypertension	70 (75)	57 (78)	13 (65)	
IPAH	34 (37)	26 (36)	8 (40)	
Non-responders at vasoreactivity testing	24 (26)	20 (27)	4 (20)	
Acute responders at vasoreactivity testing	10 (11)	6 (8)	4 (20)	
Heritable	1 (1)	1 (1)	0 (0)	
Drugs and toxins induced	1 (1)	1 (1)	0 (0)	
APAH	33 (35)	28 (38)	5 (25)	
Connective tissue disease	23 (25)	21 (29)	2 (10)	
HIV infection	3 (3)	3 (4)	0 (0)	
Portal hypertension	2 (2)	1 (1)	1 (5)	
Congenital heart disease	4 (4)	2 (3)	2 (10)	
Schistosomiasis	1 (1)	1 (1)	0 (0)	
PVOD	1 (1)	1 (1)	0 (0)	
Group 4 - distal CTEPH	23 (25)	16 (22)	7 (35)	
Residual PH after PEA	6 (6)	2 (3)	4 (20)	
6 min walk distance, m	451±128	434±129	509±109	0.045*
Oxygen saturation at the end of 6-minute walk test, %	88±8	88±8	90±6	0.323
NT-proBNP, ng/L	1288±2204	1536±2425	394±468	<0.001*
WHO functional class				0.741
WHO-FC I	6 (6)	6 (8)	0 (0)	
WHO-FC II	35 (38)	27 (37)	8 (40)	
WHO-FC III	47 (51)	35 (48)	12 (60)	
WHO-FC IV	5 (5)	5 (7)	0 (0)	
Simplified four-strata risk category				0.063
Low	27 (29)	21 (29)	6 (30)	
Intermediate-low	36 (39)	23 (32)	13 (65)	
Intermediate-high	24 (26)	23 (32)	1 (5)	
High	6 (6)	6 (8)	0 (0)	
Resting haemodynamics during RHC 0.21				
Heart rate, min^{-1}	78±15	77±13	78±20	0.823
Systolic blood pressure, mm Hg	130±18	131±19	127±16	0.346
Diastolic blood pressure, mm Hg	79±11	79±12	77±8	0.520
Mean pulmonary artery pressure, mm Hg	41±15	42±15	39±14	0.416
Pulmonary artery wedge pressure, mm Hg	11±4	11±4	10±3	0.492
Right atrial pressure, mm Hg	8±4	9±4	7±3	0.110
Cardiac index, L/min/m^2	2.7±0.6	2.7±0.6	2.8±0.5	0.667
Cardiac output, L/min	5.0±1.3	4.9±1.3	5.3±1.3	0.243
Pulmonary vascular resistance, WU	6.8±4.2	7.0±4.2	5.9±4.0	0.281

Continued

Table 1 Continued

	Overall cohort (n=93)	Adherent (n=73)	Non-adherent (n=20)	P value
Arterial blood gases				
Haemoglobin, g/dL	14.4±1.8	14.5±2.0	14.2±1.3	
Oxygen saturation, %	92±5	92±5	93±3.8	
pH	7.43±0.03	7.44±0.03	7.43±0.03	
Partial pressure of oxygen, kPa	9.4±1.7	9.3±1.7	9.9±1.7	
Partial pressure of carbon dioxide, kPa	4.5±0.6	4.5±0.7	4.6±0.6	
Pulmonary function tests				
FEV1, % predicted	85±21	84±18	88±31	
FVC, % predicted	89±21	88±18	91±30	
TLC, % predicted	90±17	90±17	89±15	
DLCO, % predicted	58±20	57±22	62±13	
KCo, % predicted	68±21	65±20	78±25	

Data are presented as mean±SD or number (%).
APAH, associated pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, diffusion capacity of carbon monoxide; FEV1, forced expiratory volume in the 1 s of expiration; FVC, forced vital capacity; IPAH, idiopathic pulmonary arterial hypertension; KCo, carbon monoxide transfer coefficient; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; RHC, right heart catheterisation; TLC, total lung capacity; WHO-FC, WHO-functional class; WU, Wood units.

annual franchise of SFr300–2500 and a 10% co-payment on additional costs, capped at a maximum of SFr700 per year. Consequently, total out-of-pocket expenses range from SFr1000 to a maximum of SFr3200 annually, which minimises cost-related issues in this study. However, in the questionnaire, two patients categorised as non-adherent strongly agreed that they felt burdened by the high cost of medication.

Medication adherence to pulmonary hypertension treatment and clinical outcome

First follow-up (t_2) investigation occurred on average 7±2 months after initiation of treatment, while the last follow-up (t_3) took place on average 6±0.3 years after t_1. Baseline characteristics for each adherence group separately are presented in table 1. On comparing clinical parameters at baseline (t_1), a significant age disparity was evident with the non-adherent group being notably younger (59±17 vs 49±16 years, p=0.032). While haemodynamics were not significantly different between groups, they were slightly lower in the non-adherent group. Baseline 6MWD revealed significant differences with values of 434±129 m for the adherent group and 509±109 m for the non-adherent group (p=0.045). Similarly, baseline NT-proBNP differed significantly between groups, with values of 1536±2425 ng/L for the adherent group and 394±468 ng/L for the non-adherent group (p<0.001). Thus, the non-adherent group was showing overall less risk scores, with the majority being categorised as low or intermediate-low risk.

During the follow-up visits, adherent patients demonstrated significant changes across all variables (WHO-FC p=0.007; 6MWD p=0.013; NT-proBNP p=0.008) as well as the overall risk category (p=0.001) (table 3). Conversely, patients classified as non-adherent showed a significant change solely in WHO-FC over the entire time period (p<0.001).

Changes in NT-proBNP levels, 6MWD and WHO-FC over time for each group separately are visualised in figure 1 and alterations in risk categories over time are illustrated in online supplemental figure S3. The evolution of the low-risk category appears comparable between both groups over time. However, it is noteworthy that the non-adherent group had superior baseline values, with no patients classified as high risk and only very few patients classified as intermediate-high risk. In contrast, the adherent group showed a reduction in the number of patients classified as high or intermediate-high risk over time.

The comparison between groups also involved analysing medication usage, including changes in prescription over time, the quantity of oral medications taken and the specific PH drugs prescribed (table 2). Patients classified as non-adherent exhibited a significantly higher frequency of medication prescription changes compared with those categorised as adherent (95% vs 66%, p=0.010). The incidence of adverse drug reactions (ADR) was notably higher in the non-adherent group (50%) compared with the adherent group (26%), although this difference was not statistically significant (p=0.075).

Univariate logistic regression to predict adherence is displayed in online supplemental table S2 and shows age, NT-proBNP, change in treatment and ADR as significant factors associated with adherence. In the multivariate logistic regression analysis, we included risk category, age and ADR by using forward selection and backward elimination. The model reached statistical

Table 2 Medication overview by adherence groups

	Overall cohort (N=93)	Adherent (N=73)	Non-adherent (N=20)	P value
Questionnaire data, %	89±10	94±5	77±10	
Specialty pharmacy data, %	94±14	98±4	80±26	
Change in medication over time	67 (72)	48 (66)	19 (95)	0.010*
Reason for change in medication overall (more than one possible reason)				
Escalation	30 (32)	22 (30)	8 (40)	0.571
Adverse drug reactions	29 (31)	19 (26)	10 (50)	0.075
Change of treatment direction	9 (10)	5 (7)	4 (20)	0.100
No benefit	9 (10)	9 (12)	0 (0)	0.197
Delivery difficulties	1 (1)	1 (1)	0 (0)	
Change without consultation	2 (2)	1 (1)	1 (5)	
Number of oral medications at t_3				
Single oral therapy	43 (46)	31 (43)	12 (60)	0.254
Combination therapy	50 (54)	42 (58)	8 (40)	0.254
Oral medication intake at t_3				
Endothelin receptor antagonist	70 (75)	56 (77)	15 (75)	1.000
Phosphodiesterase-5 inhibitors	47 (51)	40 (55)	7 (35)	0.188
Soluble guanylate cyclase stimulator	16 (17)	13 (18)	3 (15)	1.000
Prostacyclin receptor agonist	13 (14)	11 (15)	2 (10)	0.727
Calcium channel blocker	10 (11)	6 (8)	4 (20)	0.214
Patients with intravenous or s.c. medication today	9 (10)	8 (11)	1 (5)	
Patients with inhaled medication today	1 (1)	1 (1)	0 (0)	

Data are presented as mean±SD or number (%).
*More than one reason for change in medication over time per patient possible. Statistically significant values are marked with.
s.c., subcutaneous.

significance (p=0.002). Patients were 75% more likely to be non-adherent to medication if they experienced ADR (OR=0.25; 95% CI=0.08 to 0.77). While older patients were more likely to adhere (OR=1.03; 95% CI=1.01 to 1.07), being classified in a higher risk category more than doubled the likelihood of adherence (OR=2.13; 95% CI=1.11 to 4.64) (online supplemental table S3).

DISCUSSION

In this study, we evaluated the adherence to PH-targeted drugs among patients diagnosed with either PAH or distal CTEPH within the Zurich PH-cohort (figure 2). The overall adherence rate, determined through both MPR calculations and questionnaire responses, was 78% in our study population. A cut-off value of ≥80% was used for defining adherence, consistent with existing literature,[22] particularly within this field.[13] The average adherence rate reported in a recent meta-analysis was 60.9% (95% CI=52.3% to 69.1%)[13] with a reported adherence assessed by questionnaire of 52.9%, while adherence assessed using prescription data yielded a proportion of 62.9%.[13] In our study, adherence based on questionnaire responses was notably higher at 78%, whereas adherence assessed using prescription data was even much higher at 87%. Indeed, our study is in line with several other studies[24–26] that also reported similarly high rates of medication adherence among patients with PAH or CTEPH. It is noteworthy to acknowledge that investigations in literature regarding adherence have used diverse assessment methods, potentially contributing to differences in reported adherence rates. The MPR used in our study tends to produce higher values of adherence, which may lead to overestimation, as it does not account for duplications or overlapping dosages.[23] To address the potential overestimation, our study was augmented with self-report via questionnaire to follow a multimeasure approach. Patients were moreover already classified as non-adherent if the adherence value for one specific drug was <80% or if they reported a score <80% in the questionnaire. Adherence based on self-reported data may be susceptible to distortion, as patients might tend to overestimate their medication intake, as previously described.[15] Interestingly, in our study, adherence calculated through questionnaire responses was lower than adherence determined by prescription data. According to the WHO's report from 2003,[15] patients tend to report

Table 3 Clinical performance parameters compared between different point of measurement for adherent and non-adherent group separately

Adherent group (n=73)	Baseline (t_1)	First follow-up (t_2)	Last follow-up (t_3)	$P_{t1/t2}$	$P_{t2/t3}$	$P_{t1/t3}$	$P_{ANOVA/Friedman}$
WHO functional class				0.002*	0.705	0.019*	0.007*
WHO-FC I	6 (8)	10 (15)	13 (18)				
WHO-FC II	27 (37)	33 (49)	34 (47)				
WHO-FC III	35 (48)	23 (34)	20 (27)				
WHO-FC IV	5 (7)	2 (3)	6 (8)				
6-minute walk test							
6MWD, m	434±129	473±134	433±152	0.014*	0.008*	0.195	0.013*
SpO_2 at end exercise, %	88±8	88±9	89±8	0.547	0.939	0.96	0.860
NT-proBNP, ng/L	1536±2425	559±678	958±1787	0.001*	0.067	0.08*	0.008*
Four-strata risk category				<0.001*	0.169	0.028*	0.001*
Low	21 (29)	33 (48)	31 (42)				
Intermediate-low	23 (32)	23 (33)	26 (36)				
Intermediate-high	23 (32)	10 (15)	10 (14)				
High	6 (8)	3 (4)	6 (8)				
Non-adherent group (N=20)							
WHO functional class				0.005*	0.299	<0.001*	<0.001*
WHO-FC I	0 (0)	6 (32)	4 (20)				
WHO-FC II	8 (40)	5 (26)	13 (65)				
WHO-FC III	12 (60)	8 (42)	3 (15)				
WHO-FC IV	0 (0)	0 (0)	0 (0)				
6-minute walk test							
6MWD, m	509±109	519±92	446±129	0.059	0.308	0.397	0.438
SpO_2 at end exercise, %	90±6	87±8	87±8	0.833	0.523	0.554	0.819
NT-proBNP, ng/L	394±468	167±156	389±664	0.008*	0.093	0.289	0.074
Four-strata risk category				0.11	1.000	0.308	0.103
Low	6 (30)	10 (53)	11 (55)				
Intermediate-low	13 (65)	8 (42)	7 (35)				
Intermediate-high	1 (5)	1 (5)	2 (10)				
High	0 (0)	0 (0)	0 (0)				

Data are presented as mean±SD or number (%).
*Statistically significant values are marked with.
ANOVA, analysis of variance; 6MWD, 6-minute walking distance; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SpO_2, oxygen saturation; WHO-FC, WHO-functional class.

their adherence accurately when admitting to not taking their medication. Hence, it is reasonable to assume that patients identified as non-adherent in our study truly display non-adherent behaviours.

Additionally, within our cohort significant differences in the progression of clinical parameters over time were observed between both groups based on adherence status. Adherent patients demonstrated improvement in all parameters used to determine the simplified four-strata risk category over time, including WHO-FC, 6MWD and NT-proBNP levels, whereas non-adherent patients did not. It is noteworthy that patients categorised non-adherent initially displayed better overall baseline conditions, as indicated by higher values in 6MWD and lower NT-proBNP levels. Consequently, 30% of these patients were categorised into the low-risk category and a further 65% into the intermediate-low risk category. In contrast, among the adherent group, baseline values were poorer, with 29% falling into the low and only 32% into the intermediate-low risk category, while 32% were categorised into the intermediate-high risk and even 8% into the high risk category. When looking at the clinical parameters at

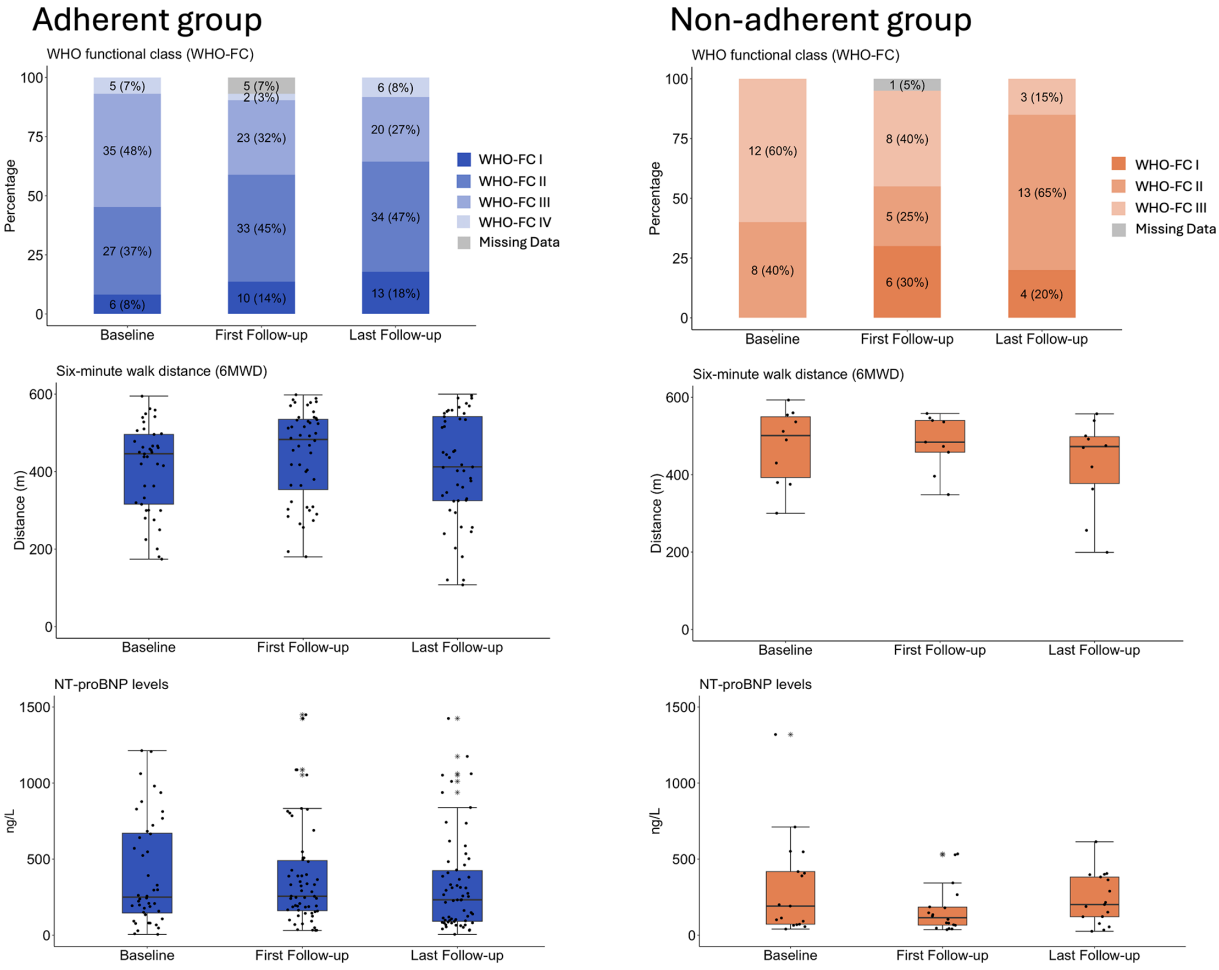

Figure 1 Parameters used to calculate four-strata risk categories over time for group by adherence. FC, functional class; NT-proBNP, NT-pro brain natriuretic peptide; 6MWD, 6-minute walk distance.

three different time points within each group separately, it becomes apparent that both groups experienced the most significant improvement between baseline (t_1) and the first follow-up (t_2), which was registered on average 7±2 months after treatment initiation. Adherent patients improved in each parameter used to determine the four-strata risk category, as well as in the overall risk category. In contrast, non-adherent patients showed significant improvement in WHO-FC and NT-proBNP levels only. Hence, there was no detectable overall improvement in the risk category. During the second interval (from t_2 to t_3), spanning a period of 5±3.8 years, there was no significant improvement observed overall. Whether this can be explained by potential weakening of adherence during the treatment period, as described previously,[17 18 20] or a plateauing effect of the drugs despite regular intake is unclear. Disease progression might have played a role as well in this rather long observation period. During the entire time frame (from t_1 to t_3), patients identified as adherent exhibited noteworthy improvements in WHO-FC, NT-proBNP levels and risk category. Conversely, non-adherent patients experienced improvements only in WHO-FC. It is apparent that patients who remained adhered to treatment showed more sustained improvement over time.

In our cohort, several factors could have influenced whether a patient adhered to treatment or not. Patients categorised as adherent initially presented with significantly worse health conditions. This suggests they were likely aware of their poor health status and the presence of a serious illness motivating them to conscientiously take their medication. A meta-analysis on cardiovascular diseases[27] has shown that preventive treatments, characterised by the absence of symptoms, often result in poor adherence. Despite being diagnosed and treated according to guidelines, non-adherent patients within our cohort displayed fewer impairments in their daily lives at baseline when taking 6MWD and NT-proBNP levels into account, potentially leading to a higher quality of life and less awareness of their illness. However, this could ultimately lead to negligence in medication intake.[15] Aside from that, non-adherent patients exhibited significantly more changes in PH-targeted treatment over time, potentially driven by adverse drug reactions, which are widely acknowledged as a common reason for poor medication adherence.[25 28] Finally, it is noteworthy that non-adherent

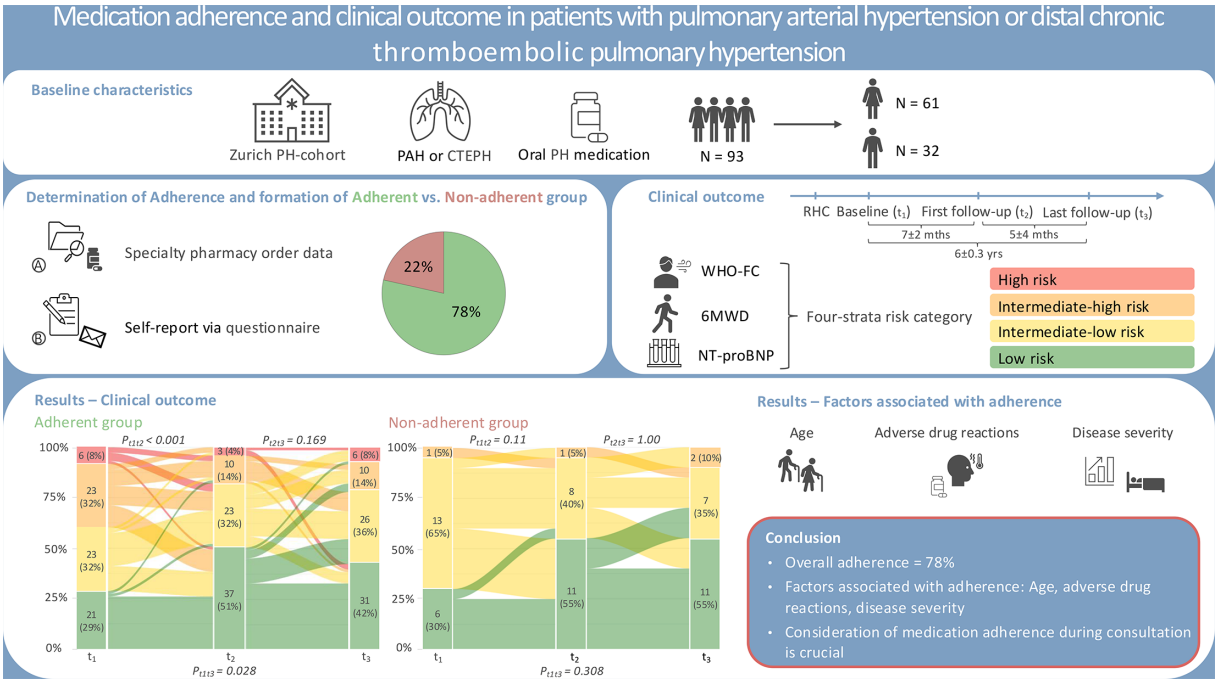

Figure 2 Visual summary of the study. CTEPH, chronic thromboembolic pulmonary hypertension; FC, functional class; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterisation; 6MWD, 6-minute walk distance.

patients were significantly younger than adherent patients, which may be part of a larger discussion, within the field of adherence research, about the relationship between age and complying with adherence. While some studies[18 21 29] identified age as not being a predictor of adherence in patients with PH, other scientific investigations[20 30] established that increasing age is predictive of conscientious medication intake.

The logistic regression conducted to identify factors associated with adherence did mostly align with our assumptions. Patient-related factors such as sex or diagnosis, with the exception of age, had no noteworthy effect on adherence within our cohort. In line with Le Bozec *et al*[30] and Grady *et al*[20] younger age was associated with negligent medication intake. Interestingly, variables commonly known for predicting adherence such as number of prescribed drugs[31] or duration of treatment[18 20] had no significant influence on either direction of medication adherence within our cohort with the exception of ADR. Patients with PH, particularly those who are more symptomatic, may have a greater fear of illness progression than patients with other chronic disorders and that might contribute to greater adherence. Also, they do recognise that, in most cases, their medications, while not curative, help their symptoms and that is an incentive for adherence. In line with our assumption, a higher risk category was associated with an increased probability of adherence, showing that patients with superior clinical parameters at treatment start are particularly vulnerable to non-adherence to medical treatment.

Despite observing relatively high rates of adherence within our cohort, it is crucial to recognise that PAH and distal CTEPH are still fatal diseases associated with high morbidity and mortality.[32] Consequently, the results of our study must be interpreted in light of the severity of the disease. As morbidity increases due to poor adherence, healthcare costs also escalate.[33] Therefore, it is very important to reflect on strategies for better identification methods of adherence, but also strategies for increasing adherence. To address barriers to adherence, enhancing patient education about the importance of consistent medication use and the chronic nature of PH is essential. Proactive questioning, supplemented by validated adherence questionnaires during outpatient visits, can help to monitor and address adherence issues early, particularly for low-risk patients. Additionally, improving the management of side effects through timely adjustments in treatment or changes in medication can significantly enhance adherence. Within the field of PH, discovering new medication pathways is challenging. Therefore, patients' adherence to established treatment strategies is of utmost importance for effective PH therapy.[34]

Limitations

The adherence assessment methods used in this study, such as MPR and self-report via questionnaire, are subject to critique for possibly inflating the determined level of adherence. Additionally, although the questionnaire is based on established tools for assessing treatment adherence based on literature research, it has not been formally validated and has been administered in German language. We have added the original and translated version for the interested reader in the

supplements (online supplemental figure S4 and figure S5). Test performance characteristics indicate that while the questionnaire effectively identifies adherent patients, as shown by its high specificity and negative predictive value, the lower sensitivity and positive predictive value suggest potential challenges in accurately detecting non-adherence. Nonetheless, it is crucial to acknowledge the absence of a universally accepted gold standard for assessing medication adherence, given that each measurement approach has inherent constraints. Moreover, in our specific scenario, we believe the likelihood of overestimation was rather low, given the utilisation of a multimeasure approach and the stringent classification criteria where even a single instance of medication non-adherence resulted in classification as non-adherent. It is also important to highlight that in studies focusing on medication adherence, a diverse array of adherence measurement methods is used alongside assessments of different drug combinations. Consequently, caution is warranted when interpreting and comparing data on medication adherence, particularly within the field of pulmonary vascular disease.

Second, only patients participating in the Zurich PH Cohort study were included in our analysis and thus were potentially more compliant than patients not willing to participate in the study, possibly influencing the calculated level of adherence.

Conclusion

The overall adherence to PH-targeted medications was 78% among patients with PAH or distal CTEPH within this patient cohort. Patients identified as adherent improved clinical outcomes contrary to non-adherent patients. Factors associated with insufficient adherence included young age, the occurrence of adverse drug reactions and classification into a low-risk category. Especially in patients without improvement after starting PH-targeted therapy, insufficient adherence and potential contributing factors should be carefully considered and assessed during patient consultation.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Cantonal Ethics Committee Zurich (No. 2014-0214).

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