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Early View

Original article

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Adherence to disease-specific drug treatment among patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension

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Abstract

Background: Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) require lifelong treatment. The aim of the present study was to investigate adherence to disease specific treatment in patients with PAH or CTEPH.

Methods: The study comprised an adult population diagnosed with PAH (n=384) or CTEPH (n=187) alive in 2016-2017. The study utilized three registries; the Swedish PAH registry, the National Board of Health and Welfare and, Statistics Sweden. Withdrawals from pharmacies of disease-specific oral treatments were studied. Adherence was assessed as; 1) *Number of days covered* defined as the difference between the total number of daily dosages dispensed and the total number of days covered and 2) M*anual assessment* by two persons that independently reviewed each patient's prescription fill history to detect anomalies or patterns of deteriorating or improving adherence over time.

Results: The mean age was 61±16 years, 61% were female and mean time since diagnosis was 4.6 years. Adherence was 62% using the *Number of days covered* method and 66% by the *Manual assessment* method. Drug specific adherence varied from 91% for riociguat to 60% for sildenafil. Good adherence was associated to shorter time since diagnosis in patients with PAH and to lower number of concomitant other chronic treatments in patients with CTEPH. Age, sex, socioeconomic status, or number of PH-treatments were not associated to adherence.

Conclusion: Adherence to oral disease specific treatment was 60-65% and associated to time since diagnosis and number of concomitant chronic treatments. Sex, age or socioeconomic factors did not affect adherence.

Introduction

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are serious, chronic diseases that require life-long, disease specific treatment [1] The medical treatment is focused on improving symptoms, physical work ability, quality of life and survival. Over the last two decades, new drugs and optimized treatment strategies have increased survival and quality of life [1, 2]. PH-targeted therapies include endothelin receptor antagonists (ERA), phosphodiesterase 5 inhibitors (PDE-5i), soluble guanylate cyclase stimulators (s-GCs), as well as prostacyclin analogues and a prostacyclin receptor agonist [1]. Current guidelines recommend mono- or upfront combination-therapy, based on risk assessment [1, 3]. Treatment side effects can make it challenging to motivate patients to follow the prescribed treatment plan over time [4]. Medication adherence as low as 50% has been reported among patients with PAH and CTEPH [5-8]. High age, the number of comorbidities and the integration of a specialist in pharmacology at the outpatient clinic have been shown to correlate with increased treatment adherence [8, 9]. Treatment with mono- versus combination therapy, on the other side, is showing conflicting results [8, 10]. In a recent Swedish survey, almost all patients with PAH or CTEPH said they understood why they took their drugs, but a third reported that they did not always take them according to the prescription [7]. Concerns about side effects, reported by half of the study population, likely contributed to the low adherence. Further, a longer elapsed time since diagnosis and start of treatment related to lower self-reported treatment adherence [7].

The aim of the present study was to investigate to which extent patients with PAH or CTEPH adhere to their disease specific treatment by utilizing available national registries in Sweden. In addition, concomitant medical treatments and socioeconomic status was investigated.

Methods

The study included a retrospective population comprising patients registered in the Swedish PAH registry [11], with a diagnosis of PAH or CTEPH, aged ≥18 years and alive January 2016 through December 2017. In Sweden, individual-level data for all residents can be linked across multiple national databases. This study was based on an interconnection between three available quality registries; SPAHR [11], Socialstyrelsen (the National Board of Health and Welfare) [12] and Statistiska centralbyrån (Statistics Sweden) [13]. Socioeconomic factors including age, education, occupation, family situation, and income during 2016 were used for the current analyses. The study complies with the Declaration of Helsinki and was approved by the Regional ethics committee in Lund, Sweden (LU 2016/766).

The Swedish pulmonary arterial hypertension register (SPAHR)

SPAHR was started in 2008 and constitutes an open continuous register of patients diagnosed with PAH or CTEPH according to the Nice classification [11]. All Swedish PAH/CTEPH-expert centres participate and thus, SPAHR includes >90% of all Swedish patients alive on January first, 2000 and all subsequent newly diagnosed patients thereafter. SPAHR is approved by the National Board of Health and Welfare and by the Swedish Data Protection Authority. All patients were informed about their participation in SPAHR and had the right to decline.

The National Board of Health and Welfare's pharmaceutical and population registers

The National Board of Health and Welfare's pharmaceutical register covers all medicines that have been dispensed at pharmacies in Sweden. The registration takes place on an individual level. The National Board of Health and Welfare's population register contains information on

socio-economic factors that may affect the ability to pay for the treatment [12].

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA).

LISA is a part of Statistics Sweden and contains information on marital status, number of children, education level, socioeconomic index, vocational code, employment status, welfare benefits, and income for all adult individuals in Sweden [13].

Medical treatment and analyses of adherence

Withdrawals of PH-specific treatments administered from pharmacies in 2016-2017 were studied. For each drug, adherence was assessed as;

1) *Number of days covered* [14]. This was defined as the difference between the total number of daily dosages dispensed from the pharmacy and the total number of days covered between the first to the last prescription fill. For good adherence the difference between the dispensed daily dosages and the total number of days had to be one or less than one missed daily dosage per month.

2) A *manual assessment* was performed by two persons that independently reviewed each patient's prescription fill history to detect anomalies or patterns such as deteriorating or improving adherence over time. When the assessments were not in agreement, the results were discussed and a consensus reached.

The studied PH-specific treatments included ERA, PDE-5i and SGCs. Adherence to prostacyclin analogues and the prostacyclin receptor agonist was not analysed due to the individualized dosages that is used for this group of drugs. Less than three concomitant

prescription fills during the study period were excluded [14]. If a prescription was not filled for 180 days or more and the patient was on another PH-targeted treatment during that period that could explain why the prescription was not filled, the period was not considered non-adherence. Administration of PH-specific treatments were; Ambrisentan and Macitentan once daily, Bosentan and Tadalafil twice daily, and Sildenafil and Riociguat three times a day.

Other concomitant medical treatments of interest were also studied and allocated as *chronic treatment*, e.g. treatment for chronic diseases with ≥3 filled prescriptions in one year and as *temporary treatment*, e.g. treatment generally used for temporary diseases and with ≥1 filled prescriptions in a year.

Statistical methods and data management

Descriptive statistics were used to characterize the data. Logistic regression analyses were performed, calculating odds ratios (OR) with 95-% confidence intervals (CI). All analyses were carried out by use of the SAS statistical software (The SAS system for Windows 9.4. SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of the study population

A total of 571 patients were alive 2016-2017 and included in the analyses. Of those, 384 were diagnosed with PAH (idiopathic/hereditary (IPAH/HPAH) n=201, associated to connective tissue disease n=86, or congenital heart disease n=66, or other diseases n=31) and 187 with CTEPH. The mean age at time of diagnosis was 56±18 years and at the time of the study

61±16 years, the proportion of women was 61% (Table 1). Mean time since diagnosis to study start was 4.6 years.

Half of the population had a highest degree of education as high school and the other half was equally divided between primary school and college/university degree. A majority of the study population was not working and this was similar in men and women. Forty-five percent were married or had a registered partner and 22% of the households had children living at home, of which 12% were 18 years or older. The disposable household income was slightly below the average Swedish household income (Table 1).

Of patients on monotherapy (38%), 49% were treated with PDE-5i or SGCs, and 37% with ERA, while among patients on double therapy (37%), 95% were treated with ERA and PDE-5i or SGCs (Table 2). Fifteen percent did not have a registered prescription fill of a PAH-specific drug, a majority of those were patients with CTEPH. All patients with CTEPH and 66% of patients with PAH were prescribed anticoagulant-treatment.

Treatment adherence

There were 443 patients that filled their prescriptions for ERA or PDE-5i, or a combination of ERA and PDE-5i, ≥3 times during the study period and hence, could be included in the analyses of adherence (Table 3). Adherence for the whole population was 62% using the *Number of days covered* method and in the subgroup analyses, 61% for PAH and 64% for CTEPH. Corresponding numbers for the *Manual assessment* method was 66% for all, 66% for PAH and 67% for CTEPH. Drug specific adherence for the whole population varied from 91% that filled their prescriptions of riociguat to 60% that filled their prescriptions of sildenafil (Table 3). Patients with combination treatment including prostacyclin therapy (n=66) had an adherence of 74 and 70% for the *Numbers of days covered* and *Manual*

assessment methods respectively (Table 3). The *Manual assessment* detected more patients that missed two or less dosages per month than *Numbers of days covered* (Figure 1).

Good adherence to oral PH-specific treatment, assessed by the *Manual assessment* method, was associated to shorter time since diagnosis in patients with PAH and to lower number of concomitant other chronic treatments in patients with CTEPH (Table 4). Age, sex, socioeconomic status, or number of PH-treatments were not associated to adherence in either group (Table 4). In addition, good adherence assessed by the *Number of days covered* method was also associated to not working in patients with PAH (OR 0.595; CI95% 0.357-0.991).

Concomitant treatments

Diuretics, beta-blockers, statins and calcium channel blockers were the most commonly used chronic concomitant treatment for all patients. Patients with IPAH/HPAH that had a positive vasoreactivity test at time of diagnosis and who did not receive any other PH-targeted treatment at the time of the present study were not included among those reported using calcium channel blockers as concomitant treatment. Patients with PAH were more often treated with a chronic concomitant treatment than patients with CTEPH (Table 5). Antidiabetic drugs and treatment for hypothyroidism were twice as common among patients with PAH as for patients with CTEPH (Table 5).

Of temporary treatments, 67% of the patients were treated with antibiotics at least once during the study period and 51% of the patients filled a prescription for a proton pump inhibitor (Table 5). Other common drugs were treatment of obstipation and anaemia as well as steroids, asthma inhalers and antifungal crème/solution for external use.

Discussion

The main finding of the present study was that the overall adherence to oral ERA and/or PDE-5i/SGCs treatment was 60-65%. Adherence was associated to time since diagnosis, especially in patients with PAH and to number of concomitant chronic treatments in patients with CTEPH. Sex, age or socioeconomic factors, such as level of education, income or marital status, did not affect adherence.

The present study used a strict method for treatment adherence, allowing only one missed daily dosage per month to be categorized as low adherence. In support of this method, the overall adherence to PAH-treatment found in the study was in good concordance with the self-reported treatment adherence of 57% from the Swedish PAH and CTEPH population that has been published earlier [7]. The patient's perception of adverse side effects that might occur, has been shown to affect the patient's decisions weather to take the drugs as prescribed or not [15, 16]. In addition, previous experiences with pharmacological therapies might lead to a lack of motivation to adhere to a treatment [17]. Thus, it is important to address the patients concerns about a treatment, both at the time of first prescription as well as at subsequent meetings with the patient [18, 19]. As shown in the present study, as well as in earlier studies, the longer time since diagnosis that has elapsed, the lower is the adherence to treatment [7, 8].

In the present study, of those who did not meet the criteria of adherence, and with the exception of treatment with sildenafil, approximately half missed two or less daily dosages per months. This might be considered a medium level of adherence while the quarter that missed more than five daily dosages per month might be at a low level. Patients on sildenafil, would then be reckoned as a third in each category of medium, medium-low and low adherence. The effect adherence to PH-treatments has on disease progression is not known. Neither is the threshold of adherence that should be considered low. While not taking the

medication once or twice in one month might not seem a problem, the present study investigated prescription fill over a two-year period. Thus, the number of daily dosages not taken represent an average of missed daily dosages per month over a longer period.

Adherence to PH-treatment varied from a 91% adherence to riociguat to a 60% adherence to sildenafil in the present study. However, these results should be interpreted with caution. The use of riociguat was approved in Sweden the year before the present study and only a small proportion of the patients, and almost all with CTEPH, were treated with it. Both sildenafil and riociguat are prescribed three times a day, a treatment regimen, which has earlier been associated with low adherence [5, 8, 10, 20]. With riociguat being the only drug in Sweden approved for CTEPH at the time being, this might support a high adherence, at least initially [21]. In addition, riociguat requires more frequent contact with the PAH clinic during the dose-adjustment period, which might also lead to higher adherence. With the exception of riociguat, and in concordance with earlier results, treatments administered once a day had the best adherence [8, 20].

There was no association between adherence and number of PH-treatments in the present study. This is in contrast to a previous study by *Studer et al.* that showed that patients on combination therapy had higher adherence [10]. Study design and treatment regimen likely explain some of the differences. Patients in that study were newly diagnosed and only a quarter of the identified patients met the inclusion criteria and were investigated. A majority were treated with monotherapy, in particular PDEI5, after diagnosis and at the end of the 12 months the study lasted, 75% were still treated with only one PH-treatment [10]. In the present study, only 38% were treated with monotherapy during the course of the study. Time since diagnosis and number of concomitant chronic drugs were the only investigated variables that showed an association with low adherence in the present study, the latter likely reflecting a higher comorbidity burden [8, 23]. Similar results have been shown in two previous studies

using self-reported adherence instruments [7,8]. However, both those studies showed an association with higher age that was not present in the current study. In addition, *Grady et al.* showed an association between monotherapy and adherence [8] while *Ivarsson et al*., similar to the present study, saw no association between neither single or combination PH-treatment and adherence [7]. The discrepancy between the results might be related to the low proportion of patients on combination therapy in the *Grady et al.* study [8].

All patients included in the present study have regular contact with the PAH/CTEPH-expert centres [24] which may have increased their understanding of the PAH-disease, improved involvement in treatment decision, and supported good medical literacy, factors that have been related to adherence [17, 25]. Building trust between patients, caregivers and staff might affect the patient's health beliefs and attitudes concerning the effectiveness of the treatment [19, 25, 26]. However, this might also have an opposite effect as the health-care staff feels they know the patient, and thus, information about the disease and the importance of treatment is not repeated regularly, leading to declining adherence over time. In a recent study it was shown that despite agreeing that they received appropriate information, about half of the patients wanted more information [27].

High costs or co-payments for treatment and health care have been shown to contribute to poor medication adherence [17, 28]. However, in the present study there was no relation between socioeconomic factors and adherence, despite the household income being at, or slightly lower than, the average disposable income in Sweden. The cost ceiling in the Swedish health care system that covers almost all costs related to care, including drug prescriptions, likely contributed to this finding.

The rather high proportion of patients in the present study that filled three or more prescriptions of treatments for other chronic diseases indicate that comorbidities were common in this patient population. In addition, prescriptions for temporary treatments such as

antibiotics, proton pump inhibitors, and other treatments related to digestive symptoms were also frequently filled. This might be related to side effects of the PAH-specific drugs or might mirror the comorbidity burden related to increasing mean age of the PAH patients, seen all over the world [22, 29]. The number of patients prescribed antibiotics, about two thirds of the study population, was surprisingly high. One might speculate that some overuse of antibiotics to avoid severe infections in these patients might occur, especially as patients generally contact the primary care for common colds and infections. The PAH/CTEPH expert centres are essential for coordinating the contacts with other parts of the health care system, such as being accessible for questions from the primary care givers in the context of these rare diagnoses [30].

A quarter of the patients with PAH had children living at home and of those, two thirds were 19 years old or younger showing that it is a disease that still affects the young in high proportion [1, 29]. In this study, there was no relation between age, sex or the family situation to treatment adherence. The proportion of patients living alone was higher than in the general Swedish population, a finding in concordance with other reports that divorce is not uncommon in this patient group [31]. However, there was no relation between marital status and adherence in the present study, despite an earlier study showing that spouses want to support treatment adherence to prolong life for their partner [32].

It is obvious that low treatment adherence will contribute to suboptimal clinical benefits. This has further been highlighted by WHO which stated that increasing adherence may have a greater effect on health than any improvement in specific medical treatments [22]. It has been suggested that the best strategy to improve treatment adherence is to involve the patient in the medical decision process and stress the immediate advantages of treatment instead of future complications [17].

Methodological considerations

The adequate sample size in form of a total national cohort of patients 2016-2017, registered in a register with >90% national coverage is a strength. The proportion of patients with PAH and CTEPH are in alignment with the proportions of patients in the Swedish PAH registry [11]. The analysis of adherence was based on filled prescriptions and thus, the study has assumed that this reflects the patients actually taking the drug they have collected from the pharmacy. Adherence to prostacyclin analogues and the prostacyclin receptor agonist was not analysed due to the individualized dosages that is used for this group of drugs. In the analysis of other temporary treatments, there is likely a non-optimal reporting of treatments like anti-fungal, antihistamines, and treatments for gastro-intestinal symptoms, that can be purchased without a prescription in Sweden.

Conclusions

Adherence to oral ERA and/or PDE-5i/SGCs treatment was 60-65% and associated to time since diagnosis and to number of concomitant chronic treatments. Sex, age or socioeconomic factors such as, level of education, income or marital status, did not affect adherence.

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Conflicts of interest

BK reports unrestricted research grants from Actelion Pharmaceuticals Sweden AB and Merck & Co., Inc., Kenilworth, NJ, USA

AS is an employee of Actelion Pharmaceuticals Sweden AB

CH reports personal lecture fees from Actelion Pharmaceuticals Sweden AB and unrestricted research grant from Merck & Co., Inc., Kenilworth, NJ, USA

MN has been primary or co-investigator in clinical trials or studies sponsored by United Therapeutics and received lecture as well as consultation fees from Actelion Pharmaceuticals Sweden AB, Pfizer, Bayer HealthCare, NordicInfu Care and GlaxoSmith-Kline.

PN have no conflicts of interest related to this manuscript

BI reports unrestricted research grants from Actelion Pharmaceuticals Sweden AB

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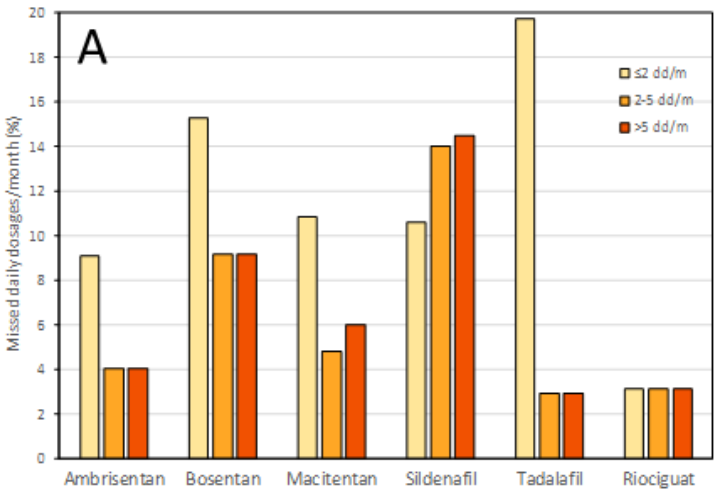
Figure legend

Figure1. Proportion of low adherence by number of missed daily dosages per month shown for manual assessment (panel A) and number of days covered (panel B).


A
Missed daily dosages/month (%)
≤2 dd/m
2-5 dd/m
>5 dd/m
0
2
4
6
8
10
12
14
16
18
20
Ambrisentan
Bosentan
Macitentan
Sildenafil
Tadalafil
Riociguat

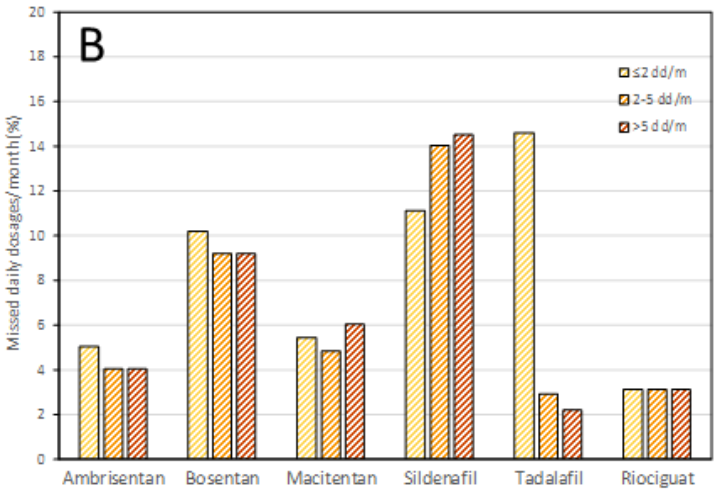

B
Missed daily dosages/month (%)
≤2 dd/m
2-5 dd/m
>5 d d/m
0
2
4
6
8
10
12
14
16
18
20
Ambrisentan
Bosentan
Macitentan
Sildenafil
Tadalafil
Riociguat

Table 1. Socioeconomic factors. Data presented as mean±SD or n (%).

	All	**PAH**	**CTEPH**
	n=571	**n=384**	**n=187**
Age (years)	61±16	58±16	67±14
Age Men (years)	64±15	60±15	68±14
Age Women (years)	60±17	58±17	67±15
Sex (Women)	349 (61)	269 (70)	80 (43)
Time since diagnose (years)	4.6±4.2	4.8±4.4	4.2±3.3
Highest level of education			
Primary school	147 (26)	97 (25)	50 (27)
High school	264 (47)	183 (48)	81 (43)
College/University	147 (26)	93 (24)	54 (29)
Occupation			
Working	152 (27)	103 (27)	49 (26)
<65 / ≥65 years	135 (89)/17 (11)	98 (95)/5 (5)	37 (76)/12 (24)
Men / Women	62 (41)/90 (59)	30 (29)/73 (71)	32 (65)/17 (35)
Not working	419 (73)	281 (73)	138 (73)
<65 / ≥65 years	149 (36)/270 (64)	126 (45)/155 (55)	23 (17)/115 (83)
Men / Women	161 (38)/258 (62)	85 (30)/196 (70)	76 (55)/62 (45)
Marital status			
Married/Registered partner	257 (45)	164 (43)	93 (50)
Not married/Divorced/Widowed	314 (55)	220 (57)	94 (50)
Number of households with children living at home			
0	447 (78)	286 (74)	161 (86)
1	70 (12)	56 (15)	14 (7)
2	38 (7)	32 (8)	6 (3)
≥3	16 (3)	10 (3)	6 (3)
Number of individual children in different age groups living at home			
0-6	31 (19)	25 (19)	6 (18)
7-19	80 (48)	67 (51)	13 (38)
≥20	55 (33)	40 (30)	15 (44)
Disposable income (kSEK)*			
Individual	202±137	193±134	221±142
Men	234 ±157	219±166	249±146

Women	181±118	181±116	182±126
Household	340±274	337±290	346±239
Men	361±233	352±239	371±227
Women	327±297	331±309	313±251

PAH=pulmonary arterial hypertension, CTEPH=chronic thromboembolic pulmonary hypertension, *Average disposable income in Sweden 2016-17 was 360 kSEK (https://www.scb.se/en/finding-statistics/statistics-by-subject-area/household-finances/income-and-income-distribution/income-and-tax-statistics/pong/tables-and-graphs/income--households-the-entire-country/disposable-income-by-type-of-household-2011-2017/)

Table 2. PH-specific treatment. Data presented as n (%).

	All	**PAH**	**CTEPH**
	n=571	**n=384**	**n=187**
Endothelin receptor antagonists	346 (60)	289 (75)	57 (30)
Phosphodiesterase type 5 inhibitors/ Soluble guanylate cyclase stimulator	370 (65)	265 (69)	105 (56)
Prostacyclin analogues	68 (12)	60 (16)	8 (4)
Single	217 (38)	137 (36)	80 (43)
ERA	80	65	15
PDE-5i/SGC	106	43	63
PRO	2	0	2
CCB	29	29	
Double	214 (37)	175 (46)	39 (21)
ERA + PDE-5i/SGC	204	167	37
ERA + PRO	6	5	1
PDE-5i/SGC + PRO	4	3	1
Triple	56 (10)	52 (14)	4 (2)
ERA + PDE-5i/SGC + PRO	56	52	4
Untreated	84 (15)	20 (5)	64 (35)
Anticoagulants			
Warfarin	349 (61)	180 (47)	169 (90)
Other	92 (16)	74 (19)	18 (10)
Oxygen	52 (9)	37 (10)	15 (8)

PAH=pulmonary arterial hypertension, CTEPH=chronic thromboembolic pulmonary hypertension, ERA=Endothelin receptor antagonists, PDE-5i=Phosphodiesterase type 5 inhibitors, SGCs=Soluble guanylate cyclase stimulator, PRO=Prostacyclin analogues, CCB=Calcium channel blocker

Table 3. Adherence to PH-specific treatment. Data presented as number of patients who filled a prescription and were included in the analyses, and proportion of those with good adherence shown for number of days covered (NoDC) and manual assessment (Man).

	All			PAH			CTEPH		
	Number included	**% Adherence (NoDC)**	**% Adherence (Man)**	**Number included**	**% Adherence (NoDC)**	**% Adherence (Man)**	**Number included**	**% Adherence (NoDC)**	**% Adherence (Man)**
ERA									
Ambrisentan	99	87	83	90	87	82	9	89	89
Bosentan	98	71	66	73	71	68	25	72	60
Macitentan	166	84	78	146	82	77	20	95	90
PDE-5i									
Sildenafil	207	60	61	146	61	62	61	59	59
Tadalafil	137	80	74	117	80	74	20	80	75
SGCs									
Riociguat	32	91	91	2	0	0	30	90	90
Single treatment	209	68	65	131	69	66	78	67	63
Double treatment	234	64	59	198	64	58	36	67	67
Oral* + PRO	66	74	70	60	73	70	6	83	83

*adherence to oral treatment reported. PAH=pulmonary arterial hypertension, CTEPH=chronic thromboembolic pulmonary hypertension, ERA=Endothelin receptor antagonists, PDE-5i=Phosphodiesterase type 5 inhibitors, SGCs=Soluble guanylate cyclase stimulator, PRO=prostacyclin therapy

Table 4. Logistic regression analysis showing the relationship between adherence and explanatory variables. Data presented as OR and (95% CI).

	All **n=571**	**PAH** **n=384**	**CTEPH** **n=187**
Sex (female vs. male)	0.725 (0.486-1.081)	0.704 (0.434-1.144)	0.808 (0.374-1.746)
Age (continuous)	1.009 (0.997-1.020)	1.010 (0.996-1.024)	1.002 (0.975-1.029)
Age (≤65 years vs. >65 years)	0.749 (0.510-1.100)	0.725 (0.461-1.141)	0.870 (0.379-1.995)
Time since diagnosis			
≤1 year vs. >1 year	2.036 (1.201-3.454)	1.813 (0.998-3.294)	3.027 (0.948-9.664)
≤2 year vs. >2 year	1.912 (1.243-2.943)	1.786 (1.092-2.920)	2.421 (0.978-5.996)
≤3 year vs. >3 year	1.933 (1.304-2.864)	1.962 (1.246-3.088)	1.876 (0.850-4.142)
Education (primary/high school vs. college/university)	0.930 (0.597-1.448)	1.082 (0.644-1.818)	0.605 (0.256-1.429)
Marital status (married/registered partner vs. not married/divorced/widowed)	1.138 (0.774-1.671)	1.120 (0.717-1.751)	1.154 (0.536-2.484)
Children living at home (yes vs. no)	0.865 (0.538-1.393)	0.985 (0.579-1.674)	0.515 (0.167-1.589)
Working (yes vs. no)	0.782 (0.503-1.216)	0.683 (0.413-1.131)	1.252 (0.487-3.219)
Household income (≤median vs. >median*)	1.142 (0.760-1.717)	1.009 (0.627-1.623)	1.642 (0.740-3.645)
Individual income (≤median vs. >median[ɬ])	0.944 (0.643-1.386)	0.903 (0.578-1.411)	1.114 (0.516-2.404)
Number of PAH treatments (one, two or three)	0.938 (0.705-1.248)	0.880 (0.631-1.227)	1.380 (0.678-2.809)
Number of Other treatments - chronic (0 to >8)	1.171 (1.033-1.328)	1.118 (0.969-1.290)	1.430 (1.074-1.905)
Number of Other treatments – temporary (0 to >9)	0.945 (0.847-1.055)	0.970 (0.857-1.098)	0.867 (0.678-1.109)

PAH=pulmonary arterial hypertension, CTEPH=chronic thromboembolic pulmonary hypertension, *360 kSEK, [ɬ]163 kSEK

Table 5. Other concomitant treatment at time of study. Data presented as n (%).

	All	**PAH**	**CTEPH**
	n=571	**n=384**	**n=187**
Chronic treatment (≥3 filled prescriptions/year)			
Angiotensin converting enzyme inhibitors	108 (19)	81 (21)	27 (14)
Angiotensin-receptor blockers	101 (18)	65 (17)	36 (19)
Beta-blocker	226 (40)	156 (41)	70 (37)
Calcium channel blocker	138 (24)	106 (28)	32 (17)
Anti-arrhythmia drugs	82 (14)	61 (16)	21 (11)
Statins	174 (30)	123 (32)	51 (27)
Diuretics	380 (66)	267 (70)	113 (60)
Antidiabetics	80 (14)	67 (17)	13 (7)
Thyroid replacement hormones	88 (15)	69 (18)	19 (10)
Number of patients that filled prescriptions for chronic treatments (≥3/year)			
0	83 (15)	45 (12)	38 (20)
1	103 (18)	58 (15)	45 (24)
2	114 (20)	78 (20)	36 (19)
3	117 (20)	86 (22)	31 (16)
4	75 (13)	54 (14)	21 (11)
5	51 (9)	42 (11)	9 (5)
≥6	29 (5)	21 (6)	8 (5)
Temporary treatment (≥1 filled prescriptions/year)			
Drugs for anaemia	146 (26)	107 (28)	39 (21)
Antibiotics	384 (67)	275 (72)	109 (58)
Antihistamines	101 (18)	68 (18)	33 (18)
Anti-viral drugs	51 (9)	44 (11)	7 (4)
Asthma – oral therapy	12 (2)	7 (2)	5 (3)
Asthma – inhaler therapy	171 (30)	119 (31)	52 (28)
Anti-diarrheal drugs	79 (14)	62 (16)	17 (9)
Anti-emetics	61 (11)	52 (14)	9 (5)
Anti-acid drugs	47 (8)	41 (11)	6 (3)
Proton pump inhibitors	294 (51)	219 (57)	75 (40)

Laxatives	204 (36)	143 (37)	61 (32)
Antifungal – oral therapy	2 (<1)	2 (1)	0
Antifungal – cutaneous/solution	191 (33)	142 (37)	49 (26)
Steroids – oral therapy	177 (31)	132 (34)	45 (24)
Number of patients that filled prescriptions for temporary treatments (≥1/year)			
0	56 (10)	30 (8)	26 (14)
1	79 (14)	43 (11)	36 (19)
2	100 (17)	64 (17)	36 (19)
3	73 (13)	45 (12)	28 (15)
4	92 (16)	69 (18)	23 (12)
≥5	172 (30)	133 (35)	39 (21)

PAH=pulmonary arterial hypertension, CTEPH=chronic thromboembolic pulmonary hypertensi