Characteristics and survival of adult Swedish PAH and CTEPH patients 2000–2014

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ABSTRACT

Objectives: The Swedish Pulmonary Arterial Hypertension Register (SPAHR) is an open continuous register, including pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) patients from 2000 and onwards. We hereby launch the first data from SPAHR, defining baseline characteristics and survival of Swedish PAH and CTEPH patients.

Design: Incident PAH and CTEPH patients 2008–2014 from all seven Swedish PAH-centres were specifically reviewed.

Results: There were 457 PAH (median age: 67 years, 64% female) and 183 CTEPH (median age: 70 years, 50% female) patients, whereof 77 and 81%, respectively, were in functional class III–IV at diagnosis. Systemic hypertension, diabetes, ischaemic heart disease and atrial fibrillation were common comorbidities, particularly in those >65 years. One-, 3- and 5-year survival was 85%, 71% and 59% for PAH patients. Corresponding numbers for CTEPH patients with versus without pulmonary endarterectomy were 96%, 89% and 86% versus 91%, 75% and 69%, respectively. In 2014, the incidence of IPAH/HAPAH, associated PAH and CTEPH was 5, 3 and 2 per million inhabitants and year, and the prevalence was 25, 24 and 19 per million inhabitants.

Conclusion: The majority of the PAH and CTEPH patients were diagnosed at age >65 years, in functional class III–IV, and exhibiting several comorbidities. PAH survival in SPAHR was similar to other registers.

ARTICLE HISTORY

Received 13 December 2015
Revised 20 April 2016
Accepted 22 April 2016
Published online 2 June 2016

KEYWORDS

Incident; prevalent; pulmonary hypertension; survival

Introduction

Clinical research registries have been fundamental in defining the natural history and outcome of diseases related to underlying mechanisms, presentation at diagnosis and response to treatment strategies. Registries have also been important in characterising patient populations and developing risk stratification tools.[1] This is evident in pulmonary arterial hypertension (PAH), where an early register showed a median survival of only 1–2.8 years for untreated PAH patients from diagnosis, depending on the underlying cause.[2] PAH is characterised by pulmonary vasoconstriction and remodeling, the latter including medial hypertrophy, intimal proliferation and fibrosis, adventitial thickening, in situ thrombosis and complex lesions. These changes lead to elevated pulmonary vascular resistance, right ventricular failure and eventually death.[3]

Pulmonary hypertension (PH) includes a broad spectrum of diseases, diagnosed by right heart catheterisation and categorised into five groups and a number of subgroups,[3] where treatment and outcome vary.[1] In 2013, an extensive review including 11 major PH/PAH registers [1,4–21] from six countries was published.[1] Ten registers presented PAH populations, as a whole or as selected subgroups, and one register included chronic thromboembolic pulmonary hypertension (CTEPH) besides PAH.[19] The number of participating centres in each register ranged from 1 to 55 and the
number of patients from 72 to 3515.\[1\] The registers varied with respect to prospective or retrospective design, the inclusion of prevalent and/or incident cases and the time period of inclusion. Furthermore, most register reports did not include patient comorbidities, a factor of growing importance considering the increased age at the time of diagnosis.

The Swedish Pulmonary Arterial Hypertension Register (SPAHR) constitutes an open continuous register initiated in 2008 that includes patients with PAH or CTEPH from 2000 and onwards (Appendix). For the first time, in an era of changing demographic patterns and the initiation of new PAH therapies, we report baseline characteristics, comorbidities and survival of prevalent and incident Swedish PAH and CTEPH patients from 2000 to 2014, but with a focus on the incident cases from 2008 to 2014.

Materials and methods

Study subjects and ethical consideration

The patients were locally informed about their participation in SPAHR, including clinical follow-up, and had the right to refuse participation. SPAHR was approved by the National Board of Health and Welfare and the Swedish Data Inspection. The study was approved by the local ethics board in Lund (Dnr 2014/92) and adhered to the Declaration of Helsinki.

Study design and methods

The Swedish Pulmonary Arterial Hypertension Register and recruiting PAH centres

SPAHR constitutes an open continuous register with the intention to register all Swedish patients with PAH (Group 1), including idiopathic/hereditary (IPAH/HPAH) and associated PAH (APAH), or with CTEPH (Group 4). Registration of PAH and CTEPH patients in SPAHR began January 2008, with the aim to retrospectively include those that were alive in the year of 2000, or diagnosed afterwards. The main objective of the present report was to describe baseline characteristics, comorbidities and survival of the adult Swedish PAH and CTEPH patients, with a focus on the incident population from 2008 to 2014. Data from the whole population, e.g. prevalent and incident cases from 2000 to 2014, are reported in the online supplement (Supplementary Tables I and II).

All Swedish PAH-centres located at the University hospitals in Gothenburg, Linköping, Lund, Stockholm, Umeå, Uppsala and Örebro have been including patients in SPAHR since the start. Swedish PAH-centres, in addition, to evaluate and treat patients with PAH, are also responsible for the investigation and treatment of CTEPH patients. The PAH-centres therefore refer the completed evaluation of their CTEPH patients, including pulmonary angiography, for operability assessment, to specialised centres in pulmonary endarterectomy (PEA), such as Karolinska University hospital in Stockholm, Sweden, and Skejby hospital in Århus, Denmark.

Each PAH centre was responsible for allocating their patients to the correct PH group. Pulmonary function test and computer tomography were clinically used to rule out PH due to lung disease (PH group 3). Echocardiography along with invasive pulmonary artery wedge pressure (PAWP) from right heart catheterisation was additionally clinically used to rule out PH due to left heart disease (PH group 2). Validation of the data entered in the register was performed by on-site monitoring by an independent monitor where missing data and erroneous values were checked against original medical journal source data. The monitoring met all predefined criteria.

The national coverage was calculated with the support of the National Board of Health and Welfare. It was estimated that in 2014 approximately 85% of all patients in Sweden with a PAH diagnosis on PAH-targeted therapy had been included in SPAHR. The lack of full completeness may partly be due to registration in the Swedish national register for patients with grown-up congenital heart disease.

Diagnosis and demographic data in SPAHR

Baseline in the register was defined as the date of the right heart catheterisation that established the PH diagnosis. Pre-capillary PH was defined at rest by a mean pulmonary arterial pressure (MPAP) ≥ 25 mmHg, a PAWP ≤ 15 mmHg, at a normal or reduced cardiac output, according to the Dana Point Classification.\[3\] Vasoreactivity test by NO-inhalation at baseline had been registered in 89% of the incident IPAH/HPAH patients.

Data from clinical investigations at the time of diagnosis and follow-up visits have been entered at each PAH-centre. Beside haemodynamic evaluations, these investigations include demographics, comorbidities, World Health Organization Functional Class (FC), 6-min walk test and blood biochemistry (e.g. NT-proBNP). Electrocardiography, echocardiography, pulmonary function test, pulmonary ventilation/perfusion scintigraphy, pulmonary angiography and high-resolution computer tomography may also have been entered when locally feasible. In 2010, the patient reported outcome measurements (Cambridge Pulmonary Hypertension Outcome Review, CAMPHOR) were added.

Analysis

To reflect the adult incident population, aged 18 or older, patients diagnosed with PAH (PH group 1) or CTEPH (PH group 4), from 1 January 2008, through 31 December 2014, were included in the treatment and survival analysis. Moreover, adult patients alive anytime between 1 January 2000 and 31 December 2007, were included in a separate cohort survival analysis. The combined prevalent and incident population 2000–2014 is described in the Supplementary Tables I and II. Baseline characteristics, comorbidities and treatment allocations are presented as medians with interquartile ranges (IQR) and as proportions with 95% confidence intervals (CI). Decimals were rounded off to the nearest whole numbers. National population data
from Statistics Sweden (in Swedish, Statistiska Centralbyrå, SCB, http://www.statistikdatabasen.scb.se) were used for calculation of prevalence and incidence rates. Data in the survival analysis were censored at death, transplantation, change of baseline diagnosis or loss to follow-up, or 31 December 2014, whatever came first. Survival stratified by diagnosis and by cohort years are presented as Kaplan–Meier survival plots with Log-Rank tests for overall comparisons. For comparison of outcomes, univariate and multivariable Cox regression analyses, adjusted for age and sex were used. Hazard ratios with 95% CI are presented as (HR [95% CI]). A p value <0.05 was considered statistically significant. SPSS version 23.0 (Armonk, NY) was used for statistical computation.

Results

Demographic data

Combined prevalent and incident population 2000–2014

On 31 December 2014, SPAHR included 697 patients with PAH and 247 patients with CTEPH, registered since 1 January 2000, whereof 392 and 153 were alive, respectively (Supplementary Tables I).

Incident population 2008 through 2014

The number of incident patients 2008–2014 (Table 1) with PAH or CTEPH, respectively, were 457 and 183, respectively, whereof 301 and 130, respectively, were alive, 31 December 2014. Baseline diagnosis for the incident population was divided even between IPAH/HPAH of 35% and APAH of 36%, whereas 29% were diagnosed with CTEPH (Figure 1A). In 2014, the proportions had changed such that 50%, 29% and 21% were diagnosed with IPAH/HPAH, APAH and CTEPH (Figure 1B), respectively. The age distribution for the incident PAH and CTEPH patients, divided by gender are shown in Figure 2.

In 2014, the prevalence of IPAH/HPAH, APAH and CTEPH were 25, 24 and 19 per million inhabitants, respectively, whereas the corresponding incidence were 5, 3 and 2 per million inhabitants and year, respectively.

Clinical variables at diagnosis

Combined prevalent and incident population 2000–2014

The median age at baseline, for the combined population of PAH patients 2000–2014, was 63 years, 66% were females and 80% in functional class III–IV (Supplementary Tables I). The median age at baseline for the CTEPH patients was 68

Table 1. Baseline characteristics of the incident patients with PAH, its subgroups, as well as CTEPH, registered in SPAHR from 1 January 2008 to 31 December 2014.

| Group 1 PAH | IPAH/HPAH | APAH-CTD | APAH-CHD | APAH-others | Group 4 CTEPH |
|------------|-----------|----------|----------|-------------|--------------|
| n = 457    | n = 227   | n = 140  | n = 61   | n = 29      | n = 183      |
| Age (year) | 67 (22)   | 69 (21)  | 68 (11)  | 43 (31)     | 54 (12)      | 70 (14)      |
| Female gender (%) | 64        | 55       | 78       | 69          | 52           | 50           |
| BMI (kg/m²) | 25 (6)    | 26 (6)   | 25 (5)   | 23 (7)      | 25 (6)       | 25 (6)       |
| FC (I/II/III/IV; %) | 2/21/69/9 | 1/167/3 | 1/20/68/9 | 1/20/67/12 | 8/32/55/5   | 0/41/59/0   |
| 6MWD (m)   | 280 (224) | 255 (210) | 279 (210) | 325 (296)  | 410 (94)    | 345 (198)   |
| SBP (mmHg) | 130 (30)  | 131 (33) | 131 (29) | 126 (19)   | 120 (22)    | 139 (28)    |
| DBP (mmHg) | 74 (18)   | 74 (20)  | 74 (15)  | 72 (21)    | 74 (21)     | 78 (15)     |
| NT-proBNP (ng/l) | 1370 (2842) | 1720 (2801) | 1451 (3092) | 626 (2391) | 318 (1211) | 1430 (3095) |
| MRAP (mmHg) | 7 (6)     | 7 (7)    | 6 (7)    | 7 (6)      | 6 (6)       | 7 (7)       |
| MPAP (mmHg) | 45 (16)  | 47 (14)  | 39 (16)  | 63 (40)    | 45 (15)     | 46 (17)     |
| PAWP (mmHg) | 8 (5)    | 8 (6)    | 8 (6)    | 10 (5)     | 7 (6)       | 10 (6)      |
| CI (l/min/m²) | 2.4 (1)  | 2.2 (1)  | 2.5 (1)  | 2.9 (1)    | 2.2 (1)     | 2.2 (1)     |
| PVR (WU)   | 8.7 (6)   | 9.3 (5)  | 7.0 (5)  | 9.9 (8)    | 8.1 (4)     | 8.5 (5)     |
| SvO₂ (%)   | 62 (14)   | 61 (12)  | 64 (15)  | 71 (12)    | 64 (11)     | 60 (11)     |
| SaO₂ (%)   | 92 (7)    | 91 (7)   | 93 (6)   | 92 (9)     | 93 (7)      | 92 (7)      |

Data are presented as a median and interquartile range (IQR).

BMI: body mass index; FC: World Health Organization Functional Class; 6MWD: 6-min walk distance; SBP: systolic blood pressure; DBP: diastolic blood pressure; NT-proBNP: N-terminal prohormone brain natriuretic peptide; MRAP: mean right atrial pressure; MPAP: mean pulmonary arterial pressure; PAWP: pulmonary artery wedge pressure; CI: cardiac index; PVR: pulmonary vascular resistance; SvO₂: oxygenation saturation from mixed venous blood; SaO₂: oxygenation saturation from arterial blood; PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: hereditary PAH; APAH: associated PAH; CHD: congenital heart disease; CTD: connective tissue disease; CTEPH: chronic thromboembolic pulmonary hypertension.

Figure 1. Distribution of incident patients with PAH or CTEPH diagnosis. The patients diagnosed (A) from 1 January 2008 to 31 December 2014 and (B) in 2014.
years, 49% were females and 82% in functional class III–IV (Supplementary Table I).

**Incident population 2008–2014**

The median age at baseline, for the incident population 2008–2014, was 67 years, 64% were females and 77% were in functional class III–IV (Table 1). The median age of the CTEPH patients at baseline was 70 years, 50% were females and 81% in functional class III–IV (Table 1). Both the PAH and CTEPH patients showed exercise limitations as measured by 6-min walk distance and increased levels of NT-proBNP. Baseline haemodynamic profiles were similar in patients with IPAH/HPAH, 58% had hypertension, 31% diabetes, 26% ischaemic heart disease and 23% atrial fibrillation (Table 2). The corresponding numbers for CTEPH patients >65 years, in the incident population 2008–2014, were 46% hypertension, 6% diabetes, 16% ischaemic heart disease and 14% atrial fibrillation (Table 2). Notably, in patients >65 years with APAH-CHD, in the incident population 2008–2014, as many as 50% had atrial fibrillation and 20% a history of stroke.

**Comorbidities at diagnosis**

The comorbidities increased with age for both PAH and CTEPH patients, both in the combined prevalent and incident population 2000–2014 (Supplementary Table II), as well as in the incident population 2008–2014 (Table 2). Among the incident patients, 2008–2014, >65 years with IPAH/HPAH, 58% had hypertension, 31% diabetes, 26% ischaemic heart disease and 23% atrial fibrillation (Table 2). The corresponding numbers for CTEPH patients >65 years, in the incident population 2008–2014, were 46% hypertension, 6% diabetes, 16% ischaemic heart disease and 14% atrial fibrillation (Table 2). Notably, in patients >65 years with APAH-CHD, in the incident population 2008–2014, as many as 50% had atrial fibrillation and 20% a history of stroke.

**Survival**

**Survival for the incident population 2008–2014**

Survival curves for PAH subgroups and CTEPH are shown in Figure 3. Between 1 January 2008, and 31 December 2014,
132 out of 457 incident PAH and 39 out of 183 incident CTEPH patients died. Three hundred and one PAH and 130 CTEPH patients were alive at the end of 2014. The remaining 38 patients were censored due to lung transplantation (n = 15), change of diagnosis (n = 12) or other reasons (n = 11).

In patients with a baseline diagnosis from 2008 to 2014 (Figure 3), the 1-, 3- and 5-year survival were 85%, 71% and 59%, respectively, for the PAH patients and 93%, 80% and 74%, respectively, for the CTEPH patients. Altogether, 60 of the 183 CTEPH patients underwent PEA. The 1-, 3- and 5-year survival were 96%, 89% and 86%, respectively, for the CTEPH patients that underwent PEA, and 91%, 75% and 69%, respectively, for the CTEPH patients without PEA (Figure 3).

Mean survival time for IPAH/HPAH, APAH-CTD, APAH-CHD and APAH-others were 4.7, 4.3, 5.8 and 5.1 years (Log-Rank, p = 0.013), respectively (Figure 3). The mean survival times for CTEPH patients with versus without PEA were 6.2 versus 5.2 years (Log-Rank, p = 0.015), respectively (Figure 3). In the univariate analyses, APAH-CHD patients had a better survival compared to IPAH/HPAH (0.42 [0.21–0.82]). The survival point estimates for APAH-others versus IPAH/HPAH was 0.41 [0.15–1.13] and for APAH-CTD versus IPAH/HPAH was 1.23 [0.86–1.77]. After adjustment for age and sex, none of the PAH groups differed in survival. CTEPH patients who had undergone PEA had a better survival compared to those without PEA (0.36 [0.15–0.85]), although attenuated after adjustments for age and sex (0.51 [0.20–1.29]).

Survival appeared better for the cohort diagnosed 2000–2007 compared to the cohort diagnosed 2008–2014 (Log-Rank, p = 0.028) (Supplementary Figure 1), reflecting survival bias of prevalent versus incident cases of PAH (0.75 [0.58–0.97]). There was, however, no difference between the cohorts after adjustment for sex and age (1.0 [0.78–1.32]).
Discussion

The Swedish PAH Register SPAHR include incident and prevalent patients with PAH or CTEPH from 2000 and onwards, and is here presented for the first time, with a focus on the incident population from 2008 to 2014. To the best of our knowledge, this represents the first multicentre PAH and CTEPH register study in Scandinavia. All Swedish PAH centres, located to the seven Swedish University hospitals, report to SPAHR. Thus, the vast majority of patients with PAH-specific therapy in Sweden have been included in the analysis. This allows a description of a contemporary real-life Swedish patient population, including baseline characteristics, comorbidities and initial treatments, as well as survival.

In line with other registers [1], the present report shows an improved survival compared to historical data of untreated IPAH patients,[2] with a mean survival for the incident IPAH/HPAH and APAH-CTD populations of 4.7 and 4.3 years, respectively. This improvement is attributed to new treatments and treatment strategies as well as an increased awareness of PAH and its phenotypes. Survival is, however, still severely impaired, which may be explained by diagnosis late in the disease and patients being old at the time of diagnosis, thus exhibiting more comorbidities. In addition, the response to PAH therapy among older patients may differ compared to the younger population.[1,14] Among the PAH subgroups, APAH-CHD showed the best and APAH-CTD the worst survival. Similar results have previously been found in a local report from Southern Sweden [22] and in studies emphasising the devastating outcome in patients with connective tissue disease.[15] Our data further support the concept of survival bias with regards to prevalent and incident cases of PAH [9], however, the difference disappeared when the cohorts were adjusted for age and sex.

PAH has for long been considered a disease that predominantly affect young to middle age women, but recent reports suggest a different scenario. The majority of the PAH patients in the present report were 60 years or older at the time of diagnosis and it was only below the age of 70 that more women than men were diagnosed. This was reflected both in those living with the disease and those newly diagnosed. The present report complement findings from registries in the United Kingdom and Ireland [20], suggesting two subtypes of patients, older with worse functional capacity and more comorbidities and younger with more severe haemodynamic impairment, but a better response to PAH treatment and better survival. The COMPERA register indeed also showed IPAH more frequently diagnosed in elderly patients with a more balanced gender ratio, exhibiting other clinical features and lower response to medical therapy and a higher age-adjusted mortality.[23] The REVEAL register from the USA also reported IPAH patients as older than earlier believed, however, the mean age of 49 was lower than in SPAHR and the female predominance was maintained.[12,17,18] Our SPAHR evaluation represents an up-to-date, multicentre Swedish register study that additionally also complement the Swiss PH register, reporting a mean age at diagnosis of 57 and 63 years for PAH and CTEPH, respectively [24], as well as the Danish single centre study where incident PAH patients exhibited a mean age of 50 years at diagnosis between January 2000 and March 2012.[26] These studies [24,25] did, however, not describe patient comorbidities to the same extent as our SPAHR investigation. The older age at PAH diagnosis in SPAHR, with a median age at diagnosis of 67 years is also supported by the study of incident cases in Germany 2014, exhibiting a mean age at diagnosis of 64 years.[26] Finally, the CTEPH population in SPAHR showed a predominance of diagnosis at 60 years or older and those who underwent PEA exhibited a better survival than those who were not operated. Even though these patient cohorts differ, depending on the location of the vascular disease, or with regards to comorbidities and age, it emphasises the importance of referring CTEPH patients for operability assessment.

The high prevalence of IPAH/HPAH patients in Sweden of 25 per million inhabitants exceeded those reported from the Scottish (9 per million), French (5.9 per million) and Spanish (4.6 per million) registers.[1,6,8–10,19] In addition, the incidence of 5 per million inhabitants and year was also higher than in most other reports of 1–2.6 per million inhabitants and year.[1,6,8–10,19] However, a recent report from Germany in 2014, shows similar numbers as in SPAHR, with a prevalence of 25.9 per million inhabitants and an incidence of 3.9 per million inhabitants and year.[26] Interestingly, both SPAHR and the German cohort share the high age at diagnosis.[26] This might reflect an increased awareness of PAH as well as an improved screening process of patients with dyspnoea. However, it might also indicate that present haemodynamic criteria may not be sufficient discriminators for PAH in the elderly population. New criteria for PAH diagnosis that take into account the numbers and combination of comorbidities could therefore potentially be of importance in future definitions of PAH, even when a diastolic dysfunction is not found. Systemic hypertension, diabetes, atrial fibrillation and ischaemic heart disease were common among the PAH patients >65 years in the present report. While it is not surprising that an elderly population have more comorbidities than younger individuals, it possibly highlights the importance of accounting for the relation between comorbidities and age at the time of diagnosis. Thus, it is possible, that even though the elderly fulfilled the Dana Point haemodynamic criteria for PAH, the comorbidities may have had an additional influence, even though not detected by echocardiography, or by an elevated PAWP.

In conclusion, the present evaluation of the Swedish incident PAH and CTEPH patients from 2008 to 2014, as well as the combined population of prevalent and incident cases from 2000 to 2014, represents an up-to-date uniform national coverage of these patient cohorts, including baseline characteristics, comorbidities and survival, in a Scandinavian country in the modern treatment era. The diversity and increase of comorbidities with older de novo PAH patients at diagnosis, predominantly diagnosed late in FC III–IV, are highlighted. Though survival has improved, as new PAH-targeted treatments and treatment strategies have evolved, survival remains poor and differ between PAH subgroups.
Identifying individual treatment strategies, as well as new markers for earlier diagnosis and detection of treatment response, are therefore essential. In addition, the influence of comorbidities on present criteria for the diagnosis of PAH and response to PAH-targeted treatment need further attention in future studies, especially in the elderly group.

Acknowledgements
The efforts of all SPAHR registrars at each PAH centre are greatly acknowledged. We also acknowledge Uppsala Clinical Research Centre (UCR) for developing and administering the platform for SPAHR.

Disclosure statement
The financial supporters and foundations above have no role in data collection, analysis or interpretation and have no right in disapproving of the manuscript. The authors alone are responsible for the content and writing of the paper. Göran Rådegran reports unrestricted research grants from Anna-Lisa and Sven-Erik Lundgren's, Maggie Stephens's, ALF's, Skåne University Hospital's Foundations and Actelion Pharmaceuticals Sweden AB, during conduct of the study; and personal lecture fees from Actelion Pharmaceuticals Sweden AB, Bayer Health Care, Glaxo-SmithKline, NordicInfu Care AB and Sandoz/Novartis outside the submitted work. He is, and has been, primary- or co-investigator in; clinical PAH trials for Glaxo-SmithKline, Actelion Pharmaceuticals Sweden AB, Pfizer, Bayer Health Care and United Therapeutics; and in clinical heart transplantation immunosuppression trials for Novartis; and has also been involved in research advisory boards for Actelion Pharmaceuticals Sweden AB, Bayer Health Care, Eli-Lilly and Sanofi Aventis. Babaro Kjellström reports no conflicts of interest. Björn Ekmechag has received honoraria for serving as a consultant and/or speaker from Actelion, AstraZeneca, Bayer Schering, Lilly, NordicInfu Care, Pfizer and United Therapeutics. He has also received funds for a member of staff and/or funds for research from Actelion and NordicInfu Care; and he has conducted clinical trials supported by Actelion, Bayer Schering, GE HealthCare, Glaxo-SmithKline, Lilly, Novartis, Pfizer and United Therapeutics. Flemming Larsen reports participation in research advisory boards for Actelion Pharmaceuticals Sweden AB and Schering AG (Bayer Health Care). Bengt Rundqvist reports no conflicts of interest related to the present study. Kjell Jansson has been primary- or co-investigator in clinical PAH trials for Glaxo-SmithKline, Actelion Pharmaceuticals Sweden AB, Pfizer and Bayer Health Care; and in clinical heart transplantation immunosuppression trials for Novartis. Stefan Söderberg reports research grants from the Swedish Heart and Lung Foundation, the Västerbotten County Council (ALF and Visare Norr), and Actelion Pharmaceutical Sweden AB and Pfizer, during the conduct of the study; as well as personal lecture fees from Actelion and Bayer Health Care outside the submitted work. He is, and has been, primary- or co-investigator in clinical PAH trials for Glaxo-SmithKline, Actelion Pharmaceuticals Sweden AB, Pfizer and Bayer Health Care, and has been involved in research advisory boards for Actelion Pharmaceuticals Sweden AB, Bayer Health Care and Eli-Lilly. The authors above have written the manuscript on behalf of SveFPH and SPAHR. The present manuscript preparation group also included the persons below: Sofia Berg Blomquist reports no conflicts of interest. Carola Gustafsson reports no conflicts of interest. Roger Wikström has received lecture fees from Actelion Pharmaceuticals Sweden and Glaxo-SmithKline outside the submitted work. Kent Wall, reports no conflicts of interest. Gerhard Rådegran has received lecture fees from Actelion Pharmaceuticals, Bayer Health Care, GSK, Orion Pharma and Pfizer. He is, and has been, primary- and co-investigator for clinical trials for Glaxo-SmithKline, Actelion Pharmaceuticals Sweden AB, Pfizer, Bayer Health Care, United Therapeutics and Novartis. Maria Willehdson reports personal lecture fees from Actelion and Glaxo-SmithKline.

Funding information
In the phase of initiating SPAHR, financial support was given by Actelion Pharmaceuticals Sweden AB, Bayer Health Care, Eli Lilly Sweden, Glaxo-SmithKline, NordicInfu Care and Pfizer. Since 2011, SPAHR has qualified as a national quality register and financial support is given by SALAR (SKL). The writing of the manuscript was enabled through “ALF” foundations and individual grants.

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**Appendix**

*The Swedish Association of Pulmonary Hypertension* (in Swedish, Svensk Förening för Pulmonell Hypertension, SveFPfH) was initiated in 2007 to survey PAH and CTEPH patients, as well as to support education, research and clinical development in the area of PH in Sweden. SPAHR and its steering committee were subsequently initiated in 2008 by SveFPfH and have since evolved as a national quality register, where the Swedish Association of Local Authorities and Regions (SALAR; in Swedish, Sveriges Kommuner och Landsting, SKL) has the economic responsibility. The SPAHR steering committee meets regularly for data validation, quality control as well as continuous register management and update.

SPAHR, furthermore, provide national data on PAH and CTEPH diagnosis as well as treatment distribution. Regional differences in diagnosis and treatment may be studied. Such evaluation is supplied on a yearly basis to all Swedish PAH centres, which is of value to provide a basis for equal national treatment no matter the regional location of diagnosis, age and gender (http://www.ucr.uu.se/spahr/index.php/arsrapporter).