Study Report P2-C1-003

DARWIN EU® - Co-prescribing of endothelin receptor antagonists (ERAs) and phosphodiesterate-5 inhibitors (PDE-5is) in pulmonary arterial hypertension (PAH)

24/10/2023

Version 1.0

03/04/2024

Version 2.1

1 Contents

DOCUMENT HISTORY

Version	Date	Description
V1.0	24/10/2023	First version for EMA review
V2.1	03/04/2024	Final version

Study Title	DARWIN EU® Co-prescribing of endothelin receptor antagonists (ERAs) and phosphodiesterate-5 inhibitors (PDE-5is) in pulmonary arterial hypertension (PAH)
Study Report Version identifier	2.1
Dates Study Report updates	20/11/2023
EU PAS register number	EUPAS106052
Active substance	**Drugs** / **Class** / **ATC code** Ambrisentan / Endothelin receptor antagonist / C02KX02 Bosentan / Endothelin receptor antagonist / C02KX01 Macitentan / Endothelin receptor antagonist / C02KX04 Sitaxentan / Endothelin receptor antagonist / C02KX03 Sildenafil / Phosphodiesterate-5 inhibitors / G04BE03 Tadalafil / Phosphodiesterate-5 inhibitors / G04BE08
Medicinal product	Endothelin receptor antagonists and Phosphodiesterate-5 inhibitors for the treatment of pulmonary arterial hypertension.
Research question and objectives	Research question What is the utilization pattern of endothelin receptor antagonists (ERAs) and phosphodiesterase-5 inhibitors (PDE-5is) in pulmonary arterial hypertension (PAH)? Study objectives Objective 1: To estimate the proportion of patients with newly diagnosed pulmonary arterial hypertension (PAH) who initiate treatment with endothelin receptor antagonists (ERAs) or phosphodiesterase-5 inhibitors (PDE-5is), either as monotherapy or in combination, during the period from January 1, 2012, to December 31, 2022. Objective 2: To estimate the duration of prescription for ERAs and PDE-5is in patients with newly diagnosed PAH between January 1, 2012, and December 31, 2022. Objective 3: To describe the prescription patterns and sequences of ERAs and PDE-5is in patients with newly diagnosed PAH between January 1, 2012, and December 31,

	2022. Objective 4: To estimate the proportion of patients with newly diagnosed PAH who experience specific events of interest, namely cardiovascular hospitalization, all-cause hospitalization, and death, after initiating treatment with ERAs and PDE-5is between January 1, 2012, and December 31, 2022.
Country(-ies) of study	Estonia, France, Germany, and the United Kingdom.
Author	Johnmary T. Arinze (j.arinze@darwin-eu.org) Katia Verhamme (k.verhamme@darwin-eu.org)

1. DESCRIPTION OF STUDY TEAM

Study team Role	Names	Organisation
Study Project Managers/Principal Investigators	Johnmary T. Arinze Katia M.C. Verhamme	Erasmus MC Erasmus MC
Epidemiologists	Johnmary T. Arinze Katia M.C. Verhamme	Erasmus MC Erasmus MC
Clinical Domain Expert	Johnmary T. Arinze	Erasmus MC
Data Analyst/programmer	Cesar Barboza	Erasmus MC
Data Partner*	**Names**	**Organisation – Database**
Local Study Coordinator/Data Analyst	James Brash Romain Griffier Marek Oja Hezekiah Omulo Antonella Delmestri	IQVIA Germany University of Bordeaux - CHUBX University of Tartu - Estonian Biobank University of Oxford – CPRD data University of Oxford – CPRD data

*Data partners' role is only to execute code at their data source, review and approve their results. These people do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for these people is not needed.

2. DATA SOURCES

This study was conducted using routinely collected data from 4 databases in 4 European countries (3 EU countries and United Kingdom). All databases were previously mapped to the OMOP CDM.

1. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. Estonian Biobank (EBB), Estonia
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

Detailed information on data source is described below.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
France	CHUBX	Database covers hospital care setting where PAH treatment may be initiated	Secondary care (in and outpatients)	EHR	2.1 million	05/05/2023
UK	CPRD GOLD	Database covers primary care setting where ERAs/ PDE-5is prescriptions are issued. Also research on PAH has already been conducted using CPRD data.[1]	Primary care	EHR	3 million	20/03/2023
Estonia	EBB	Database covers information from primary care and secondary care setting (insurance claims, digital prescriptions) where ERAs/ PDE-5is prescriptions are issued.	Biobank	Claims data	0.2 million	20/03/2023
Germany	IQVIA DA Germany	Database covers primary care and secondary care setting (outpatient specialist care) where ERAs/ PDE-5is prescriptions are issued. Research on PH (including PAH) has been conducted using IQVIA DA Germany data.[1]	Primary care and outpatient specialist care	EHR	8.5 million	13/03/2023

PAH = Pulmonary arterial hypertension, CHUBX= Bordeaux University Hospital, UK = United Kingdom, CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, DA = Disease Analyzer, EHR = Electronic Heath record. Exposure is based on prescription data.

[1] https://doi.org/10.1002/pul2.12000

3. ABSTRACT

Title

DARWIN EU® - Co-prescribing of endothelin receptor antagonists (ERAs) and phosphodiesterate-5 inhibitors (PDE-5is) in pulmonary arterial hypertension (PAH)

Rationale and Background

Pulmonary Arterial Hypertension (PAH) is a rare type of pulmonary hypertension characterized by increased mean pulmonary arterial pressure. PAH can be idiopathic, heritable, drug-induced, or secondary to other chronic diseases such as HIV infection, congenital heart diseases, portal hypertension. Median survival is about 7 years from the time of diagnostic catheterisation. The therapeutic management differs based on type and severity and usually involves a mono or combination therapy from the following agents: Endothelin receptor antagonists (ERAs), and Phosphodiesterase-5 inhibitors (PDE5-is). There is interest in understanding how these therapies are used in clinical practice to contextualise assessments of potential future development programs in this indication.

Research question and Objectives

Research question:

To understand how PAH is treated in clinical practice. Specific objectives of this study are listed below.

Study objectives:

(1) To estimate proportions of patients with newly diagnosed pulmonary arterial hypertension (PAH) who initiate treatment with endothelin receptor antagonists (ERAs) or phosphodiesterase-5 inhibitors (PDE-5is), either as monotherapy or in combination, during the period from January 1, 2012, to December 31, 2022.

(2) To estimate the duration of prescription for ERAs and PDE-5is in patients with newly diagnosed PAH between January 1, 2012, and December 31, 2022.

(3) To describe the prescription patterns and sequences of ERAs and PDE-5is in patients with newly diagnosed PAH between January 1, 2012, and December 31, 2022.

(4) To estimate the proportion of patients with newly diagnosed PAH who experience specific events of interest, namely cardiovascular hospitalization, all-cause hospitalization, and death, after initiating treatment with ERAs and PDE-5is between January 1, 2012, and December 31, 2022.

Research Methods

Study design

Retrospective cohort study in patients with newly diagnosed PAH.

Population

Patient-level characterization – Disease epidemiology study: The patient-level characterization included patients with newly diagnosed PAH between January 1, 2012, and December 31, 2022 (or the latest available date if earlier), with at least 1 year of data availability prior to their diagnosis, and no record of being

diagnosed with PAH in the previous year. To investigate treatment patterns, a minimum follow-up time of 30 days were applied to capture PAH treatment (objective 1), and treatment sequences (objective 3).

Patient-level drug utilization: New users of ERAs/PDE-5is in patients newly diagnosed with PAH in the period between January 1, 2012, and December 31, 2022 (or latest date available), with at least 1 year of data visibility prior to index date, and no use of the respective ERAs/PDE-5is in the previous 1 year, were included for patient-level drug utilisation analyses. Therefore, children aged <1 year were excluded.

Variables

Drug of interest: Drugs of interest were identified through RxNorm drug codes.

1. Endothelin receptor antagonists: Ambrisentan, Bosentan, Macitentan, and Sitaxentan.
2. Phosphodiesterate-5 inhibitors: Sildenafil and Tadalafil.

Condition of interest: PAH was identified through SNOMED disease codes.

Outcomes of interest: Study outcomes were identified based on the presence of events of cardiovascular hospitalisation, all-cause hospitalisation, and death.

Data sources

1. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. Estonian Biobank (EBB), Estonia
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

Sample size

Sample size was not calculated for this descriptive study, as our primary focus was to examine the characteristics and treatment patterns of all incident PAH patients, irrespective of the sample size.

Data analyses

The number and % of patients receiving each of a pre-specified list of PAH treatments (objective 1) and treatment combinations (objectives 1 and 3) were described at index date, 1 to 30, 1 to 90, and 1 to 365 days post index date. A treatment pattern analysis was conducted to describe the sequence of prescribing of the specific ERAs/PDE-5is following diagnosis. Index date was the date of diagnosis of PAH. Sunburst plots and Sankey diagrams were used to describe treatment patterns and sequences over time (objective 3).

Large-scale patient-level characterisation was conducted to describe age and sex at time of PAH diagnosis and for 365 to index date. The medical history included clinical symptoms and signs (chest pain, dyspnea, fatigue, syncope), comorbidities (obesity, congenital heart disease, heart failure, pulmonary embolism, chronic obstructive pulmonary disease, pulmonary fibrosis, obstructive sleep apnea and chronic kidney disease), and important factors possibly related to PAH diagnosis (idiopathic, heritable, connective tissue disease, corrected congenital shunts, drug or toxin induced PAH, and others). We also reported the proportion of patients with outcomes of interest for 1-, 3-, and 5-years post index date (objective 4).

Patient-level ERAs/PDE-5is use: Patient-level features were characterized, and the treatment duration of prescriptions of the respective drugs of interest was estimated. Index date was the date of the first prescription of the specific ERAs/ PDE-5is for each person. Treatment duration was estimated for the first treatment era and the minimum, p25, median, p75, and maximum was provided.

For all analyses a minimum cell count of 5 was used when reporting results, with any smaller counts obscured.

Results

During the study period, 9,474 patients newly diagnosed with PAH were identified namely 75 (0.8%) in EBB, 2,061 (21.8%) in CHUBX, 3,378 (35.7%) in CPRD and 3,960 (41.8%) in IQVIA DA Germany. In all databases, patients with PAH were mainly diagnosed at the age of 65 years or above (49-81%) and the proportion of females (51-65%) was slightly higher than the proportion of males. Comorbidity was high in all databases and consisted of heart failure (19.3 - 66.7%), COPD (17.6 - 22.7%), connective tissue disorder (14.0 - 64.0%), diabetes mellitus (17.3-24.4%), systemic hypertension (28.0 - 64.9%), and ischemic heart disease (14.8 - 45.3%). Use of drugs known to be associated with PAH was low or non-existing except for selective serotonin reuptake inhibitors (SSRIs) (1.4-14.7% in the year prior to the index date (i.e. date of diagnosis of PAH)) and tramadol (1.1-10.5%). Use of concomitant drugs was the lowest for IQVIA DA Germany.

Amongst patients with newly diagnosed PAH and with at least 30 days of follow-up post-PAH diagnosis, there were 117 (3.3%)) individuals treated in IQVIA DA Germany, 210 (6.4%) in CPRD GOLD, 335 (19.1%) in CHUBX, and 15 (20.8%) in EBB.

The use of PAH-targeted drugs varied across different databases during the observation period. The predominant therapeutic category of PAH-targeted drugs used as index treatment was PDE-5is (mainly sildenafil), with prescription rates of 1.3% in both CPRD GOLD and IQVIA DA Germany, 2.1% in CHUBX, and relatively higher rate in EBB (6.9%). Unlike the other databases, ERAs were the most common therapeutic category of PAH-targeted drugs used as index treatment in CHUBX (2.5%), predominately bosentan (2.3%). Conversely, ERAs were not used as index treatment in CPRD GOLD and EBB. In IQVIA DA Germany, ERAs were sparingly prescribed (0.4%).

The post-index treatment with PDE-5is demonstrated increasing prescription rates within the year following PAH diagnosis across all databases namely 13.1% for CHUBX, 4.7% for CPRD Gold, 20.8% EBB and 2.2% for IQVIA DA Germany at 365 days post-index. A similar trend was observed for ERAs, although the increase in their utilization demonstrated a more moderate pattern, notably in CHUBX. In general, the use of combination therapy, which entails the prescription of both ERAs and PDE-5is, remained minimal, with rates remaining below 1% in all databases and throughout various time intervals.

The median duration of ERAs was one day in CHUBX and CPRD GOLD but 30 days in EBB and IQVIA DA Germany. One specific ERA, ambrisentan, was usually prescribed for one day in all databases, except for IQVIA DA Germany, where it extended to 30 days. Bosentan was prescribed for much longer duration, with median duration of 28 days in both CPRD GOLD and IQVIA DA Germany, 30 days in EBB, and typically one day in CHUBX. The median duration of the first prescription of PDE-5is was 30 days in both EBB and IQVIA DA Germany, 28 days in CPRD GOLD. Notably,in CHUBX, the median duration was just one day. Overall, the median duration of PAH-related therapy ranged from 1 to 189 days across all databases. In IQVIA DA Germany, patients consistently underwent more extended treatment periods with ERAs compared to PDE-5is.Treatment sequences varied between databases. In primary care settings, a predominant treatment sequence emerged where the majority of patients initiated treatment with monotherapy (CPRD - 89%, and IQVIA DA Germany - 81%). Notably, monotherapy in these instances predominantly involved the use of PDE-5is, accounting for 83% in CPRD and 73% in IQVIA DA Germany. Conversely, a distinct shift in treatment initiation was observed in hospital settings, where more than half of the patients initiated treatment with combination therapy (CHUBX - 52%). The predominant combinations in this context included bosentan-tadalafil (21%), followed by ambrisentan-tadalafil (16%) and bosentan-sildenafil (9%).

With regard to hospitalisation as outcome, percentages were 100% for CHUBX which is a hospital database and thus all patients were inherently hospitalised. Estonian Biobank database (EBB) had a high hospitalisation

rate of 86.7% at index date, and notably, within one year following PAH diagnosis, all patients in EBB had experienced hospitalisation. A parallel pattern was discerned in cardiovascular hospitalization, with both CHUBX and EBB starting at high rates at index (99.7% and 93.3%, respectively) and reaching 100% in both databases within one-year post-index. No hospitalisation rates could be provided for IQVIA DA Germany and CPRD Gold.

The trend of mortality rates over the years showed distinct patterns among the databases. EBB had a relatively stable mortality rate of less than 1%. In contrast, CHUBX and CPRD GOLD demonstrated a progressively increasing mortality rate (14.3% mortality at three years post-index for CHUBX and 31.9% for CPRD Gold).

Discussion

This study provides a comprehensive analysis of 9,474 patients diagnosed with incident pulmonary arterial hypertension (PAH) between 2012 and 2022 in four European countries, offering insights into real-world settings. The patient population was predominantly comprised of older adults with a slight female preponderance, and common symptoms preceding PAH diagnosis included dyspnea and chest pain. Furthermore, over 75% of the participants had pre-existing cardiovascular disease. Pre-index exposure to certain medications was notable, with selective serotonin reuptake inhibitors and tramadol showing high usage. Importantly, the utilization of PAH-specific therapies varied across databases, with CHUBX having the highest prescription rate before the index date.

In terms of PAH treatments, PDE-5 inhibitors, particularly sildenafil, were the primary choice as index treatment for newly diagnosed PAH patients. The study revealed an increasing trend in the prescription of PDE-5 inhibitors and ERAs in the year leading up to the PAH diagnosis. Monotherapy with PDE-5 inhibitors was the predominant treatment strategy for PAH, with less frequent use of combination therapy, usually involving bosentan. Notably, sildenafil was frequently used as a standalone treatment, while tadalafil was preferred in combination therapy, often in conjunction with bosentan or ambrisentan for dual therapy. The duration of the first prescriptions for these therapies varied, with combination therapy lasting the longest in IQVIA DA Germany and other PAH-specific therapies having extended durations in the Estonian Biobank database.

The findings on PAH treatment outcomes and prognosis revealed that hospitalization was universal within a year of PAH diagnosis in CHUBX (a hospital data source) and EBB (the other data source for which hospitalisation rates could be provided), with high cardiovascular hospitalization rates observed at the index date across the databases. Importantly, a pattern of progressively increasing mortality rates, doubling between one and three years post-index, was observed in CHUBX and CPRD GOLD, indicating the importance of further research to improve the outcomes and prognosis for PAH patients.

4. LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
CHUBX	Bordeaux University Hospital
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DOI	Declaration Of Interests
DUS	Drug Utilization Study
EBB	Estonian Biobank
EGCUT	Estonian Genome Center at the University of Tartu
EHR	Electronic Healthcare Records
EMA	European Medicines Agency
ERAs	Endothelin receptor antagonists
GP	General Practitioner
ID	Index date
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
PAH	Pulmonary arterial hypertension
PDE-5is	Phosphodiesterase-5 inhibitors
SNOMED	Systematized Nomenclature of Medicine

5. AMENDMENTS AND UPDATES

Number	Date	Section of study report	Amendment or update	Reason
1	20/11/2023	Abstract, Results, and Discussion	Updated	Additional analysis was performed to address the duration of therapy
V2.1	03/04/2024	Document History	Updated	Edit header and comments table 21

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Draft Study Protocol	23rd June 2023	23rd June 2023
Final Study Protocol	21st July 2023	24th August 2023
Creation of Analytical code	August 2023	August - September 2023
Execution of Analytical Code on the data	September 2023	September - October 2023
Interim Study Report (if applicable)	Not applicable	Not applicable
Draft Study Report	13th October 2023	24th October 2023
Final Study Report	17th November 2023	20th November 2023
Draft Manuscript (if agreed on)		
Final Manuscript (if agreed on)		

7. RATIONALE AND BACKGROUND

Pulmonary arterial hypertension (PAH) is a rare, chronic, and severe medical condition characterized by elevated pulmonary arterial pressure and vascular resistance(1). Its global prevalence ranges from 0.4 to 1.4 cases per 100,000 persons, with significant regional variations.(2) Idiopathic PAH is more common in North America and Europe, while acquired PAH is prevalent in Africa and Asia. PAH primarily affects females, especially in idiopathic and heritable cases, and can occur across all age groups(2). Patients with PAH experience progressive dyspnea, fatigue, exercise intolerance, impaired functional capacity, and reduced quality of life, imposing a substantial clinical burden.(3) Complications such as right heart failure, arrhythmias, and thromboembolic events further contribute to the disease burden.(4) The median survival time from the time of diagnosis is approximately 6 – 9 years.(5, 6)

The aetiology of PAH is multifactorial and involves various risk factors and underlying conditions, including genetic mutations, exposure to drugs or toxins, connective tissue diseases, congenital heart defects, HIV infection, portal hypertension, and chronic liver disease.(7, 8) The pathophysiology of PAH involves complex mechanisms such as vasoconstriction, vascular remodelling, inflammation, and endothelial dysfunction. Endothelial injury and dysfunction lead to impaired production of vasodilators and increased secretion of vasoconstrictors, while pulmonary vascular smooth muscle cells undergo hypertrophy and proliferation, resulting in elevated vascular resistance.(1, 8)

Pharmacotherapy plays a critical role in managing PAH, aiming to improve symptoms, exercise capacity, and hemodynamics.(9) Commonly used medications include endothelin receptor antagonists (ERAs) like ambrisentan, bosentan, macitentan, sitaxentan, as well as phosphodiesterase-5 inhibitors (PDE-5Is) such as

sildenafil and tadalafil. Prostacyclin analogues and calcium channel blockers have also demonstrated positive therapeutic outcomes.(8, 10) The choice of therapy depends on the type and severity of PAH, and both monotherapy and combination therapy approaches are employed to achieve optimal outcomes.(11)

Despite therapeutic advancements, the prognosis of PAH remains poor, highlighting the need to understand how specific therapies are utilized in clinical practice.(11) A comprehensive evaluation of current pharmacological approaches in managing PAH could provide valuable insights for future development programs in this indication.

This study aims to provide valuable insights into the prescription patterns of ERAs/ PDE-5Is, user characteristics, and clinical outcomes among patients with pulmonary arterial hypertension in Europe. This will offer crucial context for effective post-marketing surveillance and evaluation of the real-world benefit-risk profiles of these medications in managing pulmonary arterial hypertension.

8. RESEARCH QUESTION AND OBJECTIVES

To understand how PAH is treated in clinical practice. The specific objectives of this study are listed below.

Study objectives:

(1) To estimate proportions of patients with newly diagnosed pulmonary arterial hypertension (PAH) who initiate treatment with endothelin receptor antagonists (ERAs) or phosphodiesterase-5 inhibitors (PDE-5is), either as monotherapy or in combination, during the period from January 1, 2012, to December 31, 2022.

(2) To estimate the duration of prescription for ERAs and PDE-5is in patients with newly diagnosed PAH between January 1, 2012, and December 31, 2022.

(3) To describe the prescription patterns and sequences of ERAs and PDE-5is in patients with newly diagnosed PAH between January 1, 2012, and December 31, 2022.

(4) To estimate the proportion of patients with newly diagnosed PAH who experience specific events of interest, namely cardiovascular hospitalization, all-cause hospitalization, and death, after initiating treatment with ERAs and PDE-5is between January 1, 2012, and December 31, 2022.

All results were reported by country/database, overall and stratified by age and sex when possible.

Table 1: Primary and secondary research questions and objective

Objective:	To describe the patient characteristics, treatment patterns of ERAs/PDE-5is, and the proportion of patients with newly diagnosed PAH who experience the events of interest (cardiovascular hospitalization, all-cause hospitalization, and death) after initiating treatment with ERAs and PDE-5is, stratified by country/database.
Hypothesis:	Not applicable
Population ***(mention key inclusion-exclusion criteria):***	All patients with a first diagnosis of PAH identified in the database between January 1, 2012, and December 31, 2022 (or the latest available date if earlier), with at least 1 year of data availability prior to their diagnosis, and no record of being diagnosed with PAH

	in the previous year. Therefore, children aged <1 year will be excluded.
Exposure:	1. Endothelin receptor antagonists: Ambrisentan, Bosentan, Macitentan, and Sitaxentan. 2. Phosphodiesterate-5 inhibitors: Sildenafil and Tadalafil.
Comparator:	None
Outcome:	Cardiovascular hospitalisation, all-cause hospitalisation, and death
Time *(when follow up begins and ends):*	Follow-up started on the date of treatment initiation (index date) until the earliest of loss to follow-up, end of data availability or death, or end of study period (31st December 2022).
Setting:	Inpatient and outpatient setting using data from the following data sources: CPRD GOLD (UK), IQVIA DA (Germany), CHUBX (France), and Estonian Biobank (Estonia).
Main measure of effect:	Proportions, patient level drug utilisation to assess duration of use of the first exposure episode of the respective drugs of interest.

9. RESEARCH METHODS

9.1 Study Type and Study Design

This study is a **patient-level characterization and Drug Utilization Study (DUS)** categorized as 'off-the-shelf', as outlined in the DARWIN EU® Complete Catalogue of Standard Data Analyses. It is a retrospective cohort study including all patients with incident PAH and a new drug user cohort study to characterise patient-level ERAs/ PDE-5is utilisation (treatment duration and patient characteristics of patients exposed to the drug of interest).

9.2 Study Setting and Data Sources

This study was conducted using routinely collected data from 4 databases in 4 European countries (3 EU countries and United Kingdom). All databases were previously mapped to the OMOP CDM.

Data sources:

1. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. Estonian Biobank (EBB), Estonia
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

For this study, we have carefully selected four databases from the ten databases available for DARWIN EU® in 2022. The selection process was based on two primary quality criteria: data reliability and relevance to the research question at hand. Importantly, pulmonary hypertension has been previously studied in CPRD GOLD (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6066824/), IQVIA DA Germany (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9235867/),

These selected databases demonstrate substantial record counts for both PAH and the drugs of interest. Moreover, they offer a good geographical spread, ensuring representation from diverse regions of Europe.

These selected databases met the requirements for conducting a patient-level drug utilization study as well as a patient-level characterization study, enabling us to explore PAH treatment and perform large-scale characterizations. Additionally, by including databases from different settings, we effectively captured both inpatient and outpatient drug prescriptions for PAH, enhancing the comprehensiveness of our findings. We obtained complete treatment data, which is necessary for objectives 1, 2, and 3, from all selected databases. Additionally, outcome data, required for objective 4, was available in most databases. However, it is important to note that the IQVIA DA Germany database had no information regarding the date of death.

Information on the data source(s) with a justification for their choice in terms of ability to capture the relevant data is described in **Table 2.**

Table 2: Description of data sources

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
France	CHUBX	Database covers hospital care setting where PAH treatment may be initiated	Secondary care (in and outpatients)	EHR	2.1 million	05/05/2023
UK	CPRD GOLD	Database covers primary care setting where ERAs/ PDE-5is prescriptions are issued. Also research on PAH has already been conducted using CPRD data.[1]	Primary care	EHR	3 million	20/03/2023
Estonia	EBB	Database covers information from primary care and secondary care setting (insurance claims, digital prescriptions) where ERAs/ PDE-5is prescriptions are issued.	Biobank	Claims data	0.2 million	20/03/2023
Germany	IQVIA DA Germany	Database covers primary care and secondary care setting (outpatient specialist care) where ERAs/ PDE-5is prescriptions are issued. Research on PH (including PAH) has been conducted using IQVIA DA Germany data.[2]	Primary care and outpatient specialist care	EHR	8.5 million	13/03/2023

PAH = Pulmonary arterial hypertension, CHUBX= Bordeaux University Hospital, UK = United Kingdom, CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, DA = Disease Analyzer, EHR = Electronic Heath record. Exposure is based on prescription data.

[2] https://doi.org/10.1002/pul2.12000

Bordeaux University Hospital (CHUBX), France

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records on more than 2 million patients with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures). The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and administrations), measurements (laboratory tests and vital signs) and dates of death (in or out-hospital death).(12)

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD(13) comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data are available for 20 million patients, including 3.2 million currently registered patients.

Access to CPRD GOLD data requires approval via the Research Data Governance Process. CPRD GOLD will be onboarded as Data Partner for DARWIN EU® in 2023.

Estonian Biobank – University of Tartu (Estonia)

The Estonian Biobank (EBB) is a population-based biobank of the Estonian Genome Center at the University of Tartu (EGCUT). Its cohort size is currently close to 200,000 participants (“gene donors” >= 18 years of age) which closely reflects the age, sex and geographical distribution of the Estonian adult population. Genomic GWAS analysis have been performed on all gene donors. The database also covers health insurance claims, digital prescriptions, discharge reports, information about incident cancer cases and causes of death from national sources for each donor.

IQVIA Disease Analyser (DA) Germany, Germany

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings.(14) Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

9.3 Study Period

The study period was from 01/01/2012 to 31/12/2022 or the end of available data in each of the data sources if earlier (see **Table 3** for more details).

9.4 Follow-up

Study participants were followed up from their date of first PAH diagnosis (i.e. index date) until the earliest of the following: 1) loss to follow-up, 2) 31/12/2022, 3) end of data availability, or 4) date of death.

For the Patient-level Utilisation of ERAs/ PDE-5is (i.e. to explore duration of use), participants were followed up from the day of therapy initiation, i.e. the date of the first prescription of the drugs of interest (index date), until the earliest of loss to follow-up, end of data availability, death, or end of continuous exposure.

Table 3: Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description (e.g., time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
All patients from the database eligible for the study and newly diagnosed with PAH	Patient present in the database during the study period (2012-2022) and with at least 1 year of valid database history, and no record PAH diagnosis in the previous year	Single	Incident	[-365]	IP and OP	n/a	n/a	PAH	n/a	n/a
All patients from the database eligible for the study – Analysis of incident use in patients with newly diagnosed PAH	Patient present in the database during the study period (2012-2022) and with at least 1 year of valid database history	Multiple	Incident	[-365]	IP and OP	n/a	n/a	Overall, substance	n/a	n/a

9.5 Study Population with in and exclusion criteria

The study cohort comprised all patients with newly diagnosed PAH present in the database during the study period (2012-2022) and with at least 365 days of data availability before the day they become eligible for study inclusion. The requirement of at least 365 days of data history was also applicable to children. Therefore, children aged <1year were excluded.

Given its complexity, rarity, and multifactorial nature, diagnosing PAH typically requires a comprehensive evaluation involving clinical assessment for signs/symptoms as well as various diagnostic procedures and tests. These may include electrocardiogram, chest radiography, pulmonary function tests, arterial blood gases, echocardiography, ventilation/perfusion lung scan, non-contrast and contrast-enhanced chest computed tomography examinations, digital subtraction angiography, cardiac magnetic resonance imaging, blood tests, immunology, abdominal ultrasound, cardiopulmonary exercise testing, vasoreactivity assessment, fluid challenge, and right heart catheterization. Right heart catheterization is considered the gold standard for diagnosing and classifying PAH. It provides valuable information about pulmonary arterial pressures and hemodynamic parameters.(15) In this study, cases were identified through medical records containing SNOMED (Systematized Nomenclature of Medicine) codes that indicate a diagnosis or condition of PAH. The OMOP CDM relies on the SNOMED as the standardized vocabulary for diagnosis codes, ensuring uniform and consistent classification of various conditions.

Additional eligibility criteria were implemented, requiring patients to have a minimum follow-up time of 30 days to capture important aspects of PAH treatment (objective 1), and treatment sequences (objective 3).

Table 4. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics /validation	Source for algorithm
Incident PAH	Patients with newly diagnosed PAH during the study period, that is individuals without a diagnosis of PAH 1 year prior.	After	1 year	IP, OP, OT	SNOMED	First	All study participants	N/A	N/A
Prior database history of 1 year (objectives 1, 2, 3 and 4)	Study participants were required to have a year of prior history observed before contributing observation time	After	1 year	IP, OP, OT	N/A	N/A	All patients with incident PAH	N/A	N/A
Minimum follow-up (objectives 1, 3)	Study participants were required to have at least a minimum follow-up time of 30 days.	After	30 days	IP, OP, OT	N/A	N/A	All patients with incident PAH	N/A	N/A
Minimum potential follow-up time (objective 4)	Only patients with a diagnosis of PAH (index date) occurring one year prior to end of data availability in the database were included to allow sufficient follow-up time to capture treatment and outcomes	After	1 year	IP, OP, OT	N/A	N/A	All patients with incident PAH	N/A	N/A

[1] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

9.6 Variables

9.6.1 Exposures

For this study, the exposure of interest is prescription (during study period) of Ambrisentan, Bosentan, Macitentan, Sildenafil, Sitaxentan, and Tadalafil.

Exposure were grouped at drug substance level and assessed as monotherapy or combination therapy through the treatment pattern analysis (see 8.8.3).

This list of the drugs of interests (with respective ATC code) is described in **Table 5**. Respective RxNorm codes (at ingredient level) are provided in appendix 1 – Table 1. Further exposure details are described in **Table 6**.

Table 5: Exposure of interest

Drugs	Class	ATC code
Ambrisentan	Endothelin receptor antagonist	C02KX02
Bosentan	Endothelin receptor antagonist	C02KX01
Macitentan	Endothelin receptor antagonist	C02KX04
Sitaxentan	Endothelin receptor antagonist	C02KX03
Sildenafil	Phosphodiesterate-5 inhibitors	G04BE03
Tadalafil	Phosphodiesterate-5 inhibitors	G04BE08

Table 6: Exposure details

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting	Code Type	Diagnosis position	Applied to study populations:	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Overall ERAs/ PDE-5is, substance, strength, route	Preliminary code lists provided in Table 6 (and Table 1 of Appendix 1)	– 1 year	Calendar year	Biobank, primary and secondary care	RxNorm	N/A	All patients with newly diagnosed PAH present in the database during the study period	Previous ERAs/ PDE-5is use	N/A	N/A

9.6.2 Outcome/s

This study examined the following four primary outcomes of interest. (for operational definition see **Table 7**)

- Initiation of treatment for PAH

Initiation of treatments was assessed within a window of 30, 90, and/or 365 days following diagnosis. In relation to the first outcome, a predefined list of PAH treatments were compiled to address Objectives 1, 2, and 3. PAH treatments included Ambrisentan, Bosentan, Macitentan, Sitaxentan, Sildenafil and Tadalafil as listed in Table 5.

- All-cause hospitalisation

All-cause hospitalization was determined by examining medical records with visit codes indicating inpatient visits or hospital admissions after the date of therapy initiation, i.e. the date of the first prescription of the drugs of interest (i.e. index date) following diagnosis of PAH. This was assessed in a window of 1, 3, and 5 years following treatment initiation.

- Cardiovascular hospitalization

Cardiovascular hospitalisation was identified through a SNOMED code of cardiovascular disease occurring within 7 days prior to admission, during hospitalization, or within 7 days following discharge. Cardiovascular hospitalisation was assessed in a window of 1, 3, and 5 years following treatment initiation after new diagnosis of PAH.

- Death

Overall death rate in patients with newly diagnosed PAH was identified based on the registered date of death and reported in a window of 1, 3, and 5 years following treatment initiation after new diagnosis of PAH.

Table 7. Operational Definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position	Applied to study populations:	Measurement characteristics/validation	Source of algorithm
PAH treatments	Preliminary code lists provided in Table 6	Yes	Counts and %	365 days as incident use only	IP and OP care	RxNorm	N/A	All patients with incident PAH	N/A	N/A
Hospitalization (All-cause/ cardiovascular)	Based on visit type within OMOP-CDM	Yes	%	N/A	IP and OP care	Date of inpatient visit	N/A	All patients with incident PAH	N/A	N/A
Death rate	Based on date of death	Yes	%	N/A	IP and OP care	Date of death	N/A	All patients with incident PAH	N/A	N/A

[1] IP = inpatient, OP = outpatient, n/a = not applicable

9.6.3 Other covariates, including confounders, effect modifiers and other variables (where relevant)

Age at PAH diagnosis was described and grouped as follows: 1-17; 18-44; 45-64; 65 years and over.

The sex (male/ female) of patients with incident PAH were identified.

All co-morbidities and concomitant-medications recorded prior (-30 to 1 day before ID, and-365 to 1 day before ID) was used for large-scale patient characterisation, identified as concept/code and descendants. The list of pre-specified co-morbidities and co-medications included the following:

- PAH-associated Relevant Medical History: chest pain, dyspnoea, fatigue, syncope, obesity, heart failure, pulmonary embolism, asthma, COPD, idiopathic pulmonary fibrosis, obstructive sleep apnoea, chronic kidney disease, connective tissue disorder, Human Immunodeficiency Virus (HIV) infection, diabetes mellitus, and systemic hypertension.
- Medications Implicated in Drug-induced PAH: selective serotonin reuptake inhibitors (SSRI's), aminorex, fenfluramine, benfluorex, phenylpropanolamine, dexfenfluramine, tryptophan, lithium, interferon, sofosbuvir, dasatinib, Nilotinib, ponatinib, carfilzomib, ruxolitinib, buprenorphine, tramadol, thalidomide, paclitaxel, bleomycin, cyclophosphamide, mitomycin, phentermine, mazindol.

Concept IDs of these drugs and conditions have been added to the appendix I – table 2. These codes (with descendant codes) were further reviewed prior to the analysis.

The operational definition of these covariates is described in **table 8**.

Table 8: Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Co-morbidities	Large-scale patient-level characterisation with regard to underlying comorbidities	Counts	At index date (ID), for 30 to 1 day before ID, for 365 to 31 days before ID, at any time before ID	OP, IP, OT	SNOMED	N/A	N/A	N/A	N/A
Concomitant medication#	Large-scale patient-level characterisation with regard to use of concomitant drugs	Counts	At index date (ID), for 30 to 1 day before ID, for 365 to 31 days before ID	OP, IP, OT	RxNorm	N/A	N/A	N/A	N/A

[1] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

ERAs/ PDE-5is are the exposures of interest and are not considered as concomitant medication

9.7 Study size

No sample size has been calculated as this is a descriptive Disease Epidemiology and Drug Utilization Study where we are interested in the characteristics of all incident PAH cases and their treatments, regardless of sample size.

9.8 Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed and quality control checks were performed. After all the tests were passed (see section 11 Quality Control), the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations were performed, and additional fine tuning of the code base was needed.

The study results of all data sources were checked after which they were made available to the team nd the Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

9.9 Statistical Methods

Table 9. Description of Study Types and Type of analysis

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Disease epidemiology - Patient-level characterisation	Off-the-shelf (C1)	• Large-scale characterisation • Patient-level characteristics • Standard care description

9.9.1 Patient privacy protection

Cell suppression was applied as required by databases to protect people's privacy. Cell counts < 5 were masked.

9.9.2 Statistical model specification and assumptions of the analytical approach considered

R-packages

We used the R packages "PatientProfiles" for the patient-level characterization of demographics and clinical characteristics, "TreatmentPatterns" for the patient-level characterisation of treatments, and "DrugUtilisation" for the estimation of treatment duration.

Patient-level characterisation

Large-scale patient-level characterisation was conducted (objective 1). Age and sex at time of PAH diagnosis were described. Medical history and concomitant medication (excluding PAH treatments) were assessed for anytime –and up to 365 days before index date and for 30 to 1 day before index date, and at index date. These time windows were defined based on the options currently available in the standard analytical tools

which was used in this project. Co-variates presented in a summary baseline characteristics table were pre-defined as described in section 9.6.3.
The number and % of patients with all-cause and cardiovascular hospitalization were estimated from the date of first prescription of the drugs of interests to the date of first hospital admission or inpatient care due to any cause, and additionally for any cardiovascular condition (objective 4). The number of individuals who died (objective 4) was calculated from the date of first prescription of the drugs of interests to death due to any cause and reported as proportion of patients who died. This analysis was conducted only for databases with complete information on death.

Patient-level drug utilisation

To characterise treatment of PAH, the number and % of patients receiving each of a pre-specified list of PAH treatments (objective 2, as listed in section 9.6.2) were described at index date, 1 to 30, 1 to 90, and 1 to 365 days post index date. The index date was the date of the PAH diagnosis for each patient. A treatment pattern analysis was conducted to describe how use of PAH-specific drugs evolved over time. Additionally, sunburst plots and Sankey diagrams were used to describe treatment patterns over time (objective 3).

For all analyses n and % was reported. A minimum cell counts of 5 was used when reporting results, with any smaller counts reported as "<5". All analyses were reported by country/database, overall and stratified by age and sex when possible (minimum cell count reached).

9.9.3 Missing data

Although the reasons for missing data during follow-up were not explicitly outline in this study, the number of participants available for each part of the data analysis/ results were consistently mentioned to give insights into the degree of attrition.

9.10 Evidence synthesis

Results from analyses described in section 9.9 were presented separately for each database and no meta-analysis of results was conducted.

9.11 Deviations from the protocol

None.

10. DATA MANAGEMENT

10.1 Data management

All databases are mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study was written in R. Each data partner executed the study code against their database containing patient-level data and then returned the results set which will only contained aggregated data. The results from each of the contributing data sites was then be combined in tables and figures for the study report.

10.2 Data storage and protection

For this study, participants from various EU member states processed personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were ran, which generated non-identifiable aggregate summary results.

The output files are stored in the DARWIN Digital Research Environment (DRE). These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

11. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts:

validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining PAH, a systematic search of possible codes for inclusion was previously identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP common data model to find potentially relevant codes. The codes returned were then reviewed by two clinical epidemiologists to consider their relevance. This work was done previously as part of study the DARWIN EU® study EUPAS105033. In addition, the CohortDiagnostics R package (https://github.com/OHDSI/CohortDiagnostics) was used to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This allowed for a consideration of the validity of the study cohort of patients with PAH in each of the databases, and informed decisions around whether multiple definitions were required.

The study code was based on three R packages currently developed to (1) characterise demographic and clinical characteristics, (2) characterise treatment patterns and treatment duration, and (3) estimate hospitalization and overall survival using the OMOP CDM. These packages included numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package are publicly available via GitHub at https://github.com/darwin-eu-studies/P2C1003PulmonaryHypertension/.

12. RESULTS

The results of this study can be accessed through a web application, the "shiny app," available at https://data-dev.darwin-eu.org/content/457bb408-83db-4014-a9a9-aaef7a050310 .

The specific number of individuals contributing to each study objective within the respective databases is outlined in **Table 10**. Overall, the participating databases collectively included 9,474 patients diagnosed with PAH between 2012 and 2022. The distribution of the study population across the databases is as follows: CHUBX (n=2,061, 21.75%), CPRD (n=3,378, 35.65%), EBB (n=75, 0.79%), and IQVIA DA Germany (n=3,960, 41.81%).

Table 10. Study attrition of individuals included in each cohort per database.

	CHUBX France	CPRD GOLD UK	EBB Estonia	IQVIA DA Germany
Database population between 01/01/2012 and 31/12/2022	2,371,156	17,216,081	209,457	41,974,403
with PAH diagnosis, n (%)	2,061 (0.09)	3,378 (0.02)	75 (0.04)	3,960 (0.01)

12.1. Large-scale characterisation of newly diagnosed patients with PAH

12.1.1 Patient Demographics

Table 11 provides an overview of the demographic characteristics of the study population (patients with incident PAH) according to the included databases.

Table 11. Demographic characteristics of patients with incident PAH per database

Demographics	CHUBX	CPRD GOLD	EBB	IQVIA DA Germany
Number of patients	2,061	3,378	75	3,960
Prior observation (years), Median (IQR)	8 (4 – 11)	13 (10 – 17)	12 (10 – 15)	6 (3 – 9)
Follow-up duration (days), Median (IQR)	589 (108 – 1,663)	724 (268 – 1,499)	1,595 (591 – 2,766)	750 (256 – 1,443)
Age at index (years), Median (IQR)	72 (61 – 82)	77 (68 – 83)	62 (44 – 74)	77 (68 – 82)
Age range (years)	1 – 102	1 – 101	15 – 93	1 – 96
Age group (years), n (%)				
• 1 to 17	31 (1.5)	28 (0.8)	<5 (NA)	38 (1.0)
• 18 to 44	136 (6.6)	120 (3.5)	19 (25.3)	97 (2.4)
• 45 to 64	464 (22.5)	500 (14.8)	18 (24.0)	601 (15.2)
• ≥ 65	1,430 (69.4)	2,730 (80.8)	37 (49.3)	3,224 (81.4)
Sex, n (%)				
• Female	1,048 (50.8)	1,963 (58.1)	49 (65.3)	2,138 (54.0)
• Male	1,013 (49.2)	1,415 (41.9)	26 (34.7)	1,820 (46.0)
• Missing	0 (0)	0 (0)	0 (0)	<5 (NA)

PAH – Pulmonary arterial hypertension. IQR – Interquartile range

This study comprised of 9,474 patients with newly diagnosed PAH from four distinct databases: CHUBX (n=2,061), CPRD GOLD (n=3,378), EBB (n=75), and IQVIA DA Germany (n=3,960). Each of these databases contributed unique subsets of the patient population, with discernible similarities and differences in baseline characteristics. Specifically, a substantial proportion of the study population were from IQVIA DA Germany (41.8%) CPRD GOLD (35.7%), and CHUBX (21.8%), while EBB constituted less than 1% of the total patient count. The patients included in this study had a range of median prior observation periods, spanning from 13 years in CPRD GOLD and 12 years in EBB to 8 years in CHUBX and 6 years in IQVIA DA Germany. There were varying durations of follow-up observed across the databases, with EBB (1,595 days) having the lengthiest median follow-up period, double that of IQVIA DA Germany (750 days) and CPRD GOLD (724 days), and almost three times that of CHUBX (589 days).

Age distribution within the study participants was notably diverse (1 to 102 years), prominently depicted in CHUBX (1-102 years), CPRD GOLD (1-101 years), and IQVIA DA Germany (1-96 years). In contrast, EBB had a narrower age range (15-93 years) compared to the other databases, perhaps due to the lower number of individuals in this data source. CHUBX (72 years), CPRD GOLD (77 years), and IQVIA DA Germany (77 years) had comparable median ages at the index and similar interquartile age ranges (61-82, 68-83, and 69-82, respectively). Conversely, EBB included relatively younger participants with a median age of 62 years and an interquartile range of 44-74 years. The most prevalent age group in the study was individuals aged 65 years and above, representing 49.3% to 81.4% of the total, while children (<18 years) comprised only 1% of the study population. Overall, the study population demonstrated a slight preponderance of females (50.8% - 65.3%), with EBB exhibiting the highest percentage of females (n=49, 65.3%) compared to the other databases: CPRD GOLD (n=1,963, 58.1%), IQVIA DA Germany (n=2,138, 54.0%), and CHUBX (1,048, 50.8%).

12.1.2 Prevalence of Pre-specified Co-morbidities

Table 12 presents the prevalence of pre-specified co-morbidities in the study population, categorized by the respective databases and time windows.

The most common symptoms observed in the study population one year prior to PAH diagnosis varied among the different databases. Dyspnoea was notably prevalent, with CPRD GOLD reporting 58.9%, CHUBX at 40.6%, and IQVIA DA Germany at 21.2%. Chest pain was another prevalent symptom, with CPRD GOLD at 26.3%, EBB at 13.3%, and CHUBX at 10.2%. Conversely, EBB and IQVIA DA Germany had the lowest prevalence of dyspnoea (<1%) and chest pain (4.9%), respectively. CPRD GOLD had the highest prevalence of fatigue (18.4%) and syncope (3.6%), while these symptoms were not observed in CHUBX, EBB, and IQVIA DA Germany.

Common co-morbidities, affecting more than 10% of PAH patients across all databases, included heart failure (ranging from 19.3% in CPRD GOLD to 66.7% in EBB), COPD (ranging from 17.6% in CHUBX to 22.7% in EBB), connective tissue disorder (ranging from 14.0% in IQVIA DA Germany to 64.0% in EBB), diabetes mellitus (ranging from 17.3% in EBB to 24.4% in IQVIA DA Germany), systemic hypertension (ranging from 28.0% in CPRD GOLD to 64.9% in IQVIA DA Germany), and ischemic heart disease (ranging from 14.8% in CHUBX to 45.3% in EBB). Remarkably, over three-quarters of the patient population had a prior diagnosis of cardiovascular disease (CHUBX at 75.6%, CPRD GOLD at 82.7%, EBB at 96.0%, and IQVIA DA Germany at 91.0%). Obesity was more prevalent in IQVIA DA Germany (19.7%) and EBB (17.3%) in contrast to CPRD GOLD (6.3%) and CHUBX (3.4%). Idiopathic pulmonary fibrosis and obstructive sleep apnoea were not observed in most databases, with a very low prevalence in EBB (0.6% and 1.6%, respectively). HIV was not observed in CPRD GOLD and EBB, with modest prevalence in IQVIA DA Germany (0.1%) and CHUBX (1.0%). Distinct patterns were observed in EBB. Particularly, EBB had the highest prevalence of asthma (29.3%) and pulmonary embolism (14.7%) in the study population. In contrast, asthma prevalence ranged from 3.9% in CHUBX to 9.7% in IQVIA DA Germany, while the prevalence of pulmonary embolism varied from 5.1% in IQVIA DA Germany to 6.2% in CPRD GOLD. Furthermore, the prevalence of chronic kidney disease was higher in CPRD GOLD (32.2%), CHUBX (15.8%), and IQVIA DA Germany (13.7%), compared to EBB (6.7%).

The prevalence of the predefined symptoms and co-morbidities varied considerably between the first year preceding the diagnosis of PAH and the time of diagnosis (at index date) within the same database. The most common conditions at PAH index date were dyspnoea (58.9% in both CHUBX and CPRD GOLD), heart failure (70.7% in EBB, 55.7% in CHUBX, and 50.9% in IQVIA DA Germany), and systemic hypertension (69.2% in IQVIA DA Germany, 62.9% in CHUBX, and 50.7% in EBB).

Table 12. Prevalence of pre-specified co-morbidities in patients with incident PAH by database and time window

Demographics (n=9,474)	CHUBX (n=2,061)		CPRD GOLD (n=3,378)		EBB (n=75)		IQVIA DA Germany (n=3,960)	
Prior to index date (days)	At index date	1 – 365	At index	1 – 365	At index	1 – 365	At index date	1 – 365
Chest pain	281 (13.6)	211 (10.2)	894 (26.3)	889 (26.3)	10 (13.3)	10 (13.3)	203 (5.1)	193 (4.9)
Dyspnoea	1,213 (58.9)	836 (40.6)	1,991 (58.9)	1,991 (58.9)	<5 (<1)	<5 (<1)	1,002 (25.3)	839 (21.2)
Fatigue	0 (0)	0 (0)	623 (18.4)	622 (18.4)	0 (0)	0 (0)	0 (0)	0 (0)
Syncope	0 (0)	0 (0)	125 (3.7)	123 (3.6)	0 (0)	0 (0)	0 (0)	0 (0)
Obesity	85 (4.1)	70 (3.4)	225 (6.7)	214 (6.3)	13 (17.3)	13 (17.3)	921 (23.3)	782 (19.7)
Heart failure	1,148 (55.7)	794 (38.5)	912 (26.3)	651 (19.3)	53 (70.7)	50 (66.7)	2,017 (50.9)	1,462 (36.9)
Pulmonary embolism	194 (9.4)	126 (6.1)	244 (7.2)	208 (6.2)	12 (16.0)	11 (14.7)	279 (7.0)	202 (5.1)
Asthma	102 (4.9)	81 (3.9)	330 (9.8)	324 (9.6)	22 (29.3)	22 (29.3)	415 (10.5)	386 (9.7)
COPD	521 (25.3)	363 (17.6)	764 (22.6)	706 (20.9)	18 (24.0)	17 (22.7)	989 (25.0)	877 (22.1)
Idiopathic pulmonary fibrosis	0 (0)	0 (0)	21 (0.6)	19 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)
Obstructive sleep apnoea	0 (0)	0 (0)	61 (1.8)	51 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)
Chronic kidney disease	436 (21.2)	326 (15.8)	1,096 (32.4)	1,089 (32.2)	5 (6.7)	5 (6.7)	821 (20.7)	542 (13.7)
Connective tissue disorder	542 (26.3)	433 (21.0)	1,267 (37.5)	1,242 (36.8)	48 (64.0)	48 (64.0)	579 (14.6)	553 (14.0)
HIV	26 (1.3)	21 (1.0)	<5 (<1.0)	0 (0)	0 (0)	0 (0)	5 (0.1)	5 (0.1)
Diabetes mellitus	550 (26.7)	452 (21.9)	635 (18.8)	629 (18.6)	13 (17.3)	13 (17.3)	1,044 (26.4)	966 (24.4)
Systemic hypertension	1,296 (62.9)	1,019 (49.4)	952 (28.2)	945 (28.0)	38 (50.7)	38 (50.7)	2,739 (69.2)	2,570 (64.9)
Ischemic heart disease	391 (19.0)	305 (14.8)	678 (20.1)	626 (18.5)	34 (45.3)	34 (45.3)	1,475 (37.2)	1,363 (34.4)
Cardiovascular disease	2,061 (100)	1,558 (75.6)	3,378 (100)	2,795 (82.7)	75 (100)	72 (96.0)	3,960 (100)	3,605 (91.0)

12.1.3 Use of Drugs Associated with PAH

Table 13 shows the use of drugs associated with PAH in the study population prior to index, according to the respective databases and time windows.

Most of the drugs associated with PAH were either not prescribed or sparingly used by the patient population across the databases. However, two notable exceptions were selective serotonin reuptake inhibitors (SSRIs) and tramadol, which showed relatively higher use. Prior to the index date, the use of SSRIs ranged from <1% to 24.0% in EBB, 1.0% to 2.4% in IQVIA DA Germany, 2.2% to 12.7% in CHUBX, and 11.5% to 26.4% in CPRD GOLD.

For tramadol, the proportions of users varied from <1% to 17.3% in EBB, 0.4% to 3.9% in IQVIA DA Germany, 2.3% to 28.7% in CHUBX, and 4.0% to 30.3% in CPRD GOLD in the first year leading up to the index date. At the index date, CPRD GOLD had the highest utilization of SSRIs at 9.6%, followed by CHUBX (1.8%), while IQVIA DA Germany and EBB had less than 1% SSRI users. Tramadol use was most prevalent in CHUBX (3.2%) and CPRD GOLD (2.9%), compared to IQVIA DA Germany (0.3%), and EBB (<1%).

12.1.4 Pre-index date use of PAH-targeted Drugs

Table 14 details the use of PAH-targeted drugs in the study population prior to index, according to the respective databases and time windows.

Unsurprisingly, there was minimal to no utilization of PAH-specific drugs among the patients included in the databases before the index date. Nevertheless, a low pre-index use of bosentan was evident in CPRD GOLD (below 1%), IQVIA DA Germany (0.2%), and CHUBX (ranging from 0.5% to 3.8%). The use of ambrisentan was similarly modest, ranging from below 1% in both EBB and IQVIA DA Germany to 1.4% in CHUBX. Likewise, the prescription of other PAH-specific drugs, including treprostinil, epoprostenol, iloprost, selexipag, and riociguat, remained relatively low across all databases, with prevalence under 1% in both EBB and IQVIA DA Germany, while reaching up to 2.1% in CHUBX.

The pre-index utilization of sildenafil showed notable differences across the databases, with higher rates in EBB (peaking at 8.0%) and CPRD GOLD (up to 6.6%) in comparison to CHUBX (reaching up to 2.7%) and IQVIA DA Germany (reaching up to 1.3%). In contrast, tadalafil was used by less than 5% of the study population prior to the index date, with utilization proportions ranging from less than 1% in EBB and 0.3% to 0.7% in IQVIA DA Germany to between less than 1% and 2.6% in CHUBX, and 0.2% to 2.8% in CPRD GOLD.

Table 13. Pre-index use of drugs associated with PAH in patients with incident PAH by database and time window.

Demographics (n=9,474)	CHUBX (2,061)				CPRD GOLD (n=3,378)				EBB (n=75)				IQVIA DA Germany (n=3,960)			
Prior to index date (days)	At index date	1 – 30	1 – 365	Any TP	At index date	1 – 30	1 – 365	Any TP	At index date	1 – 30	1 – 365	Any TP	At index date	1 – 30	1 – 365	Any TP
SSRIs	38 (1.8)	46 (2.2)	144 (7.0)	261 (12.7)	324 (9.6)	389 (11.5)	498 (14.7)	892 (26.4)	<5 (<1)	<5 (<1)	6 (8.0)	18 (24.0)	37 (0.9)	39 (1.0)	54 (1.4)	96 (2.4)
Aminorex	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fenfluramine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<5 (<1)
Benfluorex	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Phenylpropanolamine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<5 (<1)
Dexfenfluramine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tryptophan	0 (0)	0 (0)	0 (0)	0 (0)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<5 (<1)
Lithium	0 (0)	0 (0)	0 (0)	<5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Interferon	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sofosbuvir	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dasatinib	0 (0)	0 (0)	<5 (<1)	<5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nilotinib	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ponatinib	0 (0)	0 (0)	<5 (<1)	<5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Carfilzomib	0 (0)	<5 (<1)	<5 (<1)	<5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ruxolitinib	<5 (<1)	<5 (<1)	5 (0.2)	6 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Buprenorphine	5 (0.2)	<5 (<1)	8 (0.4)	13 (0.6)	40 (1.2)	48 (1.4)	65 (1.9)	167 (4.9)	0 (0)	0 (0)	0 (0)	0 (0)	5 (0.1)	6 (0.2)	8 (0.2)	22 (0.6)
Tramadol	66 (3.2)	48 (2.3)	216 (10.5)	591 (28.7)	98 (2.9)	135 (4.0)	265 (7.8)	1,022 (30.3)	<5 (<1)	<5 (<1)	6 (8.0)	13 (17.3)	11 (0.3)	16 (0.4)	45 (1.1)	156 (3.9)
Thalidomide	<5 (<1)	<5 (<1)	<5 (<1)	5 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Paclitaxel	0 (0)	0 (0)	0 (0)	<5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bleomycin	0 (0)	0 (0)	0 (0)	<5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cyclophosphamide	<5 (<1)	5 (0.2)	12 (0.6)	46 (2.2)	0 (0)	0 (0)	0 (0)	5 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (0.1)
Mitomycin	0 (0)	0 (0)	<5 (<1)	<5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Phentermine	0 (0)	0 (0)	<5 (<1)	<5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mazindol	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

TP= Any time prior

Table 14. Pre-index use of PAH-targeted pharmacotherapies by database and time window.

	CHUBX (n=2,061)			CPRD GOLD (3,378)			EBB (n=75)			IQVIA DA Germany (n=3,960)		
Prior to index date (days)	**1 – 30**	**1 – 365**	**Any TP**	**1 – 30**	**1 – 365**	**Any TP**	**1 – 30**	**1 – 365**	**Any TP**	**1 – 30**	**1 – 365**	**Any TP**
Ambrisentan	<5 (<1)	22 (1.1)	28 (1.4)	0 (0)	0 (0)	<5 (<1)	0 (0)	0 (0)	0 (0)	<5 (<1)	<5 (<1)	<5 (<1)
Bosentan	10 (0.5)	51 (2.5)	78 (3.8)	0 (0)	<5 (<1)	<5 (<1)	0 (0)	0 (0)	0 (0)	7 (0.2)	8 (0.2)	9 (0.2)
Macitentan	0 (0)	0 (0)	0 (0)	0 (0)	<5 (<1)	<5 (<1)	0 (0)	0 (0)	0 (0)	<5 (<1)	<5 (<1)	<5 (<1)
Sitaxentan	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sildenafil	14 (0.7)	40 (1.9)	56 (2.7)	39 (1.2)	71 (2.1)	224 (6.6)	<5 (<1)	<5 (<1)	6 (8.0)	19 (0.5)	29 (0.7)	52 (1.3)
Tadalafil	<5 (<1)	44 (2.1)	54 (2.6)	7 (0.2)	19 (0.6)	94 (2.8)	0 (0)	<5 (<1)	<5 (<1)	10 (0.3)	14 (0.4)	26 (0.7)
Other therapies	<5 (<1)	21 (1.0)	44 (2.1)	0 (0)	0 (0)	<5 (<1)	0 (0)	0 (0)	0 (0)	<5 (<1)	<5 (<1)	<5 (<1)
Other therapies include Treprostinil, Epoprostenol, Iloprost, Selexipag, and Riociguat. Any TP= Any Time Prior.												

12.2 Drug Utilisation Pattern in Newly Diagnosed Patients with PAH

12.2.1 Participants

Table 15 describes the demographics of study subjects with PAH and with at least 30 days of follow-up following their diagnosis of PAH.

In general, nearly 9 out of 10 study participants across all databases met the minimum 30-day follow-up criteria, with rates varying from 85.0% in CHUBX (n=1,751) and 90% in IQVIA DA Germany (n=3,566), to 96% in EBB (n=72) and 96.7% in CPRD GOLD (n=3,266). Importantly, the patient demographics were similar to those of the overall study population in each database.

Table 15. Demographic characteristics of the participants with 30 days minimum follow-up per database.

Demographics	CHUBX	CPRD GOLD	EBB	IQVIA DA Germany
Number of patients	2,061	3,378	75	3,960
Participants with 30 days minimum follow-up, n (%)	1,751 (85.0)	3,266 (96.7)	72 (96.0)	3,566 (90.0)
Age group (years), n (%)				
• 1 to 17	30 (1.7)	28 (0.9)	<5 (<1)	35 (1.0)
• 18 to 44	128 (7.3)	117 (3.6)	19 (26.4)	91 (2.6)
• 45 to 64	430 (24.6)	488 (14.9)	18 (25.0)	550 (15.4)
• ≥ 65	1,162 (66.4)	2,633 (80.6)	34 (47.2)	2,890 (81.0)
Sex, n (%)				
• Female	888 (50.7)	1,899 (58.1)	48 (66.7)	1,900 (53.3)
• Male	863 (49.3)	1,367 (41.9)	24 (33.3)	1,666 (46.7)

12.2.2 Initiation of PAH-specific Treatment

Table 16 provides an overview of the demographic characteristics of patients with PAH who met the criterion of at least 30 days of follow-up post-PAH diagnosis and received PAH-targeted medications during the study period. The proportion of patients who were prescribed PAH-targeted medications during the study period was under 10% in IQVIA DA Germany (n=117, 3.3%) and CPRD GOLD (n=210, 6.4%), 19.1% in CHUBX (n=335), and 20.8% in EBB (n=15). Notably, there was slight male preponderance in the treated patients in CPRD GOLD (57.1%) and IQVIA DA Germany (53.8%).

Table 17 outlines the use of PAH-targeted pharmacotherapies by database and time window.

The use of PAH-targeted drugs varied across different databases during the observation period, reflecting differences in clinical practices and patient management. 'IK, with prescription rates of 1.3% in both CPRD GOLD and IQVIA DA Germany, 2.1% in CHUBX, and relatively higher rate in EBB (6.9%). For the PDE-5is, there were more treatments with sildenafil compared to tadalafil in all the databases. EBB had the highest prescription rate for sildenafil at 6.9%, while tadalafil was not prescribed as an index treatment. The prescription rate of sildenafil (2.1%) in CHUBX was also higher than that of tadalafil (<1). In CPRD GOLD, the prescription rate for sildenafil was 1.0%, while for tadalafil, it was 0.2%. In IQVIA DA Germany, the prescription rate for sildenafil was 0.9%, and for tadalafil, it was 0.3%. Unlike other databases, ERAs were the most common therapeutic category of PAH-targeted drugs used as index treatment in CHUBX (2.5%),

predominately bosentan (2.3%). Conversely, ERAs were not used as index treatment in CPRD GOLD and EBB. In IQVIA DA Germany, ERAs were sparingly prescribed, accounting for an overall prescription rate of 0.4%, mainly consisting of bosentan (0.2%) and macitentan (0.2%).

The post-index treatment with PDE-5is demonstrated increasing prescription rates within the year following PAH diagnosis across all databases. In CHUBX, patients had an initial prescription rate of 8.5% at 30 days post-index, which steadily increased to 10.1% at 90 days post-index, ultimately reaching its peak at 13.1% at 365 days post-index. For CPRD GOLD, the prescription rate was 1.8% at 30 days post-index, and then increased to 2.8% at 90 days post-index, reaching its highest rate of 4.7% at 365 days post-index. EBB had a higher initial rate at 30 days post-index (9.7%), which further increased to 16.7% at 90 days post-index, reaching its peak of 20.8% at 365 days post-index. In IQVIA DA Germany, the prescription rate was 1.5% at 30 days post-index, which slightly increased to 1.7% at 90 days post-index, with the highest rate observed at 365 days post-index, reaching 2.2%. This trend reflects an overall rise in the utilization of PDE-5is for PAH treatment over time in all databases.

A similar trend was observed for ERAs, although the increase in their utilization demonstrated a more moderate pattern, notably in CHUBX. Within the first 30 days post-index, the prescription rate for ERAs in CHUBX was 7.0%, which gradually increased to 8.1% at 90 days post-index, and then incrementally to 10.9% at 365 days post-index. In EBB, the prescription rate was less than 1% at 90 days post-index and increased to 6.9% at 365 days post-index. The prescription rates of ERAs remained below 1% in CPRD GOLD and IQVIA DA Germany during the post-index period. Specifically, in CPRD GOLD, the prescription rate was less than 1.0% at 30 days post-index, which then increased to 0.2% at 90 days post-index, reaching its highest rate of 0.6% at 365 days post-index. In IQVIA DA Germany, the prescription rate was 0.5% at 30 days post-index, which then increased to 0.5% at 90 days post-index, with the highest rate observed at 365 days post-index, reaching 0.6%.

In general, the use of combination therapy, which entails the prescription of both ERAs and PDE-5is, remained minimal, with rates remaining below 1% in all databases and throughout various time intervals. Likewise, the utilization of other PAH therapies, including treprostinil, epoprostenol, iloprost, selexipag, and riociguat, was very low across all databases, with less than 1% of patients receiving these treatments. However, the overall use of other PAH therapies was contrastingly high in CHUBX, increasing from 0.8% at index to 4.0% at one-year post-index.

Table 16. Demographic characteristics of the patients that initiated treatment for PAH per database.

Demographics	CHUBX	CPRD GOLD	EBB	IQVIA DA Germany
Number of eligible patients	1,751	3,266	72	3,566
Number of treated participants, n (%)	335 (19.1)	210 (6.4)	15 (20.8%)	117 (3.3)
Age group (years), n (%) (percentage of treated)				
• 18 to 44	42 (12.5)	19 (9.0)	6 (40.0)	18 (15.4)
• 45 to 64	106 (31.6)	69 (32.9)	6 (40.0)	30 (25.6)
• ≥ 65	187 (55.8)	122 (58.1)	<5	69 (59.0)
Sex, n (%) (percentage of treated)				
• Female	179 (53.4)	90 (42.9)	8 (53.3)	54 (46.2)
• Male	156 (46.6)	120 (57.1)	7 (46.7)	63 (53.8)

Table 17. Use of PAH-targeted pharmacotherapies by database and time window.

	CHUBX				CPRD GOLD				EBB				IQVIA DA Germany			
Post index (days)	**At index**	**1 – 30**	**1 – 90**	**1 – 365**	**At index**	**1 – 30**	**1 – 90**	**1 – 365**	**At index**	**1 – 30**	**1 – 90**	**1 – 365**	**At index**	**1 – 30**	**1 – 90**	**1 – 365**
ERAs	44 (2.5)	122 (7.0)	142 (8.1)	190 (10.9)	0 (0)	<5 (<1)	5 (0.2)	20 (0.6)	0 (0)	0 (0)	<5 (<1)	5 (6.9)	15 (0.4)	17 (0.5)	18 (0.5)	20 (0.6)
• Ambrisentan	<5 (<1)	35 (2.0)	43 (2.5)	64 (3.7)	0 (0)	0 (0)	0 (0)	<5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)
• Bosentan	40 (2.3)	87 (5.0)	101 (5.8)	130 (7.4)	0 (0)	<5 (<1)	<5 (<1)	10 (0.3)	0 (0)	0 (0)	<5 (<1)	5 (6.9)	6 (0.2)	8 (0.2)	8 (0.2)	8 (0.2)
• Macitentan	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<5 (<1)	<5 (<1)	6 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	6 (0.2)	7 (0.2)	7 (0.2)	8 (0.2)
• Sitaxentan	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PDE-5is	36 (2.1)	148 (8.5)	177 (10.1)	229 (13.1)	43 (1.3)	60 (1.8)	92 (2.8)	152 (4.7)	5 (6.9)	7 (9.7)	12 (16.7)	15 (20.8)	46 (1.3)	55 (1.5)	60 (1.7)	80 (2.2)
• Sildenafil	29 (1.7)	52 (3.0)	65 (3.7)	82 (4.7)	33 (1.0)	53 (1.6)	83 (2.5)	135 (4.1)	5 (6.9)	7 (9.7)	12 (16.7)	15 (20.8)	33 (0.9)	43 (1.2)	46 (1.3)	60 (1.7)
• Tadalafil	<5 (<1)	97 (5.5)	114 (6.5)	153 (8.7)	5 (0.2)	7 (0.2)	9 (0.3)	17 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	11 (0.3)	12 (0.3)	14 (0.4)	21 (0.6)
Other therapies	14 (0.8)	39 (2.2)	45 (2.6)	70 (4.0)	0 (0)	0 (0)	0 (0)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	0 (0)	0 (0)	0 (0)	<5 (<1)
Combination therapy	NA	NA	NA	NA	0 (0)	<5 (<1)	<5 (<1)	<5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	<5 (<1)	5 (0.1)	5 (0.1)	8 (0.2)

Other therapies include Treprostinil, Epoprostenol, Iloprost, Selexipag, and Riociguat. Combination therapy = use of both ERAs and PDE-5is. NA = Not available.

12.2.3 Duration of PAH-specific Treatment

Table 18 presents data regarding the duration of the first prescription of PAH-targeted pharmacotherapies across different databases. Notably, there were some similarities and differences in the prescription duration.

For ERAs, the median duration was consistently one day in CHUBX and CPRD GOLD. However, EBB and IQVIA DA Germany showed a different trend with a median duration of 30 days. The specific ERA, ambrisentan, was usually prescribed for one day in all databases, except for IQVIA DA Germany, where it extended to 30 days. Bosentan was prescribed for much longer duration, with median duration of 28 days in both CPRD GOLD and IQVIA DA Germany, 30 days in EBB, and typically one day in CHUBX. In IQVIA DA Germany, the first prescription of macitentan lasted for 29 days, while the median duration of macitentan and sitaxentan was not reported due to limited (<5) prescriptions.

The median duration of the first prescription of PDE-5is was 30 days in both EBB and IQVIA DA Germany, 28 days in CPRD GOLD, and notably shorter in CHUBX, where it averaged just one day. When exploring specific PDE-5is, the prescription duration for sildenafil was 29 days in both EBB and IQVIA DA Germany, with a slightly shorter duration in CPRD GOLD (27 days). Similarly, the prescription duration for tadalafil was 27 days in both CPRD GOLD and IQVIA DA Germany.

In the case of combination therapy, the duration was considerably longer in IQVIA DA Germany, where it averaged 56 days, closely mirroring the prescription duration of PDE-5is in CPRD GOLD (28 days). Conversely, in CHUBX, combination therapy was typically prescribed for just one day, although it demonstrated a wider range of median durations.

Other PAH-specific therapies, including treprostinil, epoprostenol, iloprost, selexipag, and riociguat, were prescribed for substantially longer durations compared to ERAs, PDE-5is, and combination therapy. This was especially evident in EBB (93 days) and IQVIA DA Germany (38 days). In contrast, the prescription duration for other PAH-specific therapies in CHUBX and CPRD GOLD was consistently one day.

Table 18. Duration of first prescription of PAH-targeted pharmacotherapies by database.

Demographics	CHUBX			CPRD GOLD			EBB			IQVIA DA Germany		
Duration (days)	**Median (IQR)**	**Min.**	**Max.**	**Median (IQR)**	**Min.**	**Max.**	**Median (IQR)**	**Min.**	**Max.**	**Median (IQR)**	**Min.**	**Max.**
ERAs	1 (1 – 1)	1	1	1 (1 – 28)	1	51	30 (30 – 40)	30	79	30 (28 – 57)	7	91
• Ambrisentan	1 (1 – 1)	1	1	1 (1 – 1)	1	1	NA	NA	NA	30 (30 – 60)	30	60
• Bosentan	1 (1 – 1)	1	1	28 (1 – 28)	1	51	30 (30 – 40)	30	79	28 (23 – 54)	7	91
• Macitentan	NA	NA	NA	NA	NA	NA	NA	NA	NA	29 (29 – 54)	9	64
• Sitaxentan	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PDE-5is	1 (1 – 1)	1	1	28 (1 – 28)	1	2,002	30 (30 – 50)	30	116	30 (12 – 51)	4	526
• Sildenafil	NA	NA	NA	27 (27 – 27)	1	1,867	29 (29 – 49)	29	115	29 (11 – 44)	3	525
• Tadalafil	NA	NA	NA	27 (27 – 27)	27	2,001	NA	NA	NA	27 (11 – 55)	3	516
Other therapies	1 (1 – 1)	1	2	1 (1 – 1)	1	1	93 (54 – 136)	30	235	38 (30 – 39)	14	49
Combination therapy	1 (1 – 579)	1	4,232	28 (28 – 28)	28	37	NA	NA	NA	56 (30 – 100)	12	100

Other therapies include Treprostinil, Epoprostenol, Iloprost, Selexipag, and Riociguat. Combination therapy = use of both ERAs and PDE-5is. IQR = Interquartile range. NA = Not applicable due to no drug exposure during the study period.

12.2.4 Duration of time patients were on PAH-specific treatment

The duration of time patients was on specific PAH pharmacotherapy is detailed in **Table 19**. Overall, the median duration of PAH-related therapy ranged from 1 to 189 days across all databases.

In IQVIA DA Germany, patients were consistently treated for a longer period with ERAs compared to PDE-5is. Specifically, macitentan, bosentan, and ambrisentan had median prescription durations of 189 days, 84 days, and 30 days, respectively. In contrast, sildenafil and tadalafil had median prescription durations of 29 days and 27 days.

The duration of therapy with ERAs and PDE-5is showed mostly comparable trends across other databases. In EBB, patients were treated with bosentan and sildenafil for 35 days and 29 days, respectively. A similar pattern was observed in CPRD, where bosentan had a median duration of 28 days, while sildenafil and tadalafil were both prescribed for 27 days. Notably, ambrisentan had a shorter prescription duration, administered for a single day. In CHUBX, the duration of time patients was on bosentan was 4 days. Ambrisentan and tadalafil were both prescribed for 2 days, while sildenafil therapy lasted for 3 days.

The duration of treatment with other PAH therapies was notably longer in EBB (47 days) and IQVIA DA Germany (34 days) compared to CHUBX (3 days) and CPRD GOLD (1 day). A similar trend was observed for combination therapy across the databases: IQVIA DA Germany (45 days), EBB (37 days), CHUBX (3 days), and CPRD GOLD (1 day).

Table 19. Duration of time on specific PAH pharmacotherapies by database.

Demographics	CHUBX			CPRD GOLD			EBB			IQVIA DA Germany		
Duration (days)	**Median (IQR)**	**Min.**	**Max.**	**Median (IQR)**	**Min.**	**Max.**	**Median (IQR)**	**Min.**	**Max.**	**Median (IQR)**	**Min.**	**Max.**
Ambrisentan	2 (1 – 4)	1	91	1 (1 – 1)	1	1	NA	NA	NA	30 (30 – 90)	30	386
Bosentan	4 (2 – 7)	1	138	28 (1 – 28)	1	402	35 (30 – 85)	28	915	84 (28 – 229)	1	3,145
Macitentan	NA	NA	NA	NA	NA	NA	NA	NA	NA	189 (29 – 307)	9	2,387
Sitaxentan	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sildenafil	3 (1 – 10)	1	127	27 (27 – 74)	1	3,663	29 (29 – 69)	7	1,273	29 (23 – 90)	3	2,739
Tadalafil	2 (1 – 4)	1	155	27 (27 – 71)	1	2,001	NA	NA	NA	27 (11 – 59)	3	715
Other therapies	3 (2 – 7)	1	140	1 (1 – 1)	1	18	47 (30 – 119)	28	484	34 (30 – 46)	14	2,829
Combination therapy	3 (2 – 6)	1	126	1 (1 – 28)	1	402	37 (30 – 86)	24	915	45 (30 – 168)	7	2,727

Other therapies include Treprostinil, Epoprostenol, Iloprost, Selexipag, and Riociguat. Combination therapy = use of both ERAs (Ambrisentan, Bosentan, Macitentan, Sitaxentan) and PDE-5is (Sildenafil, Tadalafil). IQR = Interquartile range. NA = Not applicable due to no drug exposure during the study period.

9.9.4

12.2.5 PAH-specific Treatment Sequences

Table 20 describes the treatment pattern of PAH across databases.

Table 20. Use pattern of PAH-targeted pharmacotherapies by database.

Demographics	CHUBX	CPRD GOLD	EBB	IQVIA DA Germany
Number of eligible patients	2,043	3,266	72	3,566
Total number of untreated patients, n (%)	1,708 (83.6)	3,056 (93.6)	57 (79.2)	3,449 (96.7)
Total number of treated patients, n	**335**	**210**	**15**	**117**
Monotherapy, n (%)	159 (47.5)	187 (89.0)	NA	95 (81.2)
• ERAs, n (%)	57 (17.0)	12 (5.7)	NA	10 (8.5)
▪ Ambrisentan	8 (2.4)	NA	NA	NA
▪ Bosentan	48 (14.3)	7 (3.3)	NA	7 (6.0)
▪ Macitentan	NA	NA	NA	NA
▪ Sitaxentan	NA	NA	NA	NA
• PDE-5is, n (%)	102 (30.4)	175 (83.3)	8 (53.3)	85 (72.6)
▪ Sildenafil	44 (13.1)	155 (73.8)	7 (46.7)	58 (49.6)
▪ Tadalafil	54 (16.1)	20 (9.5)	NA	26 (22.2)
Combination therapy	176 (52.5)	15 (7.1)	7 (46.7)	8 (6.8)
• Ambrisentan-tadalafil	11 (3.3)	NA	NA	NA
• Bosentan-sildenafil	8 (2.4)	NA	NA	NA
• Bosentan-tadalafil	57 (17.0)	NA	NA	NA
• Sildenafil-bosentan	22 (6.6)	6 (2.9)	NA	NA
• Tadalafil-ambrisentan	42 (12.5)	NA	NA	NA
• Tadalafil-bosentan	14 (4.2)	NA	NA	NA
• Macitentan-sildenafil	NA	NA	NA	5 (4.3)

Combination therapy = use of both ERAs and PDE-5is. NA = Not applicable due to no drug exposure during the study period. Treatment refers to exposure to ERAs and/or PDE-5is. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

In CHUBX, 47.5% of PAH patients received monotherapy and 52.5% received combination therapy. Among those on monotherapy, the vast majority (30.4%) were prescribed PDE-5is, particularly sildenafil (13.1%) and tadalafil (16.1%). ERAs were used by 17% of patients, predominantly bosentan (14.3%). For combination therapy, a wide variety of combinations were used, with bosentan-tadalafil (17.0%) and tadalafil-ambrisentan (12.5%) being the most common, followed by sildenafil-bosentan (6.6%) and tadalafil-bosentan (4.2%) combinations.

Most patients in CPRD GOLD received monotherapy (89%), with PDE-5is being the dominant choice (83.3%), and sildenafil was the preferred drug within this class (73.8%). In contrast, the utilization of ERAs as monotherapy was less prevalent (5.7%) in CPRD GOLD, with bosentan being the primary choice (3.3%) within this class. Furthermore, only a small fraction of patients (7.1%) received combination therapy, with sildenafil-bosentan emerging as the most prescribed combination (2.9%).

In IQVIA DA Germany, the majority of patients received monotherapy (81.2%), with PDE-5is being the most common choice (72.6%), particularly sildenafil (49.6%). ERAs, on the other hand, were less commonly prescribed as monotherapy (8.5%), and bosentan (6.0%) was the preferred option among those who did receive ERAs. Combination therapy was relatively less common, with only 6.8% of patients receiving such treatment, primarily macitentan-sildenafil (4.3%) combination.

PDE-5is (53.3%), particularly sildenafil (46.7%), was the primary choice for monotherapy treatment in EBB was PDE-5is (53.3%), with 46.7% of patients receiving combination therapy.

Overall, the predominant treatment approach for PAH across all databases was monotherapy with PDE-5is, specifically sildenafil. ERAs were less frequently used as monotherapy, with bosentan being the most prescribed drug in this class and often initiated in combination therapy with other PAH-targeted drugs. The use of combination therapy was generally less common but was more frequent in CHUBX and EBB than in CPRD GOLD and IQVIA DA Germany.

12.2.6 Disease Outcomes and Prognosis of Patients with Newly Diagnosed PAH

Table 21 provides an overview of hospitalization rates and mortality among patients undergoing treatment for PAH by database and time window.

In CHUBX, a hospital-based database, all patients were inherently hospitalized, rendering the hospitalization rate at index as 100%. Estonian Biobank database (EBB) had a high hospitalization rate of 86.7% at index, and notably, within one year following PAH diagnosis, all patients in EBB had experienced hospitalization. A parallel pattern was discerned in cardiovascular hospitalization, with both CHUBX and EBB starting at high rates at index (99.7% and 93.3%, respectively) and reaching 100% in both databases within one-year post-index.

The trajectory of mortality rates over the years showed distinct patterns among the databases. EBB had a relatively stable mortality rate of less than 1%. In contrast, CHUBX and CPRD GOLD demonstrated a progressively increasing mortality rate, with a two to four-fold increased rate between one- and three-years post-index. In CHUBX, the percentage of patients who died within one-year post-index (7.2%) doubled at three years post-index (14.3%), reaching a high of 17.3% at five years post-index date. Similarly, in CPRD GOLD, the mortality rate was 8.1% at one-year post-index, quadrupling to 31.9% at three years post-index, and reaching a peak of 42.9% at the five-year post-index.

Table 21. Rates of hospitalization and mortality among patients undergoing treatment for PAH by database and time window.

Disease outcomes	CHUBX (n=335)				CPRD GOLD (n=120)				EBB (n=15)			
Post index (days)	**At index**	**1-yr**	**3-yr**	**5-yr**	**At index**	**1-yr**	**3-yr**	**5-yr**	**At index**	**1-yr**	**3-yr**	**5-yr**
Hospitalisation	334 (99.7)	334 (99.7)	334 (99.7)	334 (99.7)	NA	NA	NA	NA	13 (86.7)	15 (100)	15 (100)	15 (100)
Cardiovascular hospitalisation	334 (99.7)	335 (100)	335 (100)	335 (100)	NA	NA	NA	NA	14 (93.3)	15 (100)	15 (100)	15 (100)
All-cause mortality	NA	24 (7.2)	48 (14.3)	58 (17.3)	NA	17 (8.1)	67 (31.9)	90 (42.9)	NA	0 (0)	<5 (<1.0)	<5 (<1.0)
Treatment refers to the use of ERAs and/or PDE-5is. NA = Not applicable. NA = Not applicable.												

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In agreement with the guideline on good pharmacovigilance practice (EMA/873138/2011), there will be no requirement for expedited reporting of adverse drug reactions as only secondary data will be used in this study.

14. DISCUSSION

14.1 Key Results

In this study, data from 9,474 patients with incident pulmonary arterial hypertension between 2012 and 2022 in four European countries (Estonia, France, Germany, and the United Kingdom) were analysed to evaluate the demographics, clinical characteristics, treatment patterns, disease outcomes and prognosis of pulmonary arterial hypertension in diverse real-world settings.

Large-scale characterisation

The patient population was predominately older adults with slight female preponderance. Dyspnoea and chest pain were prevalent symptoms among patients in the year preceding their PAH diagnosis, while more than 10% had heart failure, COPD, connective tissue disorder, diabetes, systemic hypertension, and ischemic heart disease. Over three-quarters of the participants had cardiovascular disease prior to PAH diagnosis. Pre-index exposure to selective serotonin reuptake inhibitors and tramadol was notably high, whereas pre-index use of PAH-targeted drugs was minimal, with sildenafil showing higher pre-index use in EBB and CPRD GOLD. In contrast, CHUBX had the highest prescription rate for PAH-specific therapies before the index date.

PAH Treatments

The study showed that PDE-5is, particularly sildenafil, were the primary choice as index treatment for newly diagnosed PAH patients. PDE-5is and ERAs were increasingly prescribed in the year following PAH diagnosis. The predominant treatment strategy for PAH involved PDE-5is monotherapy, with less frequent use of combination therapy, typically involving bosentan. Notably, sildenafil was commonly used as a standalone treatment, while tadalafil was preferred in combination therapy, often paired with bosentan or ambrisentan for dual therapy. The first prescriptions of PDE-5is and ERAs typically lasted 28-30 days, with the longest duration for combination therapy observed in IQVIA DA Germany and other PAH therapies in EBB. Additionally, the median duration of PAH therapy ranged from 1 to 189 days across all databases, with patients receiving longer therapy with ERAs compared to PDE-5is, particularly in IQVIA DA Germany. Nevertheless, PAH is primarily managed in specialists' centres, which are not included in the present study. Thus, the observed treatments and therapy durations likely represent the early stages of PAH treatment before referral to specialized care centres.

PAH Treatment Outcomes and Prognosis

All patients were hospitalized within one year of PAH diagnosis, with high cardiovascular hospitalization rates of 93.3%-99.7% at index. In CHUBX and CPRD GOLD, a 2 to 4-fold increase in mortality rate was observed between one- and three-years post-index.

14.2 Limitations of the research methods

Firstly, the presence of pre-index prescriptions of PAH-specific drugs, particularly noticeable in the CHUBX database, might be attributed to the study's primary focus on pulmonary arterial hypertension (PAH) as opposed to a broader phenotype such as pulmonary hypertension. Though the use of narrow definition of PAH in this study likely reduced the potential misclassification with pulmonary hypertension, it is plausible that some patients initially received diagnoses and treatments for pulmonary hypertension before being subsequently reclassified under the more specific category of PAH. Additionally, right heart catheterization is conventionally regarded as the gold-standard diagnostic procedure for patients with suspected PAH to confirm the diagnosis and inform treatment decisions. Consequently, the initiation of medical therapy may occasionally precede the definitive PAH diagnosis, particularly considering documented delays in diagnosis, typically ranging from 2.5 to 3.9 years.(16, 17)

Secondly, it is important to acknowledge that our study might underestimate the proportion of individuals receiving treatment, especially if patients are diagnosed and managed in specialized PAH reference centres, as is the case in most countries including France (CHUBX), the United Kingdom (CPRD), Estonia (EBB) and Germany (IQVIA DA). Also, use of PAH treatment might be underestimated in primary care databases like CPRD Gold and IQVIA Germany as this treatment is initiated at specialist care centres.

Thirdly, we did not report hospitalization rates for all the databases due to the absence of hospitalization data in CPRD Gold and IQVIA Germany. This data gap in these specific databases limited our ability to provide a comprehensive assessment of hospitalization rates. Another limitation to consider is the relatively low prescription duration observed in CHUBX which could be attributed to the fact that in-patient treatments are assessed daily, creating the appearance of daily prescriptions.

Finally, feasibility of PAH within the available Darwin EU® data sources of year 1 was done based on record counts and not on patient counts. The number of record counts for PAH in the EBB from the feasibility assessment was high however the number of patients with PAH was much lower. This underlines the importance of checking patient counts and not record counts when conducting feasibility assessments using real world data. Indeed, depending on the type of databases, disease codes might be repeated which results in an overestimation of the individuals with the disease of interest.

14.3 Interpretation

The clinicodemographic characteristics of incident PAH patients in our study closely resembled findings from previous real-world studies, particularly in terms of the high prevalence of cardiovascular diseases. (18, 19) Notably, the prevalence of systemic hypertension in CHUBX (62.9%) was in line with observations in clinical PAH care in Japan (63.0%).(19) The median age at which PAH is typically diagnosed, often at 60 years or older,(20) aligns with the findings of our study, where the median age at diagnosis ranged from 62 to 77 years. Furthermore, our study revealed substantial pre-index exposure to selective serotonin reuptake inhibitors (SSRIs) and tramadol, both of which have been investigated as potential risk factors for PAH.(21, 22) These observations underscore the consistency of our findings with existing real-world data.

The study indicated that 3.3% to 19.1% of patients with PAH initiated treatment after diagnosis, a range consistent with the treatment rate of 3.5% among 342,977 patients with PAH in a US claims database.(23) Current guidelines recommend initial combination therapy with PDE-5is and ERAs for mild to intermediate PAH cases.(20) However, we observed that 48% to 89% of patients began with monotherapy, primarily PDE-5is and, to a lesser extent, ERAs. This trend is consistent with monotherapy rates in Italy (50%),(24) France (58%),(18) and Spain (78%)(25). Combination therapy rates were 47% in EBB and 53% in CHUBX, similar to rates reported in Sweden (53%)(26).

The 1-year mortality rate among PAH patients in our study corroborates previously reported rates in France(18) and the United States(27). In a French study involving 1,611 incident PAH patients, a one-year survival rate of 93% was observed(18), which is consistent with the 7% one-year mortality rate found in CHUBX (France). Similarly, the one-year mortality among 935 adult patients in the US Pulmonary Hypertension Association Registry (PHAR) was 8%, (27) identical to the one-year mortality rate in CPRD GOLD (8%). Furthermore, the 5-year mortality in CPRD GOLD (43%) was comparable to the mortality rate observed within five years of observation in PAH patients in Canada (44%).(28)

14.4 Generalisability

This study included data from four distinct databases in four European countries, each with different healthcare systems (biobank in EBB, secondary care in France, and primary care in Germany and the UK). Although consider results largely representative of patients with newly diagnosed PAH in these countries, the generalisability of our findings could be limited by observed variations in patient characteristics, treatment approaches, disease outcomes, and prognosis among the participating countries.

14.5 Other information

NA.

15. CONCLUSION

Patients with newly diagnosed pulmonary arterial hypertension (PAH) are typically older adults with a slight female preponderance, experiencing common symptoms like dyspnoea and chest pain, and often having pre-existing cardiovascular diseases. Initial PAH treatment primarily involves PDE-5 inhibitors, particularly sildenafil, with fewer patients receiving ERA monotherapy and combination therapy. The initial prescription durations for PDE-5 inhibitors and ERAs usually span one month. Patients with PAH have high hospitalization rates within one year of PAH diagnosis, and progressively increasing mortality rates.

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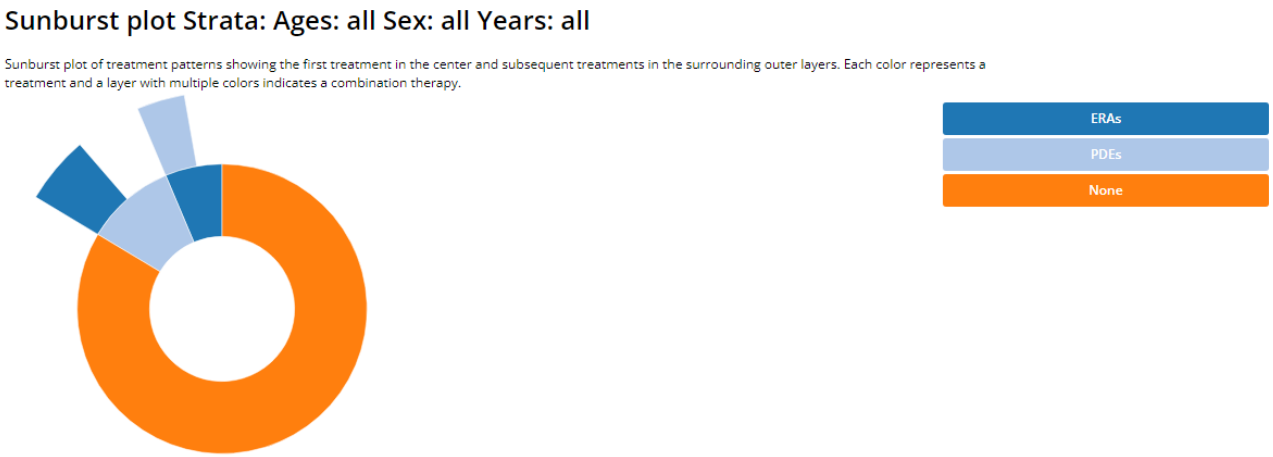
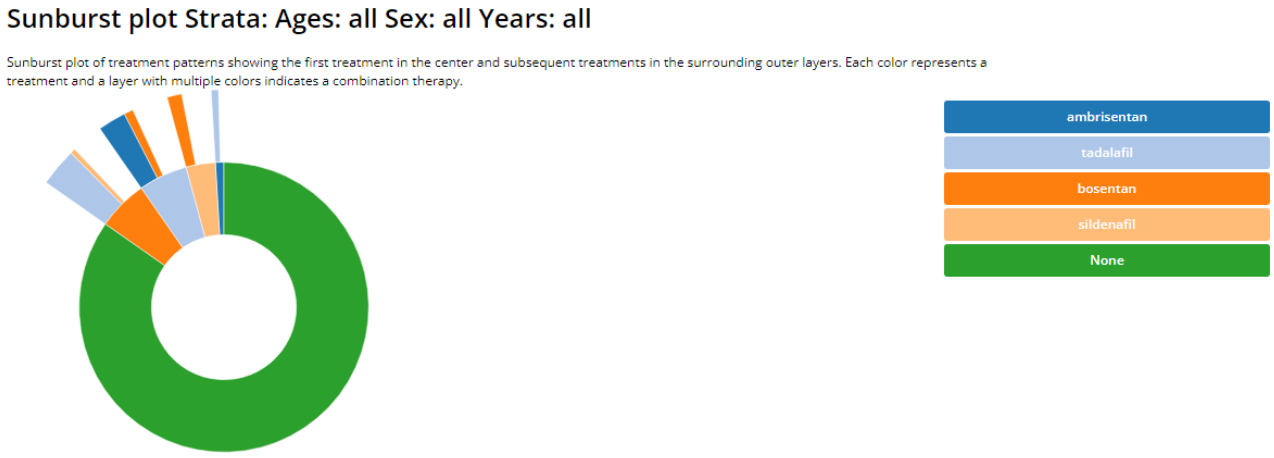
17. ANNEXES

APPENDIX I – SUNBURST PLOTS

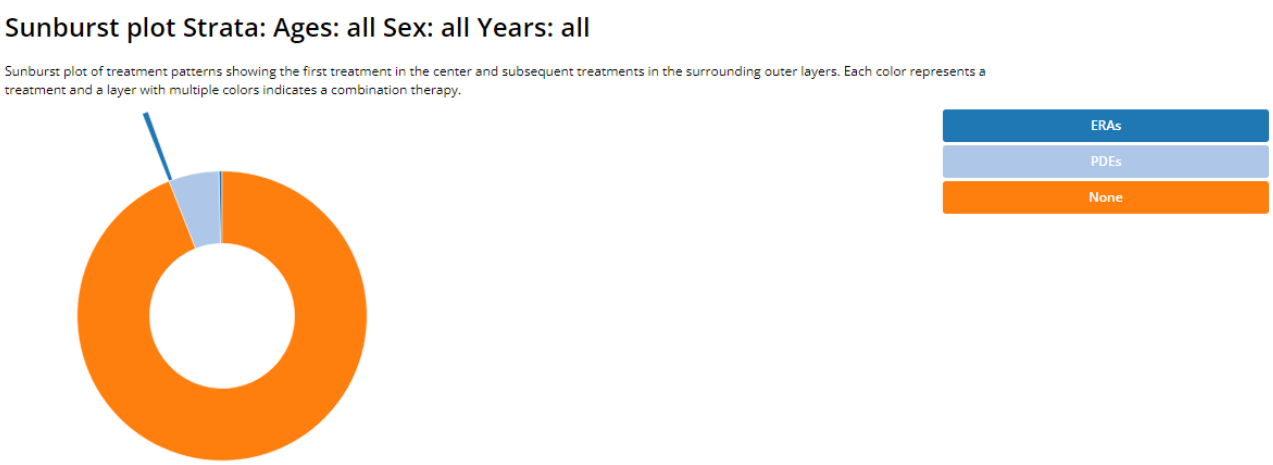
Sunburst Plot for use of PAH drugs (class level) for CHUBX



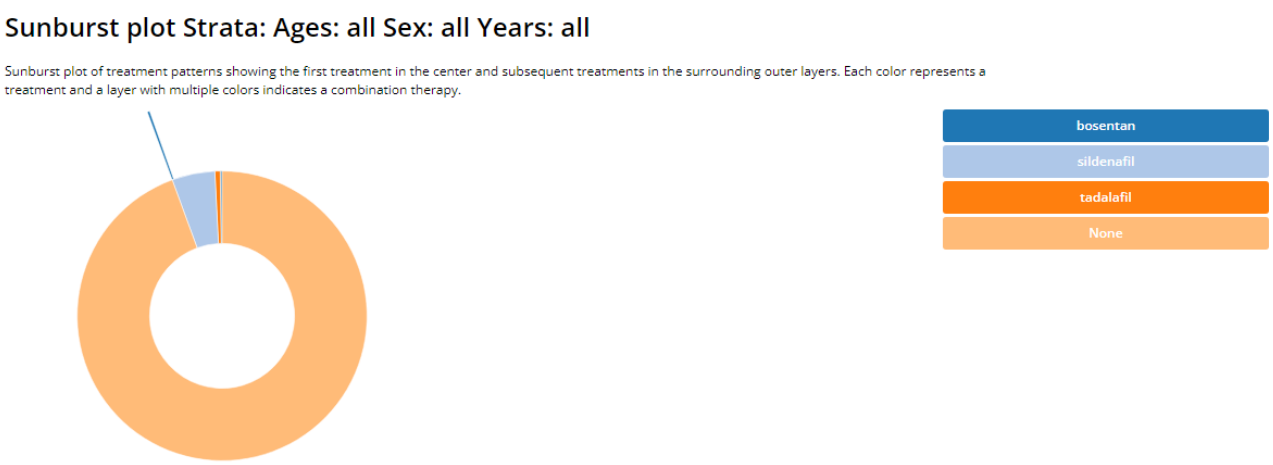
Sunburst Plot for use of PAH drugs (ingredient level) for CHUBX



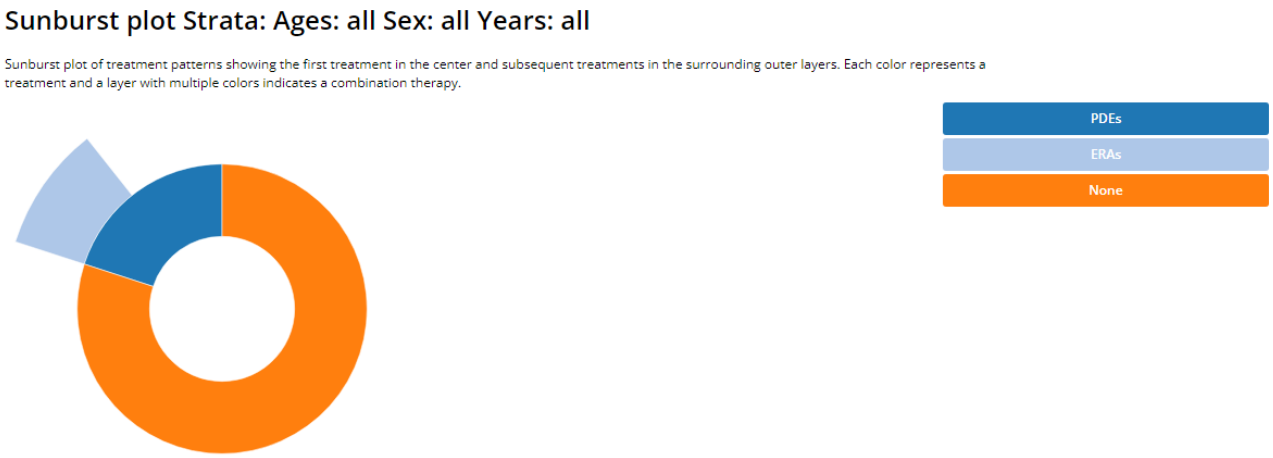
Sunburst Plot for use of PAH drugs (class level) for CPRD Gold



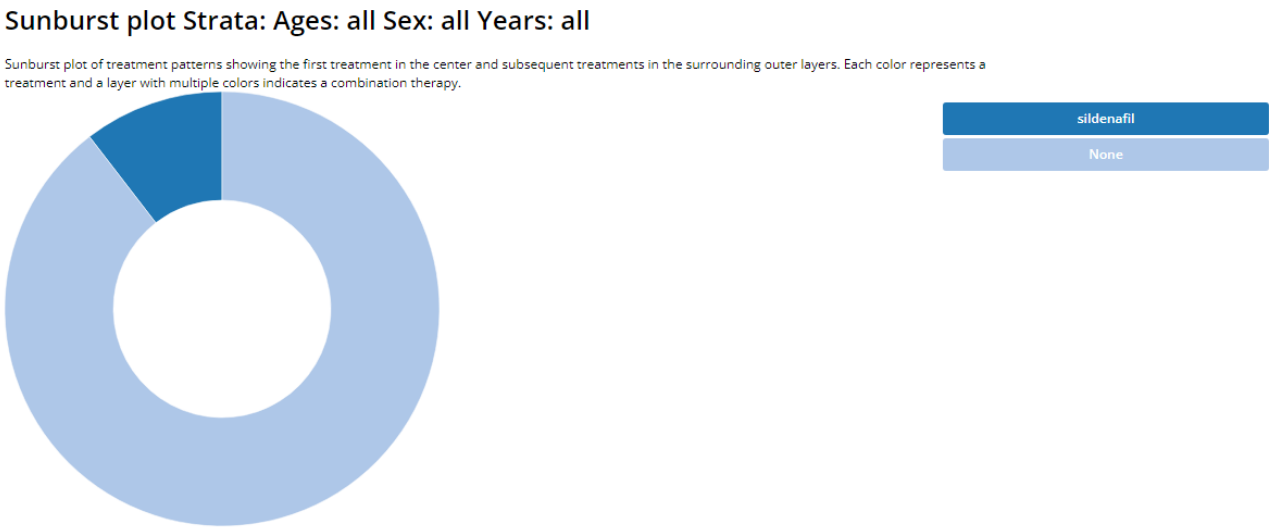
Sunburst Plot for use of PAH drugs (ingredient level) for CPRD



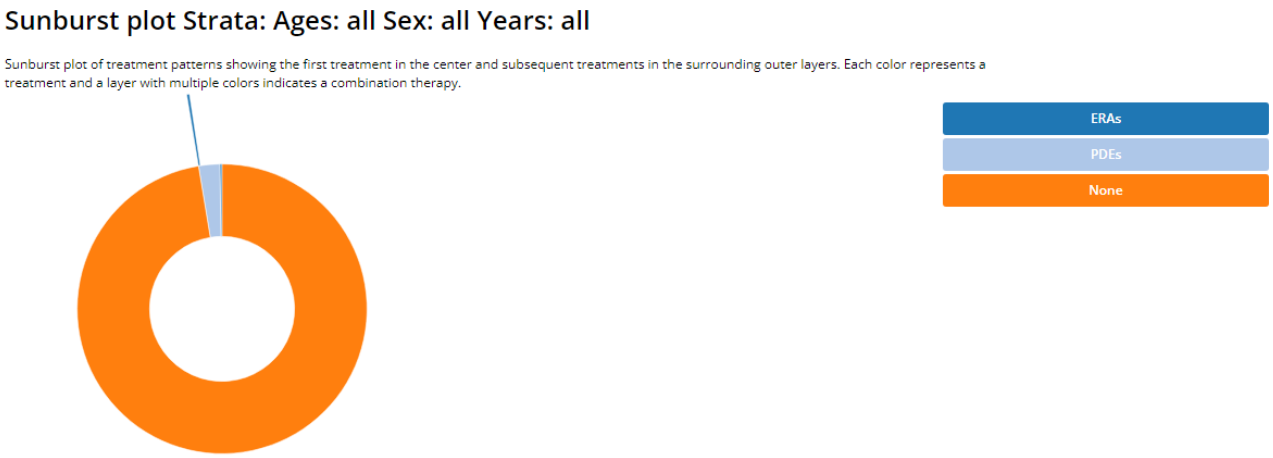
Sunburst Plot for use of PAH drugs (class level) for EBB



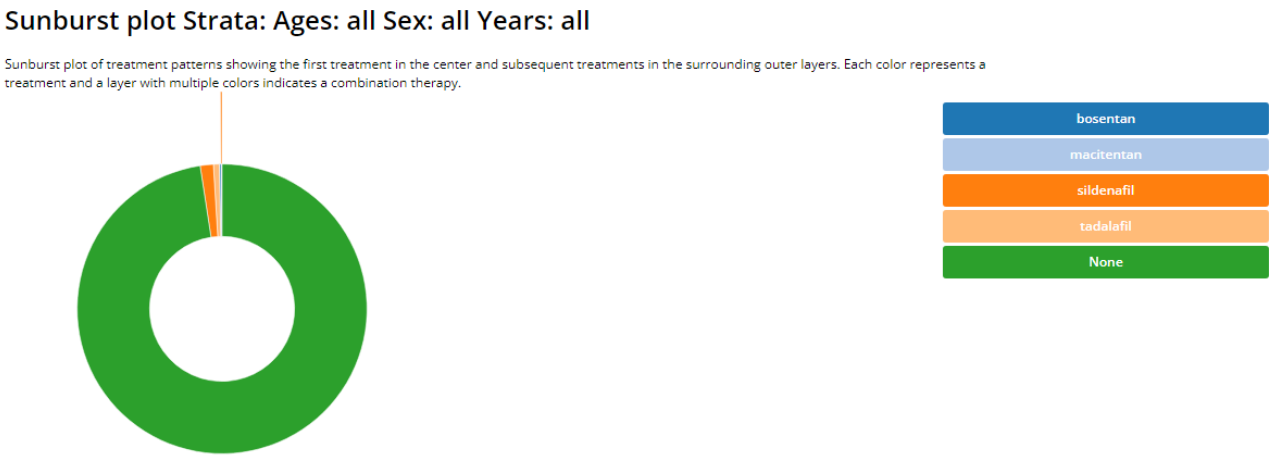
Sunburst Plot for use of PAH drugs (ingredient level) for EBB



Sunburst Plot for use of PAH drugs (class level) for IQVIA DA Germany



Sunburst Plot for use of PAH drugs (ingredient level) for IQVIA DA Germany



APPENDIX II – TABLE 1: LISTS WITH CONCEPT DEFINITIONS FOR EXPOSURE

Prescriptions will be identified based on the relevant ingredient. Non-systemic products will be excluded from the code list.

Drugs	Class	ATC code	Concept id
Ambrisentan	Endothelin receptor antagonist	C02KX02	1337068
Bosentan	Endothelin receptor antagonist	C02KX01	1321636, 19113007
Macitentan	Endothelin receptor antagonist	C02KX04	44507580
Sitaxentan	Endothelin receptor antagonist	C02KX03	36878846, 44012794
Sildenafil	Phosphodiesterate-5 inhibitors	G04BE03	1316262
Tadalafil	Phosphodiesterate-5 inhibitors	G04BE08	1336926, 36849344

APPENDIX III – TABLE 2: CODE LISTS FOR BASELINE CHARACTERIZATION

Clinical observations/ conditions	Concept ID	Code
Chest pain	77670	29857009
Dyspnea	312437	267036007
Fatigue	4223659	84229001
Syncope	135360	271594007
Obesity	433736	414916001
Heart failure	316139	84114007
Pulmonary embolism	440417	59282003
Asthma	317009	195967001
COPD	255573	13645005
Idiopathic pulmonary fibrosis	45763750	700250006
Obstructive sleep apnea	442588	78275009
Chronic kidney disease	46271022	709044004
Connective tissue disorder	253549	105969002
Human Immunodeficiency Virus (HIV) infection	439727	86406008
Diabetes mellitus	201820	73211009
Systemic hypertension	320128	59621000
Ischemic heart disease	4185932	414545008
Drugs associated with PAH		
Selective serotonin reuptake inhibitors	21604709	N06AB
Aminorex	36850446	OMOP5168063
Fenfluramine	753860	4328
Benfluorex	19035533	18880
Phenylpropanolamine	1139993	8175
Dexfenfluramine	719057	3268
Tryptophan	19006186	10898
Lithium	19124477	6448
Interferon	35884376	OMOP5031280
Sofosbuvir	44785094	1484911
Dasatinib	1358436	475342
Nilotinib	1394023	662281
Ponatinib	43013182	1364347
Carfilzomib	42873638	1302966
Ruxolitinib	40244464	1193326
Buprenorphine	1133201	1819
Tramadol	1103314	10689
Thalidomide	19137042	10432
Paclitaxel	1378382	56946
Bleomycin	1329241	1622
Cyclophosphamide	1310317	3002
Mitomycin	1389036	632
Phentermine	735340	8152
Mazindol	794229	6664