Data Base of pulmonary hypertension in the Polish population (BNP-PL) - design of the registry


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Data Base of pulmonary hypertension in the Polish population (BNP-PL) - design of the registry

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Short title: PAH and CTEPH in Poland: the design of the BNP-PL registry

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Introduction
Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are rare types of pulmonary hypertension (PH). Consequently, patient registries constitute key instruments to provide data for development of clinical research and to improve patient care and healthcare planning [1].

Currently, most of our knowledge of PAH and CTEPH epidemiology, their management, and treatment outcomes come from registries originating in the Western populations [2-5]. However, taking a global view of PH epidemiology shows important geographical differences [1].

The Data Base of Pulmonary Hypertension in the Polish population (BNP-PL, https://clinicaltrials.gov/ct2/show/NCT03959748) is the first multicenter and prospective registry of adult and pediatric PAH and CTEPH patients created in any Central-Eastern European country.

In the present report, we describe the design of the registry.

**Objectives of the BNP-PL registry**

The BNP-PL registry is an initiative of the Working Group on Pulmonary Circulation of the Polish Cardiac Society in cooperation with Polish PH reference centres [6-9] to assess prospectively the epidemiology, clinical course and disease management of patients with PAH and CTEPH. The specific study objectives are shown in Supplementary Table S1.

**Patients and Methods**

Organization of the BNP-PL registry

An invitation to participate in the study was sent to the Polish centers (22 adult and 8 pediatric centers) which were accredited to treat PAH or CTEPH by the National Health Fund (NHF), the only health care payer in Poland. Of the invited centers, all of the adult and pediatric centers
accepted the invitation and were formally involved in the project. Organization of the registry is shown in Figure 1 and is further described in Supplementary Methods S1.

The protocol of the study was reviewed and accepted by the Bioethical Committee of Physicians and Dentists Chamber in Krakow.

Participants

Patients with PAH and CTEPH aged > 3 months old treated in the participating centers are enrolled to the BNP-PL registry to form four separate arms as shown in Figure 1A. Patients with both newly and previously diagnosed PAH or CTEPH are eligible. Newly diagnosed patients are those whose diagnosis was established since March 1st 2018 (termed ‘incident cases’). Patients who were diagnosed earlier are classified as ‘prevalent cases’. For the purpose of the study, we use the most recent definitions of PAH and CTEPH as recommended by the European Society of Cardiology (Supplementary Methods S2) [10].

Patient records are submitted by local coordinators to the dedicated internet platform created and managed by the Informatics Centre of the Jagiellonian University Medical College which ensures system integrity and data protection.

Size and duration

Enrollment to our study started on March 1st 2018 and is planned to continue at least until Feb 28th 2023. We plan to gather the follow-up data for a minimum of 5 years after the enrollment of the last patient to the study. As our registry is mostly descriptive therefore the duration of data collection and follow-up, and consequently the study size are arbitrary.

Prevalence and incidence

The prevalence of PAH and CTEPH will be calculated separately for adults (≥18 years) and children (≥3 months and < 18 years) as the number of cases per 1,000,000 inhabitants, while
their incidence as the number of new cases diagnosed for PAH or CTEPH per 1,000,000 inhabitants each year. The data for the number of adults and children living in Poland will be acquired from Poland’s Statistics publications [https://stat.gov.pl/].

Baseline assessment

In incident cases, the assessment at study entry includes patient data acquired at the time of PAH or CTEPH diagnosis including the first prescribed treatment (Supplementary Table S2). We also acquire information about the first symptoms and the time elapsed from the first symptoms to proper diagnosis. In prevalent cases, the baseline assessment includes data obtained at the most recent visit occurring since March 1st 2018 and also from the most recent right heart catheterization (RHC). We also record the date of diagnosis and patient’s functional class at that time. The date of PAH or CTEPH diagnosis is defined as the date of the first RHC [11] fulfilling the hemodynamic criteria for precapillary PH.

Follow-up assessment

Follow-up data (Supplementary Table S3) will be recorded in the database every year between September 1st and October 30th starting in 2019. Accordingly, the follow-up data will include the most recent information on patients’ status before September 1st each year. The follow-up data will include information about patient’s clinical status, changes in treatment, major clinical events and outcomes and the results of additional tests performed in a patient in the last 12 months.

Treatment
Medical therapy for PAH and CTEPH patients in Poland is reimbursed by the NHF within a structured program with specific inclusion and exclusion criteria. This program is a subject to change along with new drug registrations.

**Discussion**

Bias and generalizability of results

Enrollment of both prevalent and incident cases may bias the outcome analysis as prevalent cases who did not survive until study enrollment will not be recorded. Accordingly, we plan to perform separate analysis in prevalent and incident groups. Additional bias may be related to enrollment of patients participating in clinical trials as these patients may be receiving better care than the other patients. However, exclusion of these patients would affect the real life picture of our population.

Due to specific organization of PAH and CTEPH treatment in Poland in NHF accredited centres we believe to enroll almost all diseased subject in our analysis. In that way our results will be representative for recently diagnosed patients with PAH or CTEPH and to patients who have survived with PAH or CTEPH long enough to be represented in the registry. Still our data will not be generalizable to patients with PAH or CTEPH who have not been yet diagnosed.

Comparison with other registries in PH

In his recent systematic literature search Skride et al.[12] identified 11 prospective registries performed in European PH patients. Most of them were based on a national ground (4 single centre and 6 multicenter registries) and only 1 involved multiple international centers. Three registries involved all groups of PH subjects, while the others were limited exclusively to PAH and CTEPH (3 studies) patients, PAH patients (2 studies), IPAH patients (1 study) or CTEPH patients (1 study) [13]. Six studies recruited only incident cases while the other five registries enrolled both incident and prevalent cases. With one exception the registries were performed in
Western European countries which shows that the PH patients from the Central-Eastern European countries have not been well represented in the literature. In one single center prospective study 130 PAH and 44 CTEPH adult patients were followed for a median period of 33 months to report the survival in diseased Latvian subjects [8]. The second registry held by Jansa et al. [14] was a retrospective analysis of 191 prevalent and incident adult patients diagnosed with PAH in two specialized centers in Czech Republic.

The BNP-PL registry is the first multicenter, nationwide prospective registry compiled in a Central-Eastern European country to assess PAH and CTEPH patients. The design of BNP-PL has some similarities with the largest ever PAH registry (Registry to Evaluate Early and Long-term PAH Disease Management; REVEAL) which was initiated in US in 2006 to prospectively analyze characteristics of PAH patients in the modern era of therapies [1]. Similarly to the REVEAL registry our patients are recruited from several pulmonary hypertension reference centers and we involve both adults and children as well prevalent and incident patients. In contrast to the REVEAL study and similar to the large European registries [3-5] we have planned a long-term continuous enrollment of incident study patients.

Conclusions

BNP-PL is designed to show the epidemiology and characteristics of PAH and CTEPH in a large Central-Eastern post-communist European country with a relatively short history of availability of modern PAH diagnostics and therapies.

References


Figure 1. Design of the BNP-PL registry. (A) Four arms of the BNP-PL registry including adults and children with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). Two additional arms of the CTEPH group represent patients treated with balloon pulmonary angioplasty (BPA) and pulmonary endarterectomy (PEA). (B) Time points of enrollment and follow-up of prevalent and incident cases.