International Journal of COPD

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STUDY PROTOCOL

POPE study: rationale and methodology of a study to phenotype patients with COPD in Central and Eastern Europe

This article was published in the following Dove Press journal:
International Journal of COPD
22 March 2016
Number of times this article has been viewed

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Introduction: Chronic obstructive pulmonary disease (COPD) constitutes a major health challenge in Central and Eastern European (CEE) countries. However, clinical phenotypes, symptom load, and treatment habits of patients with COPD in CEE countries remain largely unknown. This paper provides a rationale for phenotyping COPD and describes the methodology of a large study in CEE.

Methods/design: The POPE study is an international, multicenter, observational cross-sectional survey of patients with COPD in CEE. Participation in the study is offered to all consecutive outpatients with stable COPD in 84 centers across the CEE region if they fulfill the following criteria: age >40 years, smoking history ≥10 pack-years, a confirmed diagnosis of COPD with postbronchodilator FEV_1/FVC <0.7, and absence of COPD exacerbation ≥4 weeks. Medical history, risk factors for COPD, comorbidities, lung function parameters, symptoms, and pharmaceutical and nonpharmaceutical treatment are recorded. The POPE project is registered in ClinicalTrials.gov with the identifier NCT02119494.

Outcomes: The primary aim of the POPE study was to phenotype patients with COPD in a real-life setting within CEE countries using predefined classifications. Secondary aims of the study included analysis of differences in symptoms, and diagnostic and therapeutic behavior in participating CEE countries.

Conclusion: There is increasing acceptance toward a phenotype-driven therapeutic approach in COPD. The POPE study may contribute to reveal important information regarding phenotypes and therapy in real-life CEE.

Keywords: COPD, phenotypes, Central Europe, Eastern Europe, study, GOLD, comorbidity

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of death worldwide and represents an important public health challenge.[1] On the basis of multiple studies that have been published since the 1970s, the estimate of COPD prevalence ranges between 5% and 10%.[2,3] According to the World Health Organization estimates, COPD is predicted to become the third leading cause of death by 2030, and the burden of COPD is projected to further increase in coming decades due to continued exposure to COPD risk factors and aging of the population.[4–6] While the major risk factor is tobacco smoking, other risk factors include age, a previous history of bronchial asthma, genetic predisposition, and respiratory infections.[7–12] In addition to these factors, environmental and occupational exposure to gases and particles and indoor biomass inhalation may also substantially contribute to the development of COPD in affected populations.[13,14]

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http://dx.doi.org/10.2147/COPD.S88846

Although numerous studies and clinical trials regarding clinical presentation, diagnosis, and management of COPD have been recently published, very few of these studies have specifically focused on Central and Eastern Europe (CEE).[15–23] However, patients with COPD in CEE might present with different features of the disease due to differences in environmental and nonenvironmental risk factors, age of onset of disease, comorbidities, health care access, and the level of reimbursement for COPD treatment. Thus, the objectives of the "Phenotypes of COPD in Central and Eastern Europe Study" (POPE study) are to gain a better understanding of these patient characteristics and treatment patterns of patients diagnosed with COPD among different CEE countries. This is the first CEE, multicenter, investigator-initiated, collaborative project of its kind. The purposes of this paper are to provide an introduction to the study methodology and to raise awareness toward a current hot topic in COPD research, namely, the issue of COPD phenotyping.

Methods/design

Study design

The POPE study is an international, multicenter, observational cross-sectional survey in patients with COPD in CEE. Eleven CEE countries participated in the study: Austria, Bulgaria, Croatia, Czech Republic, Hungary, Latvia, Poland, Russia, Serbia, Slovakia, and Slovenia (Figure 1). The complete list of participating centers is listed in Table 1. A Steering Committee consisting of eight physicians is responsible for the scientific integrity of the study (Table 2). Each participating country is represented by one national leading expert, who coordinates the study at the national level (Table 1). Within each participating country, investigators selected by the national expert are appointed and are responsible for local data collection and organization of care. The first patient (FPI) in the database was documented in April 2014. The expected end of patient enrollment in all countries was July 2015.

The objectives

The primary aim of this study was to assess the prevalence of COPD phenotypes according to predefined criteria in an unselected group of consecutively examined patients with stable COPD in the CEE region in a real-life setting (Figure 2). Secondary aims of the study included analysis of differences in symptom load, and diagnostic and therapeutic behavior in patients classified into different phenotypes. As the POPE study will actively recruit patients with COPD due to environmental risk factors other than smoking, separate analysis will be

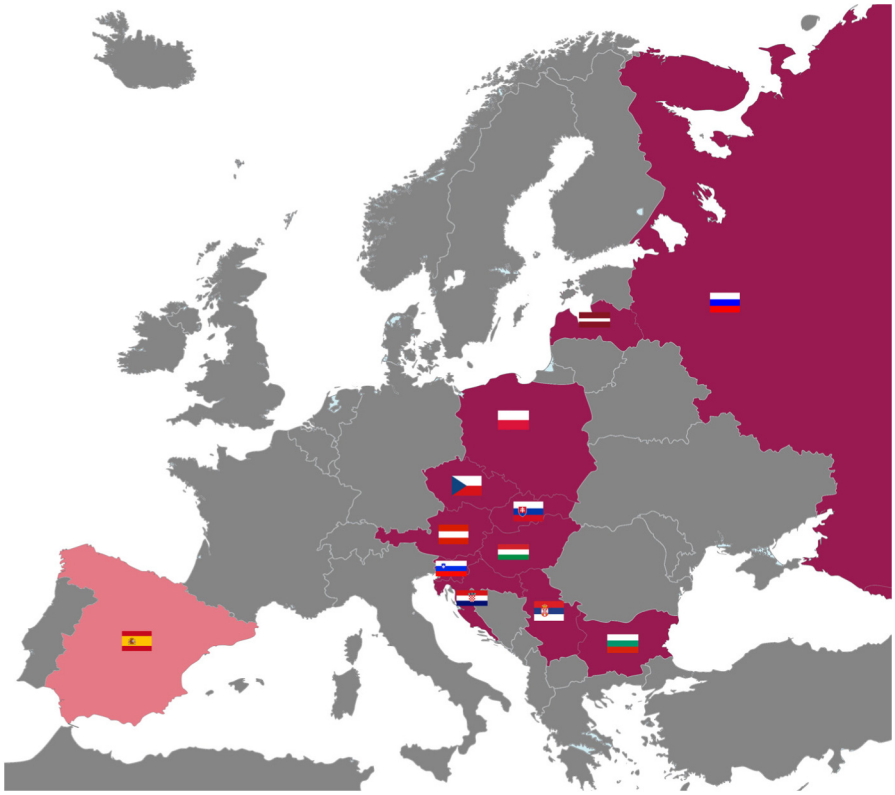

Figure 1 Map of participating countries.

Table 1 POPE study – participating centers

Austria	
National expert	Assoc Prof Arschang Valipour, MD, PhD
	Ludwig Boltzmann Institute, Wien
	AKH Linz, Department of Pulmonary Medicine
	Pulmonary Rehab Centre, Therme Wien
	Department of Internal Medicine, University Innsbruck
	SKA der PV Weyer/Enns, Mühlein
Bulgaria	
National expert	Assoc Prof Kosta Kostov, MD, PhD
	Pulmonary Diseases Clinic, Military Medical Academy, Sofia
	Clinic for Pneumonology and Phisiatry, UMHAT "Dr Georgi Stranski", Pleven
	Clinic of Pulmonology, MHAT "St Marina", Varna
	Department of Respiratory Diseases, Medical University, Plovdiv
Croatia	
National expert	Prof Neven Tudoric, MD, PhD
	University Hospital Dubrava, Zagreb
	University Hospital Centre, Zagreb
	University Hospital Centre, Split
	University Hospital Centre, Rijeka
	Clinical Hospital, Osijek
Czech Republic	
National expert	Vladimir Koblizek, MD, PhD
	Outpatient Department of Pneumology and Pulmonary Diagnostics, Karlovy Vary
	Pneumological Outpatient Department, Mepha-Centrum, Ostrava
	Pneumology Centre, Teplice
	Department of Pneumology, University Hospital Hradec Králové and Faculty of Medicine in Hradec Králové of the Charles University in Prague
Hungary	
National expert	Prof Attila Somfay, MD, PhD
	Csongrád County Hospital for Chest Diseases, Deszk
	IZO PULM Health Service Ltd., Budapest
	St Elizabeth Hospital Pulmonary Care Institute, Jászberény
	Szarvas Respiratory Ltd., Szarvas
	Újpest Non-Profit Health Care Services Ltd., Budapest
	Elizabeth House Care Ltd., Gödöllő
	Medical Institution of Dr Laszlo Romics Pulmonary Care, Érd
	Szabolcs-Szatmár-Bereg County Hospitals and University Teaching Hospital, Nyíregyháza
	Baja St Rókus Hospital Patient Lung Care Institute, Baja
Latvia	
National expert	Prof Alvis Krams, MD, PhD
	Regional Hospital of Liepaja
	Kuldīga Hospital
	SIA "BINI", Ventspils
	Health Centre Talsi
	Ambulatory Clinic Jelgava
	Bauska Hospital
	Ambulatory Clinic Dubulti, Jurmala
	Privat practice Ilona Uzbeka, Valka
	Privat practice Dace Harasimjuka, Valmiera
	Madona Hospital
	Health Centre Balvi
	Private practice Viktorija Vevere, Rezekne
	Regional Hospital of Jekabpils
	Pauls Stradins Clinical University Hospital, Riga
	Riga East Clinical University Hospital, "Gailezers", Riga
	Riga East Clinical University Hospital, In-patient Department "Centre of Tuberculosis and Lung Diseases", Riga
	LU MPI Institute private practice, Riga
	Riga 1st Hospital, Riga

(*Continued*)

Table 1 (*Continued*)

	Health Centre 4, Ltd, Riga
	UniClinic, Riga
Poland	
National expert	Assoc Prof Adam Barczyk, MD, PhD
	Oddział Chorób Płuc i Niewydolności Oddychania, Kujawsko – Pomorskie, Centrum Pulmonologii w Bydgoszczy, Bydgoszcz
	Katedra i Klinika Chorób Wewnętrznych, Pneumonologii i Alergologii, Samodzielny Publiczny Centralny Szpital Kliniczny, Warszawa
	Klinika Alergologii i Pneumonologii, Uniwersyteckie Centrum Kliniczne, Szpital Gdańskiego Uniwersytetu Medycznego, Gdańsk
	Oddział Chorób Płuc, Wojewódzkie Centrum Szpitalne Kotliny Jeleniogórskiej, Jelenia Góra
	Katedra i Klinika Pulmonologii, Alergologii i Onkologii Pulmonologicznej, Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu, Poznań
	Szpital Uniwersytecki, Oddział Kliniczny Kliniki Pulmonologii, Kraków
	Katedra i Klinika Pneumonologii, Śląski Uniwersytet Medyczny, Katowice
Russia	
National expert	Prof Kirill Zykov, MD, PhD
	Pulmonology Research Institute, Moscow
	Ufa State City Clinical Hospital 21, Ufa
	Clinic of Pulmonology of Scientific and Clinical Center of Interstitial and Orphan Lung Diseases, St Petersburg
	State Budget Educational Institution of High Professional Education "Kazan State Medical University", Kazan
	Vladivostok Clinical Hospital #1, Vladivostok
	I.M. Sechenov First Moscow State Medical University, University Hospital #1, Outpatient Department, Moscow
	GBOU VPO Samara State Medical University, Samara
	Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Moscow
Serbia	
National expert	Prof Branislava Milenkovic, MD, PhD
	Clinic for Pulmonary Diseases, Clinical Centre of Serbia, Belgrade
	Institute for Pulmonary Diseases and TB, Clinical Centre Vojvodina, Novi Sad
	Clinic for Pulmonary Diseases, Clinical Center of Niš
	Clinic for Pulmonary Diseases, Clinical Centre Kragujevac
	Municipal Institute for Lung Diseases and Tuberculosis, Belgrade
Slovakia	
National expert	Prof Ruzena Tkacova, MD, PhD
	Ambulancia pneumológie a ftizeológie Doc. MUDr Ján Plutinský, CSc, Levice
	Pľúcna ambulancia, Poprad
	MUDr Katarína Arpášová – Dionea, s.r.o., Nové Zámky
	Klinika pneumológie a ftizeológie LF SZU a UNB, Bratislava
	NsP, Považská Bystrica
	Zdravotné stredisko Fedinova, Bratislava
	Klinika tubekulózy a respiračných chorôb JLF UK a UNM, Martin
	FNsP F.D. Roosevelta, Banská Bystrica
	NsP Sv. Jakuba, Bardejov
	Zdravotné stredisko Rimava, Rimavská Sobota
Slovenia	
National expert	Jurij Šorli, MD, PhD
	Bolnišnica Topolšica, Topolšica
	Alveola, d.o.o., Maribor
	Zdravstveni dom Murska Sobota, Murska Sobota

Table 2 POPE study – Steering Committee

Steering Committee members	
Austria	Assoc Prof Arschang Valipour, MD, PhD
Croatia	Prof Neven Tudoric, MD, PhD
Czech Republic	Vladimir Koblizek, MD, PhD
Hungary	Prof Attila Somfay, MD, PhD
Poland	Assoc Prof Adam Barczyk, MD, PhD
Russia	Prof Kirill Zykov, MD, PhD
Slovakia	Prof Ruzena Tkacova, MD, PhD
Spain	Prof Marc Miravitlles, MD, PhD

conducted to ascertain differences with a matched cohort of "smokers-related" COPD. The long-term aims of the POPE study are to educate and raise awareness for COPD phenotypes among both physicians and patients to support an individualized patient treatment approach in clinical practice.

Participants

All consecutive patients with COPD examined at office-based physician and outpatient clinics from different institutions

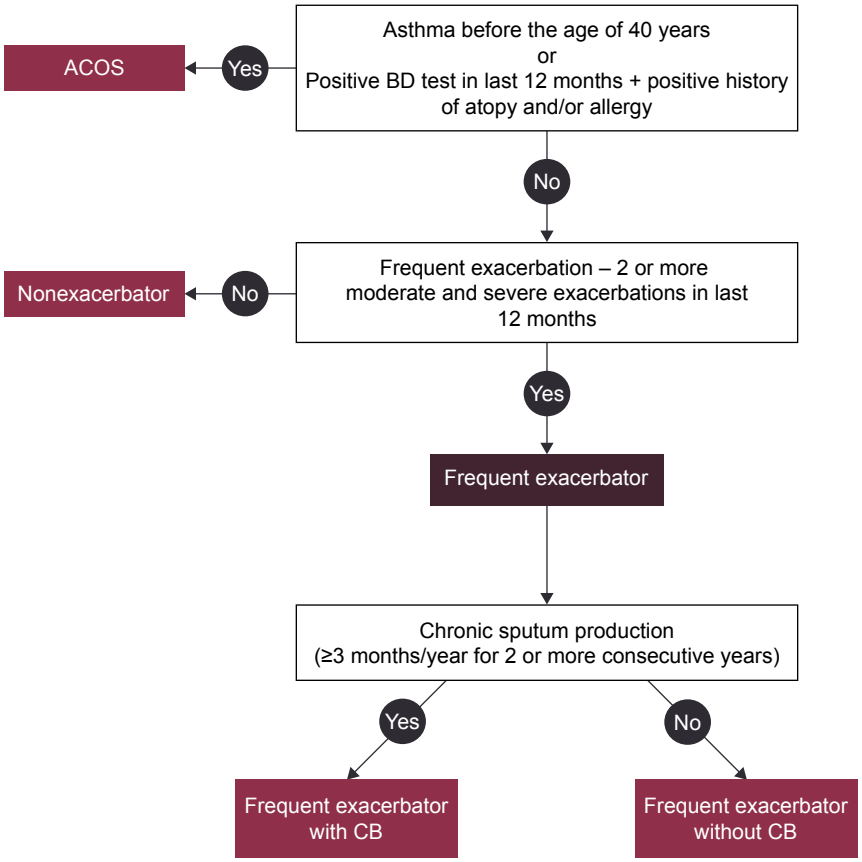

Figure 2 Definition of phenotypes.
Abbreviations: ACOS, asthma–COPD overlap syndrome; BD, bronchodilator; CB, chronic bronchitis.

were enrolled in this study if they fulfill the following inclusion criteria: age more than 40 years, confirmed diagnosis of COPD with postbronchodilator forced expired volume in 1 second/forced vital capacity (FEV_1/FVC) <0.7, and absence of exacerbation for at least 4 weeks. The rationale for inclusion criteria imply the following points. The presence of postbronchodilator airflow limitation among persons over age 40 years is the common definition of COPD cases used worldwide. Younger subjects with bronchial obstruction represent rather a rarity. Moreover, airflow limitation in people below 40 years of age may be due to other causes (asthma, bronchiolitis, primary ciliary dyskinesia, etc). Acute exacerbation of COPD has multiple negative effects on lung functions and respiratory symptoms (important parameters of our research). Therefore, we have used 4-week exacerbation-free interval as an elimination factor against bias (in term of symptoms and pulmonary functions). POPE study patients were divided into Group A if they have a smoking history equal and/or more than 10 pack-years and Group B if they were nonsmokers or smokers of less than 10 pack-years with evidence of inhalation exposure to other risk factors. Other risk factors were also counted: workplace environment, frequent exposure to outdoor pollution, frequent exposure to indoor pollution, and cooking without ventilation. COPD is clearly defined as an enhanced chronic inflammatory response to inhaled noxious particles and/or gases. Accordingly, non-/low-smoking patients without the aforementioned predefined risk factors were excluded from POPE study. Patient enrollment started in April 2014 and continued through July 2015; thus, a relevant seasonal bias of recruitment was prevented.

Study protocol

The study protocol was conceived to capture all data routinely available for clinical phenotyping during one visit. The parameters selected were identified by the Steering Committee (Table 2) together with a panel of national experts. An electronic case report form (eCRF) was used for local data collection.

For each patient, an in-depth history was obtained, including information on allergy and atopy, COPD symptoms (dyspnoea at rest/during exercise, fatigue, cough, chronic sputum production, purulent expectoration, and hemoptysis), smoking status and other respiratory risk factors, history of

acute respiratory events, including the number of COPD exacerbations with or without hospitalization, concomitant respiratory and nonrespiratory diseases, and assessment of the body composition (weight and height were routinely measured before spirometry, and self-reported weight loss or weight gain [absolute, relative rate] were registered as well). Comorbidities were scored using the Charlson comorbidity index.[24] Physical examination was performed on each patient. Pulmonary function data were obtained using standard equipment according to the ATS/ERS consensus guidelines.[25] The European Community of Coal and Steel reference equations were used in the POPE study. Postbronchodilator spirometry values for assessing COPD disease severity were reported in all patients (mandatory data). Furthermore, additional information regarding results obtained from bronchodilator reversibility testing, body plethysmography, diffusion capacity, fractional exhaled nitric oxide (FeNO), thoracic computed tomography, echocardiography, blood/sputum eosinophil assessment, serum immunoglobulin (IgE) measurement, arterial blood gases (ABG), and hematocrit (HTC) were recorded, if available, and performed within the last 12 months. Because this is a noninterventional study, obtaining the aforementioned additional information was considered optional. Thus, the information provided in this context represents the true level of diagnostic investigations for COPD in CEE countries. Patients included were classified into the Global Initiative for chronic Obstructive Lung Disease (GOLD) risk classification category on the basis of postbronchodilator FEV_1, history of COPD exacerbations, respiratory symptoms using the modified Medical Research Council (mMRC) dyspnea scale, and the COPD Assessment Test (CAT).[1,26,27] With regard to CAT, total CAT score and all CAT subitems were separately noted. Any pharmaceutical treatment prescribed for COPD for at least 1 month was recorded together with medications for typical comorbidities. Nonpharmaceutical therapeutic options, including long-term oxygen therapy (LTOT), use of noninvasive ventilation, bronchoscopic or surgical volume reduction procedures, and/or relevant vaccinations for individual patients were recorded as well. An overview of the collected data is listed in Table 3. Patients were stratified according to predefined phenotypes. The phenotypes proposed by the Steering Committee consensus were consistent with a recent recommendation from Spain proposing four clinically defined groups (Figure 2).[28] The following simple algorithm was used to determine the phenotype: 1) patients with a previous diagnosis of asthma were considered a mixed COPD–asthma phenotype (asthma–COPD overlap syndrome, ACOS), 2) patients with less than two exacerbations in the previous year were classified as nonexacerbators, 3) exacerbators with self-reported chronic cough and expectoration for more than 3 months of the year over 2 consecutive years were described as exacerbators with chronic bronchitis, and 4) the remaining exacerbators were classified as exacerbators without chronic bronchitis (predominantly with emphysema).[29]

Table 3 POPE study – captured parameters

Form	Parameter
History	Demographic data
	Age of first diagnosis
	History of allergy/atopy
	COPD symptoms
	Smoking history
	Other than tobacco smoking risk factors[a]
	History of acute respiratory events
	Concomitant respiratory diseases
	Weight assessment
	Comorbidities – Charlson comorbidity index
	Comorbidities – others
Physical examination	BMI
	Heart and breath frequency
	Physical signs of COPD and heart failure sings
Pulmonary function tests, laboratory	Postbronchodilator spirometry values
	Body plethysmography (TLC and RV)[b]
	TL_{CO} and K_{CO}[b]
	Bronchodilator test[b]
	Bronchial challenge test[b]
	FeNO[b]
	HRCT of thorax[b]
	Echocardiography[b]
	Blood/sputum eosinophil assessment[b]
	6-minute walk test[b]
	Total serum IgE measurement[b]
	ABG[b]
	HCT[b]
Questionnaires	CAT (total score and all 8 items separately)
	mMRC
Treatment	COPD pharmacological and nonpharmacological treatment
	Other respiratory treatment
	LTOT
	Surgery and BVR
	Vaccination
	Nonrespiratory concomitant treatment

Notes: [a]Required in nonsmokers, [b]optional.

Abbreviations: ABG, arterial blood gas; BMI, body mass index; BVR, bronchoscopic lung volume reduction; CAT, the COPD assessment test; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; HCT, hematocrit; HRCT, high-resolution computed tomography; IgE, immunoglobulin E; K_{CO}, Krogh factor; LTOT, long-term oxygen therapy; mMRC, modified Medical Research Council dyspnea scale; RV, residual volume; TLC, total lung capacity; TL_{CO}, transfer factor.

Analytical methods

Categorical variables were described by absolute and relative values. Median supplemented by the 5th–95th percentile range was used for continuous variables; a valid N was

reported in the case of missing values in continuous variables. Mean supplemented by standard deviation or 95% confidence interval was adopted for continuous variables when normality of the data was proven. Statistical significance of differences in continuous variables between/among groups of patients was analyzed using the Mann–Whitney *U*-test and Kruskal Wallis test, and Student's *t*-test for two groups or analysis of variance (ANOVA) followed by Tukey post hoc test. Paired *t*-test and/or the Wilcoxon paired test was used to analyze the statistical significance of differences of continuous variables between study time points; the McNemar test was used for the same purpose for categorical variables. Factors influencing binary end points without time to event and censoring (1 year mortality, etc) were analyzed using logistic regression. α=0.05 was used as a level of statistical significance. Analyses were performed using SPSS 22.0.0 (IBM Corporation, Armonk, NY, USA, 2013).

Sample size calculation

The background information from the available literature regarding the proportion of patients in different GOLD categories and occurrence of COPD phenotypes was utilized in the power analysis prior to the study.[9,10,30] The aim of the power analysis was to determine the sample size required to detect statistically significant differences in the prevalence of COPD phenotypes and other classification groups of interest, such as GOLD (1–4) and GOLD (A–D) measured as relative risk (RR) between participating countries within POPE study. Power analysis revealed that the optimal number of patients from the CEE region should be 3,500. This total number enables the observation of differences between various countries or groups of countries within the entire CEE region (sufficient precision guaranteed: approximately ±4% or ±2% within each participating country with categories/phenotypes of 20% or 5% prevalence, respectively; detectable RR of categories/phenotypes of 20% prevalence at least 1.5; detectable RR of categories of 5% prevalence nearly 2.0). Finally, we estimated a prevalence of nonsmoking subjects in approximately 5%–10% of the CEE COPD population.[31,32]

Organization of the study

The POPE study was an investigator-initiated study by a group of COPD researchers predominantly from CEE countries who recently formed a research forum called the "COPD Platform". This study was managed and supervised by the Steering Committee, which was responsible for the design and scientific integrity of the study (Table 2). The project management and statistical background was provided by the Institute of Biostatistics and Analyses, Masaryk University (Brno, Czech Republic). Data in the POPE study were entered into a database system, which was originally based on a modified version of the TrialDB system.[33–35] The TrialDB system is an easy and accessible tool for parametric data collection, validation, statistical processing, and online data management in compliance with respective legislation. A similar design was used in the multicenter, observational, cross-sectional PUMA study performed in Argentina, Colombia, Uruguay, and Venezuela.[36] The online application is accessible to users via the Internet browser. The security of individual records within the registry is ensured via deidentified data collection. An encryption protocol is used for data transfer between the user and central database to prevent tapping the communication between the client and server. For this reason, any communication between the client and server is achieved via the secure protocol HyperText Transfer Protocol Secure, using Secure Socket Layer encryption. The security of individual records within the registry is ensured via deidentified data collection.

The POPE study was registered in ClinicalTrials.gov with the identifier NCT02119494. More information can be obtained at http://www.copdplatform.com/. The sponsor of the study is the Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology, Vienna, Austria. The research institute received an unrestricted research grant from Boehringer Ingelheim RCV GmbH & Co. KG, which provided partial support for this study but had no influence on the rationale, methodology, or analysis.

Ethics

This study was performed in accordance with the European Union laws and the respective laws of participating countries. The study, protocol, informed consent, and patient information were submitted to ethic committees in the respective countries and to regulatory agencies, where required. The rights, safety, and well-being of clinical investigation subjects were protected according to the ethical principles of the Declaration of Helsinki. All patients (except Poland, where Ethic Committee approval was not required) were requested to provide their informed consent.

Discussion

Phenotyping patients with COPD has received increasing awareness in recent years.[37–41] A phenotype is defined as "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes".[37] A phenotypic approach to classify COPD has been adopted by a number of national and international societies.[9,29,42–44] It is actively used by the

Czech and Spanish COPD guidelines to promote treatment tailored to disease presentation, beyond singular treatment of airflow obstruction.[42,43] However, there is no general consensus on the number of phenotypes and the precise definition. Furthermore, we may need to acknowledge that individual patients may qualify for more than one phenotype.[42] A recent Spanish guideline proposed a classification of patients with COPD according to phenotypes similar to those used in the POPE study: infrequent exacerbators, frequent exacerbators with emphysema, frequent exacerbators with chronic bronchitis predominance, and the ACOS.[29,43] The definition of ACOS remains controversial; however, it may include the presence of COPD with either allergic rhinitis, bronchial hyperresponsiveness, and/or a previous diagnosis of asthma with reversible airflow obstruction.[45] The four (aforementioned) elementary COPD phenotypes used in the POPE study were based on routine clinical practice as they have some treatment consequences. Undoubtedly, wide scope of gathered parameters allows to evaluate the presence of COPD subjects with other disease "phenotypes", for example, COPD with pulmonary cachexia, COPD with high burden of comorbidities. Using these patient profiles in a recently published, observational, multicenter study of 3,125 patients with COPD, Miravitlles et al[28] observed a distribution of 60% nonexacerbators, 18% patients with ACOS, 19% exacerbators with chronic bronchitis, and 4% exacerbators without chronic bronchitis. While ACOS patients were more frequently females with better lung function, exacerbators presented with the most severe disease, with little difference between those with and without chronic bronchitis.

What is the clinical relevance of phenotyping patients with COPD?

First, there is evidence of differences in outcomes between different phenotypes. Burgel et al[46] observed significant differences in mortality when stratifying patients into phenotypes on the basis of airflow obstruction, evidence of emphysema, body mass index, and comorbidities. Using a very comprehensive and in-depth assessment of 342 patients with COPD, including symptoms, quality of life, exercise capacity, nutritional status, biomarkers of systemic and bronchial inflammation, sputum microbiology, computed tomography of the thorax, and echocardiography in addition lung function, Garcia-Aymerich et al[47] similarly demonstrated substantial differences in hospitalization rates and all-cause mortality between patient clusters. Second, there is increasing recognition and clinical acceptance to treat patients according to their phenotypic predominance. Infrequent exacerbators, defined as patients experiencing <2 exacerbations per year, may be treated with bronchodilation alone, and withdrawal of inhaled glucocorticoids may be safe in this particular population, according to data from recent studies.[48,49] Patients with COPD and a diagnosis of asthma may in turn have a survival benefit when treated with inhaled corticosteroids.[50] Similarly, augmented anti-inflammatory treatment, such as Roflumilast, may only improve excarbation rates in patients with chronic bronchitis and frequent exacerbations, whereas in patients with emphysema, there is no therapeutic benefit.[51] The POPE study furthermore investigated whether patients received nonpharmacological treatments in the past, such as long-term oxygen therapy, noninvasive ventilation, or lung volume reduction procedures (surgical or endoscopic).

Why performing a study of COPD phenotypes in CEE?

Many previous studies have attempted to identify and quantify the prevalence of different phenotypes of COPD using populations of various sources, severities, and particularities. The health care system, however, may substantially differ in CEE compared with other systems around the globe. Differences in environmental pollution, smoking prevalence, and comorbidities may substantially contribute to differences in the level of burden of COPD across the CEE region.[52,53] The POPE study specifically investigated symptom load, comorbidities, lung function, and exacerbation rates in both smoking and never-smoking patients with COPD in CEE and compared the results between these two groups. In fact, the prevalence of COPD in lifelong nonsmoking subjects in Poland was found to be 12%, whereas the prevalence of COPD in the nonsmoking population from Western countries usually ranged between 2% and 4%.[31,32] These differences may potentially be due to differences in mean fine particulate matter ($PM_{2.5}$) concentrations in CEE compared with Western Europe.[54] Moreover, different risks could lead to different clinical presentation of COPD syndrome. COPD of nonsmoking females due to biomass smoke exposure for instance is characterized by less emphysema but more air trapping than COPD due to tobacco smoke exposure.[55] On the other hand, access to modern therapeutic modalities due to differences in copayment may be different between Western and Eastern European countries, thus affecting prescribing behavior.[56] The POPE study shed new light onto the therapeutic relevance of phenotypes in a real-life setting in CEE. The multinational and multicenter approach in the POPE study was chosen not only to describe the status of patient care across the CEE region but also within the individual

participating countries. Finally, in contrast to many Western European countries where patients with COPD are mostly under the long-term supervising care of general practitioners, in CEE countries, these patients are rather taken care of by respiratory specialists (Table 4).[30,42,57–59]

Limitations

The POPE study design has a number of limitations that need to be acknowledged. First, it is a purely cross-sectional study aimed at assessing the prevalence of predefined phenotypes, without being able to validate these phenotypes prospectively on the basis of outcomes. Nevertheless, eligible patients underwent pre- and postbronchodilator spirometry, and completed a standardized questionnaire on demographics, environmental risk factors, symptoms, comorbidities, management, and use of health care resources.[36] The information provided through this comprehensive assessment is novel for the CEE region. Second, the POPE study was performed in multiple centers with different levels of health care access and differences in diagnostic and therapeutic approaches. Lung function assessment was performed in accordance with international guidelines, but without further standardizations or core laboratory evaluations. Thus, we cannot rule out differences in quality measures of performing these and other tests that might impact the comparability between sites and between countries. Nevertheless, the information provided in this context might also be considered the strength of the POPE study, as it provides real-life data regarding important information about the diagnostic approach and treatment modalities of patients with COPD in CEE.

Table 4 POPE study – distribution of COPD patients between general practitioners and pulmonologists in CEE

Country	Pope study cohort[a]		General approach in country[b]	
	Pulmonologists (%)	GPs (%)	Pulmonologists (%)	GPs (%)
Austria	100	0	60	40
Bulgaria	100	0	50	50
Croatia	100	0	50	50
Czech Republic	100	0	95	5
Hungary	100	0	100	0
Latvia	100	0	NA	NA
Poland	100	0	50	50
Russia	100	0	50	50
Serbia	100	0	100	0
Slovakia	100	0	100	0
Slovenia	100	0	NA	NA
Spain	Nonparticipant		25	75

Notes: [a]Clear data, [b]approximation by Steering Committee members.
Abbreviations: CEE, Central and Eastern Europe; GPs, general practitioners; NA, nonavailable.

Conclusion

The POPE provides new data regarding symptoms, clinical presentation, and treatment modalities of patients with COPD observed in daily clinical practice in the CEE region. This study may further prompt future research collaborations within participating countries with the intention to answer a number of other important unaddressed questions, such as the natural course of phenotypes, real-life prescription behavior in treatment-naive patients, and/or regional differences in treatment adherence. The long-term aims of the POPE study, however, are to educate and raise awareness for phenotypes of COPD and its potential implications regarding treatment and outcomes among both physicians and patients.

Acknowledgments

The authors thank the staff of all of the study centers for their cooperation in collecting the study data. The POPE study was supported by an unrestricted scientific grant by Boehringer Ingelheim, RCV. Special thanks to the participating countries and their national experts, who were not a part of the Steering Committee, but who greatly contributed to the enrollment of patients. National experts are part of the author collective of the main manuscript describing results of the project. The eCRF design and statistical analysis for sample size calculation was performed by J Jarkovsky, J Svancara, and M Uher, from the Institute of Biostatistics and Analyses.

Author contributions

All authors contributed to this manuscript: ZZ and VK wrote the manuscript; MM, AV, RT, AB, NT, AS, and KZ provided valuable reviews and comment. The study design was prepared by the Steering Committee: AV, VK, RT, NT, AS, KZ, AB, and MM. MM carried out the phenotype-based view of study design and coordinated the entire project proposal. AV and VK carried out the CRF and study protocol. ZZ participated in the electronic CRF design and performed statistical analysis plan and sample size calculation. RT, AB, and ZZ carried out the study validation. NT, AS, and KZ participated in the design of the study. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

Zuzana Zbozinkova is an employee of Institute of Biostatistics and Analyses, Masaryk University. Institute of Biostatistics and Analyses has received research grants

from (in alphabetical order) AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Pfizer, and Roche.

Adam Barczyk gave presentations at symposia sponsored and received fees for advisory board participation and travel grants from Boehringer Ingelheim, Chiesi, Novartis, Pfizer, Takeda, and Teva.

Ruzena Tkacova has received speaker and consulting fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Novartis.

Arschang Valipour received honoraria for consultancy services during advisory board meetings and/or lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Novartis. He received research grants from Boehringer Ingelheim.

Neven Tudoric has received reimbursement for attending scientific conferences, and/or fees for speaking and/or consulting from AstraZeneca, Boehringer Ingelheim, Cipla, Chiesi, GlaxoSmithKline, Novartis, Pliva-Teva, Sandoz, and Takeda. He was reimbursed for participation on the advisory boards for AstraZeneca, Boehringer Ingelheim, and Novartis.

Kirill Zykov is an investigator for, has received research support from, and is a consultant and/or speaker for AstraZeneca, Bayer, Boehringer Ingelheim, KrKa, Novartis, Takeda, and Thermo Fisher Scientific.

Atilla Somfay has received speaker fees from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Orion Pharma and has received consulting fees from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Orion Pharma.

Marc Miravitlles has received speaker fees from Almirall, AstraZeneca, Boehringer Ingelheim, Esteve, Chiesi, GlaxoSmithKline, Grifols, Menarini, Novartis, and Pfizer and has received consulting fees from Almirall, Boehringer Ingelheim, CSL Behring, Gebro Pharma, GlaxoSmithKline, Grifols, MedImmune, Novartis, Pfizer, and Takeda.

Vladimir Koblizek gave presentations at symposia and sponsored and received fees for advisory board participation and travel grants from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, GlaxoSmithKline, Medicom, Mundipharma, Novartis, and Takeda. He received research grants from AstraZeneca, Boehringer Ingelheim, and Novartis. The authors report no other conflicts of interest in this work.

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