ORIGINAL ARTICLE
COPD

Phenotypes of COPD patients with a smoking history in Central and Eastern Europe: the POPE Study

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ABSTRACT Chronic obstructive pulmonary disease (COPD) represents a major health problem in Central and Eastern European (CEE) countries; however, there are no data regarding clinical phenotypes of these patients in this region.

Participation in the Phenotypes of COPD in Central and Eastern Europe (POPE) study was offered to stable patients with COPD in a real-life setting. The primary aim of this study was to assess the prevalence of phenotypes according to predefined criteria. Secondary aims included analysis of differences in symptom load, comorbidities and pharmacological treatment.

3362 patients with COPD were recruited in 10 CEE countries. 63% of the population were nonexacerbators, 20.4% frequent exacerbators with chronic bronchitis, 9.5% frequent exacerbators without chronic bronchitis and 6.9% were classified as asthma–COPD overlap. Differences in the distribution of phenotypes between countries were observed, with the highest heterogeneity observed in the nonexacerbator cohort and the lowest heterogeneity observed in the asthma–COPD cohort. There were statistically significant differences in symptom load, lung function, comorbidities and treatment between these phenotypes.

The majority of patients with stable COPD in CEE are nonexacerbators; however, there are distinct differences in surrogates of disease severity and therapy between predefined COPD phenotypes.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of death worldwide and represents an important public health challenge [1]. While the major risk factor is tobacco smoking, other risk factors include age, a previous history of bronchial asthma, genetic predisposition and respiratory infections [2].

A significant heterogeneity exists with respect to clinical presentation, physiology, imaging, response to therapy, decline in lung function and survival in COPD [3]. As a result, there is consensus that forced expiratory volume in 1 s (FEV_1) alone cannot be used alone for the optimal diagnosis, assessment and management of the disease. Therefore, the identification and subsequent grouping of key features of COPD into clinically meaningful and useful subgroups, *i.e.* phenotypes, that provide prognostic information and allow the determination of appropriate therapy aiming at modifying clinically meaningful outcomes have been proposed [3].

Although multiple studies regarding the clinical presentation, diagnosis and management of COPD have been published, very few have specifically focused on Central and Eastern Europe (CEE) [4]. 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, healthcare access and the level of reimbursement for COPD treatment [4]. The primary aim of the Phenotypes of COPD in Central and Eastern Europe (POPE) 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. Secondary aims included analysis of differences in symptom load and diagnostic and therapeutic behaviour in patients classified into different phenotypes [4].

Materials and methods

Study population

The POPE study is an international, multicentre, observational cross-sectional study of COPD subjects in 11 CEE countries: Austria, Bulgaria, Croatia, Czech Republic, Hungary, Latvia, Poland, Russia, Serbia, Slovakia and Slovenia. The rationale, organisational structure and methodology of the POPE study led by a steering committee have been reported in greater detail [4]. Briefly, consecutive patients aged $\geqslant$40 years with a diagnosis of COPD confirmed by post-bronchodilator FEV_1/forced vital capacity <0.7 during a stable state ($\geqslant$4 weeks without exacerbation or worsening of any relevant comorbidity) were considered eligible. Study participation was offered to current and former smokers with >10 pack-years smoking history, as well as patients with other accepted inhaled risk factors for COPD, such as workplace, indoor and/or outdoor pollution. Patient selection in the present report is confined to smoking-related COPD. Patients were recruited in a secondary care setting; either in hospital-based pulmonary outpatient clinics or at pulmonologists' offices. The study protocol, informed consent and patient information were submitted to ethics committees in the respective countries and to regulatory agencies, where required; as a result, all patients were requested to provide their informed consent (except those in Poland, where formal ethics committee approval and written informed consent was not required due to the observational nature of the study) [4].

Data collection

For each patient, an in-depth history was obtained, including information on allergy and atopy, COPD symptoms, smoking status and other risk factors, history of acute respiratory events, including the number of COPD exacerbations, and concomitant respiratory diseases. Acute exacerbation was defined as patient-reported events of increased symptoms requiring treatment with systemic steroids and/or antibiotics with (severe exacerbation) or without (moderate exacerbation) hospitalisation [4].

Patients included were classified into Global Initiative for Chronic Obstructive Lung Disease (GOLD) risk classification categories based on post-bronchodilator FEV_1, history of COPD exacerbations, respiratory symptoms using the modified Medical Research Council (mMRC) dyspnoea scale and the COPD assessment test (CAT) [1].

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Comorbidities were scored using the Charlson comorbidity index (CCI) [5]. Pulmonary function data were obtained using standard equipment according to the American Thoracic Society/European Respiratory Society consensus guidelines [6, 7]. The European Community of Steel and Coal reference equations were used in the POPE study [8]. Any pharmaceutical or nonpharmaceutical treatment prescribed for COPD for ⩾1 month prior to inclusion was recorded, together with medications for comorbidities.

Patients were stratified according to predefined phenotypes. The phenotypes proposed by the steering committee consensus were in line with a recent recommendation from the Spanish and Czech COPD guidelines [4, 9, 10], proposing four clinically defined groups: nonexacerbators (NON-AE), asthma–COPD overlap syndrome (ACOS), frequent exacerbators with chronic bronchitis (AE-CB) and without chronic bronchitis (AE NON-CB). Chronic bronchitis was defined as a cough that occurred every day with sputum production and lasted for ⩾3 months, 2 years in a row [4]. Asthma diagnosis before the age of 40 years or a positive bronchodilator test in the previous 12 months with a history of atopy and/or allergy was defined as ACOS. NON-AE had a maximum of one acute exacerbation within the past 12 months (irrespective of severity), whereas AE-CB and AE NON-CB were required to have two or more moderate/severe exacerbations per year [4, 9, 10].

Study outcomes

The primary outcome of the POPE study was to assess the prevalence of COPD phenotypes according to predefined criteria in an unselected group of consecutively examined patients with stable disease in the CEE region in a real-life setting. Secondary aims of the study included analysis of differences in symptom load, lung function, comorbidities and treatment behaviour in the study population stratified according to the predefined phenotypes [4].

Statistical analysis

A power analysis was performed in order to determine the required sample size in each participating country given the predefined subgroups of interest (GOLD (1–4), GOLD (A–D), COPD phenotypes and number of participating countries). 3500 patients with an estimated number of 500 patients for each participating country were required to detect differences between countries with a precision of ±4% or ±2% within each participating country with categories of 20% or 5% prevalence, respectively. Detectable relative risk in categories with 20% prevalence is 1.5; detectable risk in categories with 5% prevalence is nearly 2.0. Analyses were performed using SPSS 22.0.0 (IBM Corporation, Armonk, NY, USA). Categorical variables were described as absolute and relative values. Mean±SD or median supplemented by 5th and 95th percentiles were adopted for continuous variables. Statistical significance of differences in continuous variables between/among groups of patients was analysed using Mann–Whitney test for two groups, and for more groups the Kruskal–Wallis test or analysis of variance (ANOVA) was used, followed by the Tukey *post hoc* test. Statistical significance of differences in categorical variables between/among groups of patients was tested using Fisher's exact test.

Results

Study population

Patient enrolment started in April 2014 and finished in July 2015. 3745 patients from 11 countries were enrolled, of which 3362 were considered eligible for this report (figure 1). The majority of patients were recruited at hospital-based pulmonary outpatient clinics (n=2445, 72.7%), whereas 27.3% of the study population (n=917) were recruited at pulmonologists' offices. Of those excluded, 233 were nonsmokers or smokers with <10 pack-years, 15 without a valid diagnosis of COPD, and 130 patients were excluded for lack of sufficient data for phenotyping. There was a higher proportion of female patients in those excluded than in the final cohort (62 out of 130 patients *versus* 1006 out of 3362 patients, respectively, p<0.001), but otherwise no statistically significant differences between those excluded and the final cohort with respect to age, smoking history and FEV_1. Demographics, symptom scores, lung function, Charlson comorbidity scores and exacerbation history of the final cohort are presented in table 1.

GOLD categories and COPD phenotypes

Patient characteristics were stratified according to predefined phenotypes (table 2) and GOLD classification (online supplementary table S1). 63% of the study population were considered NON-AE, 20.4% AE-CB, 9.5% AE NON-CB and 6.9% were patients with ACOS (figure 2). There were substantial differences in the distribution of phenotypes between countries, with the highest heterogeneity observed in the NON-AE cohort and the lowest heterogeneity observed in the ACOS cohort (figure 3). In addition, there were statistically significant (p<0.001) differences in the phenotypic distribution of patients presenting to hospital-based pulmonary outpatient clinics and office-based pulmonologists, with a larger proportion of nonexacerbators in the latter (figure 2). Countries with higher proportions of exacerbators (Austria,

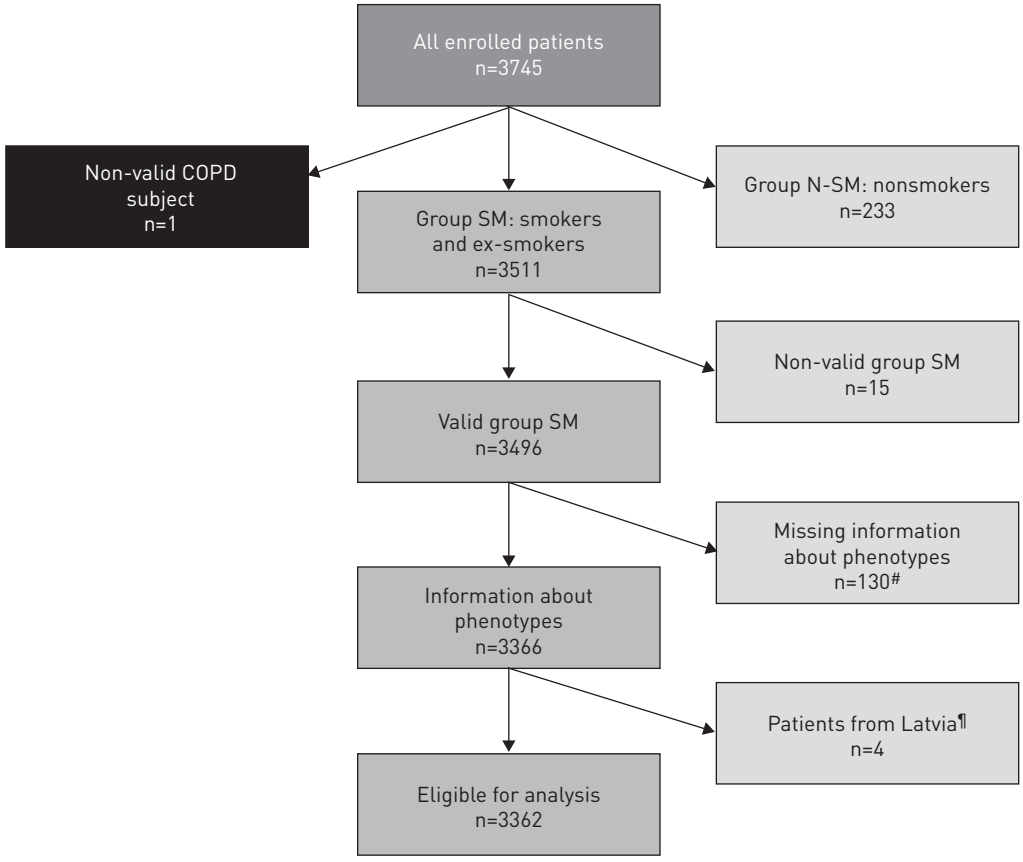

FIGURE 1 Enrolment of chronic obstructive pulmonary disease (COPD) subjects. SM: smokers or ex-smokers with COPD; N-SM: nonsmokers with COPD. #: 130 patients were excluded from the analysis because of missing information regarding bronchodilator reversibility (n=128) and exacerbation history (n=2); ¶: patients from Latvia were excluded due to small sample size.

Bulgaria, Croatia, Poland, Russia and Serbia) were largely represented by hospital-based outpatient clinics (figure 3 and online supplementary table S2). In contrast, patients presenting to the outpatient clinics had more severe airflow obstruction (FEV_1 % predicted) than patients presenting to pulmonologists' offices (online supplementary table S3).

Of the patients with ACOS, 75% had a diagnosis of asthma before the age of 40 years, 70% had atopy and 50% a positive bronchodilator test within the previous 12 months. A Venn diagram provides the distribution and the overlap of the diagnostic elements of this cohort (online supplementary figure S1).

Symptom load and comorbidities in COPD according to phenotypes

Based on symptom burden or lung function impairments, nonexacerbators were classified as either GOLD group B (45%) or group D (39%), respectively. Of the 830 NON-AE patients classified into GOLD D category, 653 patients had a FEV_1 <50% pred and 177 patients (77 patients with a FEV_1 >50% pred and 98 patients with a FEV_1 <50% pred) had one exacerbation with hospitalisation. All of these patients had a CAT score >10. The large majority of frequent exacerbators (92.5% of AE-NON CB and 97.7% of AE-CB) and 56% of patients with ACOS were in GOLD category D (online supplementary table S4).

There were statistically significant differences in age, sex and body mass index (BMI) between phenotypes (table 2). Patients with ACOS were on average younger, had a higher BMI and were more likely to be female compared with the other phenotypes. Exacerbators with or without chronic bronchitis had on average higher CAT and mMRC scores, and worse lung function compared with nonexacerbators and patients with ACOS. Similarly, a significantly higher proportion of patients with AE-CB (56.8%) had a CCI $\geqslant$2 compared with AE NON-CB (44.5%) and NON-AE (48.5%) patients (table 2).

The prevalence of comorbidities according to COPD phenotypes and GOLD categories is presented in table 3 and online supplementary table S5, respectively. Patients in the NON-AE group had the lowest prevalence of congestive heart failure and coronary artery disease. In contrast, significantly higher proportions of patients with AE-CB presented with a diagnosis of depression, anxiety, insomnia and/or

TABLE 1 Demographic data

Subjects	3362
Age at inclusion into POPE study years	66.0±8.8
Age at diagnosis years	58.4±9.0
Female	1010 (30.0)
Smoking exposure	
Ex-smoker	2147 (63.9)
Current smoker	1215 (36.1)
Duration of school education[#] years	11.3±2.8
Urban residence	2421 (73.1)
Rural residence	848 (25.6)
BMI[¶] kg·m^{-2}	27.2±5.7
CAT	17.4±7.8
mMRC	2.0±1.0
FEV_1 L	1.4±0.6
FEV_1[¶] % pred	52.8±18.5
FVC L	2.8±0.9
FVC[+] % pred	80.0±20.4
FEV_1/FVC	0.5±0.1
Moderate AEs[§] events·year^{-1}	0.9±1.3
Severe AEs[f] events·year^{-1}	0.3±0.7
Total AEs events·year^{-1}	1.2±1.6
Charlson comorbidity index[##]	
1	1684 (50.1)
2	805 (24.0)
3	458 (13.6)
⩾4	414 (12.3)

Data are presented as n, mean±SD or n (%). Relative frequencies are calculated only from the collected data. POPE: Phenotypes of COPD in Central and Eastern Europe; COPD: chronic obstructive pulmonary disease; BMI: body mass index; CAT: COPD assessment test; mMRC: modified Medical Research Council dyspnoea scale; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; AE: acute exacerbation of COPD. [#]: n=3251; [¶]: n=3360; [+]: n=3359; [§]: AE treated with antibiotics and/or corticosteroids out of hospital; [f]: AE treated in hospital; [##]: n=3361.

anaemia compared with other phenotypes. In contrast, patients with ACOS were more likely to have gastro-oesophageal reflux disease, osteoporosis and/or hyperlipidaemia compared with the other groups (table 3). According to GOLD classification, patients in GOLD groups B and D had the greatest prevalence of cardiovascular, neuropsychiatric and metabolic comorbidities (online supplementary table S5).

Treatment of COPD in CEE according to phenotypes

A statistically significant higher proportion of NON-AE patients received inhaled mono- or dual bronchodilator therapy compared with the other phenotypes (table 4). In contrast, long-acting β-adrenoceptor agonist (LABA)/inhaled corticosteroid (ICS) combinations were more prevalent in patients with the ACOS phenotype. The use of triple inhaler therapy (long-acting muscarinic antagonists (LAMA), LABA and ICS) was present in 36.8% of NON-AE patients, 60.7% of AE-CB patients, 59.9% of AE NON-CB patients and 53.7% of patients with ACOS (table 4). Overall, 98.8% of ICS were prescribed in combination with LABA and/or LAMA. ICS-containing treatment was prescribed in 98 (34%) out of 287 patients in GOLD group A and 426 (41.6%) out of 1023 patients in GOLD group B (online supplementary table S6). All 98 patients in GOLD group A who received ICS had concomitant asthma, *i.e.* had the ACOS phenotype. In GOLD group B, 68 out of the 426 patients on ICS had ACOS (15.9% of patients on ICS and 6.6% of all GOLD group B patients).

Discussion

The POPE study is an investigator-initiated, real-life, multinational study to assess the prevalence of predefined clinical phenotypes in a large sample of patients with COPD in CEE. We observed significant differences in the distribution of phenotypes between countries and significant differences in lung function, symptom scores, comorbidities and treatment patterns between patient categories of interest.

COPD has long been categorised using the FEV_1-based GOLD classification [11]; however, it is now widely recognised as a complex heterogeneous syndrome with pulmonary and extrapulmonary features [12]. Marked heterogeneity exists within each GOLD stage in terms of symptoms, exacerbations, quality of life

TABLE 2 Characteristics of patients with chronic obstructive pulmonary disease (COPD) according to phenotypes

	Subjects	NON-AE (a)	AE NON-CB (b)	AE-CB (c)	ACOS (d)	p-value
Subjects		2125	319	687	231	
Female[#]		625 (29.4)[d]	87 (27.3)[d]	193 (28.1)[d]	105 (45.5)[a,b,c]	**<0.001**
Age at diagnosis[¶] **years**		59.3±9.0[b,c,d]	57.7±8.9[a,d]	57.7±8.4[a,d]	53.6±8.6[a,b,c]	**<0.001**
Age at inclusion[¶] **years**		66.3±8.7 [d]	65.9±8.8[d]	66.6±8.3[d]	62.3±10.2[a,b,c]	**<0.001**
BMI[¶] **kg·m^{-2}**	3360	27.4±5.7[c]	26.6±5.3[d]	26.5±5.6[a,d]	28.3±6.0[b,c]	**<0.001**
FEV$_1$[¶] **% pred**	3360	56.0±18.3[b,c]	44.4±16.5[a,d]	45.7±16.9[a,d]	55.9±18.8[b,c]	**<0.001**
FVC[¶] **% pred**	3359	82.0±20.0[b,c]	74.5±20.5[a,d]	75.3±20.6[a,d]	83.3±20.3[b,c]	**<0.001**
CAT[+]		15.8±7.3[b,c,d]	18.2±7.4[a,c]	22.2±7.5[a,b,d]	17.8±7.8[a,c]	**<0.001**
mMRC[+]		1.8±1.0[b,c]	2.2±1.0[a,c]	2.5±0.9[a,b,d]	2.0±1.1[c]	**<0.001**
Atopy[#]		129 (6.1)[d]	21 (6.6)[d]	49 (7.1)[d]	161 (69.7)[a,b,c]	**<0.001**
Asthma[#]					173 (74.9)	
Moderate AEs[¶,§] **events·year^{-1}**		0.3±0.5[b,c,d]	1.9±1.3[a,d]	2.1±1.6[a,d]	1.3±1.5[a,b,c]	**<0.001**
Severe AEs[¶,*f*] **events·year^{-1}**		0.1±0.3[b,c,d]	0.8±0.9[a,d]	0.9±1.0[a,d]	0.3±0.7[a,b,c]	**<0.001**
Total AEs[¶] **events·year^{-1}**		0.4±0.5[b,c,d]	2.8±1.5[a,c,d]	3.0±1.8[a,b,d]	1.6±1.8[a,b,c]	**<0.001**
Positive bronchodilator test	2524	284 (18.5)[b,c,d]	27 (11.2)[a,d]	66 (11.8)[a,d]	92 (50.3)[a,b,c]	**<0.001**
Charlson index[#]	3361					
1		1095 (51.6)[c]	177 (55.5)[c]	297 (43.2)[a,b]	115 (49.8)	**<0.001**
2		508 (23.9)	74 (23.2)	163 (23.7)	60 (26.0)	0.884
3		290 (13.7)[b,c]	25 (7.8)[a,c]	118 (17.2)[a,b,d]	25 (10.8)[c]	**<0.001**
⩾4		231 (10.9)[c]	43 (13.5)	109 (15.9)[a]	31 (13.4)	**0.006**

Data are presented as n, n (%) or mean±SD, unless otherwise stated. n=3362, unless otherwise stated. Bold type represents statistical significance. NON-AE: nonexacerbator; AE NON-CB: exacerbator without chronic bronchitis; AE-CB: exacerbator with chronic bronchitis; ACOS: asthma–COPD overlap syndrome; BMI: body mass index; FEV$_1$: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; CAT: COPD assessment test; mMRC: modified Medical Research Council dyspnoea scale; AE: acute exacerbation of COPD. [#]: relative frequencies are calculated only from the collected data. Differences between phenotypes are tested by Fisher exact test. In variables, where the difference is significant, indices a, b, c, d show statistically significant difference between two phenotypes (Fisher exact test). [¶]: statistical significance tested by one-way ANOVA. In variables where the difference is significant, indices a, b, c, d show statistically significant difference between two phenotypes (Tukey). [+]: statistical significance tested by Kruskal–Wallis test. In variables, where the difference is significant, indices a, b, c, d show statistically significant difference between two phenotypes; [§]: AE treated with antibiotics and/or corticosteroids out of hospital; [*f*]: AE treated in hospital.

and exercise capacity [13]. Phenotypes are defined by "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes like symptoms, exacerbations, response to therapy, rate of disease progression and/or death" [3, 14].

Although prevalence data on phenotypes are rather scarce, various countries, such as the Czech Republic, England, Poland, Russia, Spain and Sweden have adopted the concept of COPD phenotyping in their respective guidelines according to a recent European survey [15]. Indeed, several of the national guidelines prefer tailored treatment recommendations on the basis of such patient phenotypes. Although this approach introduces complexity into the treatment algorithm and departs from the "one size fits all" treatment based on the level of FEV1 alone, it is likely to improve the clinical outcomes of most patients with COPD [12].

The phenotypic classification used in the present report was based on the Czech COPD guidelines and was consistent with the Spanish recommendation for patient phenotyping in COPD [9, 10]. Using the cohort definitions put forward in the latter report, a recent longitudinal study of 831 COPD patients in Spain demonstrated stability of these phenotypes over the course of 1 year, and, similar to our findings, distinct differences in lung function and symptom load according to the predefined phenotypes [16]. We observed that the majority of patients were classified as nonexacerbators. As these patients may present with exacerbations in the future, the term "low exacerbation risk" or infrequent exacerbators may have been more appropriate. However, the term "nonexacerbator" was used in the Spanish and Czech guidelines and thus been retained for the current study [4]. Indeed, using this definition we observed a prevalence of 63% non-AE patients, which was similar to a 61% prevalence rate in Spain [17], although there were substantial differences in prevalence between participating countries in the current report. Consistent with previous studies, these patients had on average better lung function and lower symptom and comorbidity scores compared with exacerbators [13, 18, 19]. A mean CAT score of 15.8 in these patients, who are characterised with stable disease and a maximum of one acute exacerbation in the past 12 months, raises questions as to the clinical usefulness of the current threshold of 10 points, discriminating patients with low symptom load,

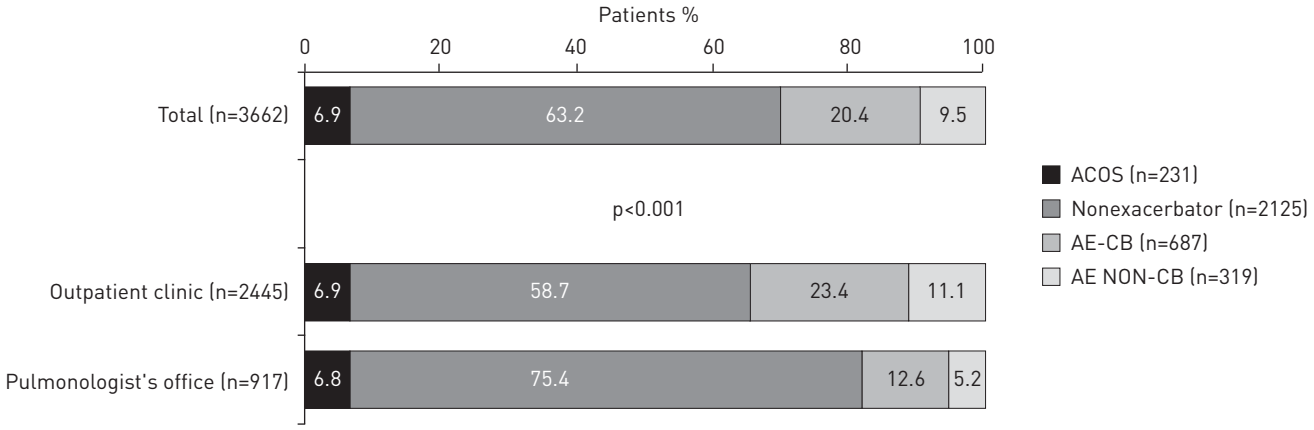

FIGURE 2 Phenotypes of chronic obstructive pulmonary disease (COPD) in central and Eastern Europe (n=3362). p-values were calculated using Fisher's exact test. ACOS: asthma–COPD overlap syndrome; AE-CB: frequent exacerbator with chronic bronchitis; AE NON-CB: frequent exacerbator without chronic bronchitis.

as opposed to those with high symptom load. In fact, a recent meta-analysis of studies using the CAT did not support the recommended cut-off of 10 points for the purpose of assessing patient symptoms [20].

Within the group of exacerbators, patients with chronic bronchitis had a greater extent of dyspnoea, higher total frequency of exacerbations and a greater prevalence of cardiovascular and other comorbidities, such as depression, insomnia and anaemia, compared with the non-chronic bronchitis and ACOS phenotypes. It is therefore not surprising that frequent exacerbators with chronic bronchitis present with higher healthcare costs and are at an increased risk of death compared with other COPD phenotypes [21, 22]. However, identifying these patients has therapeutic implications, as exacerbators with chronic bronchitis may be particularly responsive to specific anti-inflammatory treatments, such as phosphodiesterase-4 inhibitors [23].

Recently, the characterisation of ACOS as a separate phenotype has similarly attracted much interest due a consensus statement by the Global Initiative for Asthma (GINA) and GOLD on the diagnosis, assessment and treatment of this condition [24]. The prevalence of ACOS in the POPE study was 7% and ranged between 5% and 10% between the countries. In agreement with previous reports, ACOS patients were younger, more frequently female and had milder airflow obstruction [17]. Prevalence rates for ACOS in other recent reports vary between 3% and 27% [17, 25, 26]. This wide range between reports may be partially due to differences in the definition of or diagnostic criteria for ACOS [27], concentrations of fine particulate matter in the respective region of interest [28] and/or genetic variants associated with this syndrome [29]. According to a recent global expert consensus the key features of ACOS should include

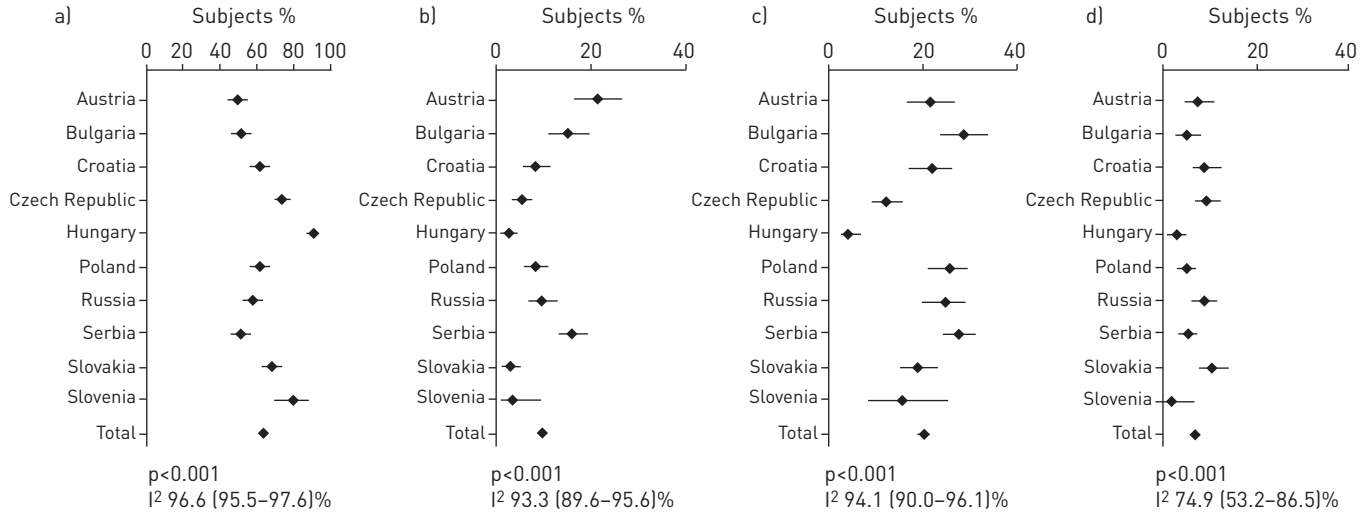

FIGURE 3 Country-specific heterogeneity distribution of chronic obstructive pulmonary disease (COPD) phenotypes. Data are presented as % (95% CI). a) Nonexacerbators; b) frequent exacerbators without chronic bronchitis; c) frequent exacerbators with chronic bronchitis; d) asthma–COPD overlap syndrome.

TABLE 3 Prevalence of comorbidities in Central and Eastern European patients with chronic obstructive pulmonary disease (COPD) according to phenotype

	Phenotypes				p-value
	NON-AE (a)	AE NON-CB (b)	AE-CB (c)	ACOS (d)	
Subjects n	2125	319	687	231	
Cardiovascular disease#	1553 (73.1)	222 (69.6)	517 (75.3)	156 (67.5)	0.070
Myocardial infarction	186 (8.8)	26 (8.2)	67 (9.8)	12 (5.2)	0.186
Congestive heart failure	230 (10.8)[b,c]	53 (16.6)[a]	133 (19.4)[a,d]	27 (11.7)[c]	**<0.001**
Peripheral vascular disease	258 (12.1)	27 (8.5)	95 (13.8)	22 (9.5)	0.061
Cerebrovascular disease	192 (9.0)	24 (7.5)	78 (11.4)	25 (10.8)	0.158
Coronary artery disease	444 (20.9)[c]	82 (25.7)	179 (26.1)[a]	59 (25.5)	**0.011**
Hypertension	1367 (64.3)	192 (60.2)	451 (65.6)	138 (59.7)	0.193
Atrial fibrillation	169 (8.0)	25 (7.8)	62 (9.0)	15 (6.5)	0.655
Pulmonary embolism	46 (2.2)	10 (3.1)	10 (1.5)	3 (1.3)	0.301
Peptic ulcer disease	160 (7.5)[c]	22 (6.9)[c]	77 (11.2)[a,b]	25 (10.8)	**0.010**
Liver disease	84 (4.0)	12 (3.8)	38 (5.5)	13 (5.6)	0.227
Gastro-oesophageal reflux disease	212 (10.0)[b,d]	46 (14.4)[a]	79 (11.5)[d]	41 (17.7)[a,c]	**0.001**
Renal disease	50 (2.4)[b,c]	18 (5.6)[a]	34 (4.9)[a]	7 (3.0)	**0.001**
Solid tumour	109 (5.1)[d]	13 (4.1)	42 (6.1)[d]	4 (1.7)[a,c]	**0.039**
Diabetes mellitus	323 (15.2)	44 (13.8)	125 (18.2)	45 (19.5)	0.082
Hyperlipidaemia	541 (25.5)[d]	81 (25.4)[d]	192 (27.9)[d]	82 (35.5)[a,b,c]	**0.010**
Anaemia	50 (2.4)[c]	8 (2.5)[c]	41 (6.0)[a,b]	7 (3.0)	**<0.001**
Osteoporosis	164 (7.7)[b,c,d]	43 (13.5)[a]	80 (11.6)[a]	34 (14.7)[a]	**<0.001**
Depression	151 (7.1)[b,c,d]	37 (11.6)[a,c]	129 (18.8)[a,b,d]	27 (11.7)[a,c]	**<0.001**
Anxiety	158 (7.4)[b,c]	37 (11.6)[a]	99 (14.4)[a,d]	15 (6.5)[c]	**<0.001**
Insomnia	231 (10.9)[c]	30 (9.4)[c]	128 (18.6)[a,b]	32 (13.9)	**<0.001**

Data are presented as n or n (%), unless otherwise stated. Differences between phenotypes were tested by Fisher's exact test. Where the difference is significant, indices a, b, c and d show statistically significant differences between two phenotypes (Fisher's exact test). Bold type represents statistical significance. NON-AE: nonexacerbator; AE NON-CB: exacerbator without chronic bronchitis; AE-CB: exacerbator with chronic bronchitis; ACOS: asthma–COPD overlap syndrome. #: any of myocardial infarction, congestive heart failure, peripheral vascular disease, coronary artery disease, hypertension or atrial fibrillation.

persistent airflow obstruction, a history of cigarette smoking and a physician diagnosis of asthma before the age of 40 years [30]. Indeed, the majority of patients within this cohort received the diagnosis of ACOS on the basis of a previous asthma history before the age of 40 years, which has also been used as a diagnostic

TABLE 4 Inhaler therapy in Central and Eastern European patients with chronic obstructive pulmonary disease (COPD) according to phenotype

	Phenotypes				p-value
	NON-AE (a)	AE NON-CB (b)	AE-CB (c)	ACOS (d)	
Subjects n	2125	319	687	231	
Mono-LAMA	286 (13.5)[b,c,d]	23 (7.2)[a,d]	33 (4.8)[a]	7 (3.0)[a,b]	**<0.001**
Mono-LABA	214 (10.1)[b,c,d]	8 (2.5)[a]	17 (2.5)[a]	8 (3.5)[a]	**<0.001**
Mono-ICS	12 (0.6)	2 (0.6)	5 (0.7)	5 (2.2)	0.077
LAMA + LABA	376 (17.7)[b,c,d]	35 (11.0)[a]	74 (10.8)[a]	18 (7.8)[a]	**<0.001**
LAMA + ICS	11 (0.5)	4 (1.3)	6 (0.9)	2 (0.9)	0.291
LABA + ICS	296 (13.9)[d]	51 (16.0)[d]	113 (16.4)[d]	58 (25.1)[a,b,c]	**<0.001**
LAMA + LABA + ICS	782 (36.8)[b,c,d]	191 (59.9)[a]	417 (60.7)[a]	124 (53.7)[a]	**<0.001**
No maintenance inhaler therapy	147 (6.9)[b,c]	5 (1.6)[a]	22 (3.2)[a]	9 (3.9)	**<0.001**

Data are presented as n or n (%), unless otherwise stated. n=3362. Differences between phenotypes were tested by Fisher's exact test. Where the difference is significant, indices a, b, c and d show statistically significant difference between two phenotypes (Fisher's exact test). Bold type represents statistical significance. NON-AE: nonexacerbator; AE NON-CB: exacerbator without CB; AE-CB: exacerbator with CB; ACOS: asthma–COPD overlap syndrome; ICS: inhaled corticosteroid; LABA: long-acting β-agonist; LAMA: long-acting muscarinic antagonist.

criterion in large epidemiological studies, such as COPDGene [31]. A recent study demonstrated that this simple criterion is equally useful to diagnose ACOS compared with a more in-depth diagnostic algorithm including sputum eosinophilia, large bronchodilator reversibility, atopy and/or elevated IgE levels [27]. In addition, the simple medical history of asthma in patients with COPD is an independent predictor of response to inhaled corticosteroids with respect to survival benefits [32]. Despite these proven benefits of ICS in patients with concomitant bronchial asthma, our data also suggest potential ICS undertreatment in patients with ACOS: only 81.1% of such subjects were receiving ICS. In contrast, a substantial proportion of GOLD group B patients received ICS treatment in the absence of ACOS, which is not in line with current GOLD strategy, GINA guidelines and several national recommendations [1, 9, 15, 24]. Similarly, in a recent analysis of prescribing patterns in the primary-care setting in the United Kingdom, most COPD patients received ICS treatment irrespective of severity of airflow limitation, asthma diagnosis and exacerbation history [33]. While we cannot rule out that the lack of exacerbations is a result of ICS treatment in some cases, our data appear to confirm other studies which have similarly demonstrated poor adherence to GOLD treatment recommendations [34, 35]. The limited adherence to guidelines may be due to multiple factors, including, but not restricted to, lack of familiarity with treatment recommendations [36], disbeliefs regarding efficacy of treatments [37] and/or difficulties in distinguishing between asthma and COPD [38].

We have to acknowledge a number of limitations in the present report. First, the cross-sectional design of the POPE study did not allow us to prospectively validate clinical outcomes of the phenotypes. However, using an almost identical phenotypic classification to that used in our study, Cosio *et al.* [16] recently reported statistically significant differences in 1-year mortality between patients with ACOS and those with AE-CB. Second, the assessment of comorbidities was based on physician diagnosis rather than on a systematic diagnostic work-up [39]. Thus, the current report may have potentially underestimated the burden of comorbidities in COPD in the CEE region. Third, as this was a real-life study across multiple countries we need to acknowledge that some of the data presented may be subject to regional or local recruitment bias and test performance. Indeed, we observed significant differences in the distribution of phenotypes depending on whether patients were recruited at hospital-based pulmonary outpatient clinics or pulmonologists' offices. At the same time, significant heterogeneity was observed in the distribution of phenotypes between the participating countries, which may reflect differences in access to healthcare, treatment patterns and/or reimbursement of therapy, and also other factors whose identification and analyses were beyond the scope of the present study. Nevertheless, it is remarkable that the global distribution of phenotypes observed in CEE is quite consistent to that reported for other countries [16, 17].

In conclusion, the POPE study provides data on clinical COPD phenotypes in a large population of COPD patients from CEE countries in a real-life setting. Prospective studies are necessary to investigate the evolution of phenotypes and their impact on selecting treatments and subsequent outcomes among COPD patients.

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