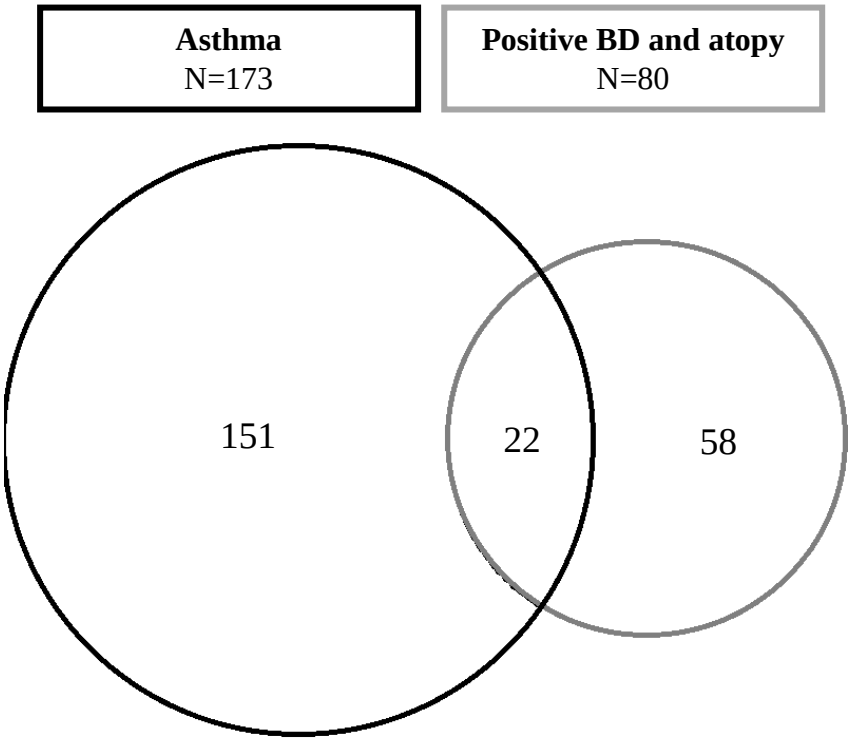
Supplementary material

Supplementary Figure S1 Venn diagram for the ACOS group (N=231)



ACOS – Asthma and COPD Overlap Syndrome, BD – bronchodilator test

Supplementary Table S1 Characteristics of patients with COPD according to GOLD classification (N=3 361)

	GOLD categories				P-value
	A N=287 (a)	**B N=1 023 (b)**	**C N=125 (c)**	**D N=1 926 (d)**	
Sex (female) [2]	94 (32.8%)	335 (32.7%)	35 (28.0%)	545 (28.3%)	0.055
Age at diagnosis[1]	58.3 (9.1) [b]	59.8 (9.2) [a, c, d]	56.6 (8.8) [b]	57.9 (8.8) [b]	< **0.001**
Age at inclusion[1]	63.8 (9.0) [b, d]	66.8 (9.1) [a, c]	63.8 (8.7) [b, d]	66.1 (8.5) [a, c]	< **0.001**
BMI[1] **(N=3 359)**	27.8 (4.4) [c, d]	28.4 (5.8) [c, d]	26.1 (4.7) [a, b]	26.5 (5.8) [a, b]	< **0.001**
FEV_1 (% predicted)[1] **(N=3 360)**	70.7 (13.3) [b, c, d]	66.8 (12.5) [a, c, d]	50.1 (18.7) [a, b, d]	42.8 (14.7) [a, b, c]	< **0.001**
FVC (% predicted) [1] **(N=3 359)**	94.5 (17.1) [b, c, d]	90.7 (16.3) [a, c, d]	80.3 (20.6) [a, b, d]	72.2 (19.1) [a, b, c]	< **0.001**
CAT (total) [3]	6.0 (2.3) [b, d]	16.6 (6.2) [a, c, d]	6.6 (2.1) [b, d]	20.3 (7.0) [a, b, c]	< **0.001**
mMRC [3]	0.7 (0.5) [b, d]	1.8 (0.9) [a, c, d]	0.8 (0.4) [b, d]	2.4 (0.9) [a, b, c]	< **0.001**
Atopy[2]	37 (12.9%)	109 (10.7%)	8 (6.4%)	206 (10.7%)	0.275
Asthma[2]	16 (5.6%)	47 (4.6%)	11 (8.8%)	99 (5.1%)	0.245
Number of moderate AE´s /year[1]	0.3 (0.4) [c, d]	0.3 (0.5) [c, d]	0.9 (1.0) [a, b, d]	1.3 (1.5) [a, b, c]	< **0.001**
Number of severe AE´s/year[1]	0.0 (0.0) [c, d]	0.0 (0.0) [c, d]	0.4 (0.5) [a, b, d]	0.6 (0.9) [a, b, c]	< **0.001**
Number of total AE´s /12year[1]	0.3 (0.4) [c, d]	0.3 (0.5) [c, d]	1.2 (1.1) [a, b, d]	1.9 (1.8) [a, b, c]	< **0.001**
Positive bronchodilator test (N=2 524)	56 (25.3%) [d]	190 (24.9%) [d]	16 (17.0%)	207 (14.3%) [a, b]	< **0.001**
Charlson index[2] **(N=3 360)**					
1	185 (64.5%) [b, d]	476 (46.5%) [a, c]	78 (62.4%) [b, d]	944 (49.0%) [a, c]	< **0.001**
2	56 (19.5%) [b]	273 (26.7%) [a, c]	22 (17.6%) [b]	454 (23.6%)	**0.017**
3	30 (10.5%)	149 (14.6%)	16 (12.8%)	263 (13.7%)	0.352
≥ 4	16 (5.6%) [b, d]	125 (12.2%) [a]	9 (7.2%) [d]	264 (13.7%) [a, c]	< **0.001**

AE´s – acute exacerbations of COPD; BMI – Body Mass Index; CAT – COPD Assessment Test,; FEV1 – forced expiratory volume in one second; FVC – forced vital capacity; MRC – modified Medical Research Council dyspnea scale;
N – number of COPD patients

[1] Continuous variables are described by mean (standard deviation). Statistical significance tested by One way ANOVA. In variables, where the difference is significant, indexes a, b, c, d show statistically significant difference between two phenotypes (Tukey).

[2] Categorical variables are described by absolute (relative) frequencies. 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, indexes a, b, c, d show statistically significant difference between two phenotypes (Fisher exact test).

[3] Continuous variables are described by mean (standard deviation). Statistical significance tested by Kruskal-Wallis test. In variables, where the difference is significant, indexes a, b, c, d show statistically significant difference between two phenotypes .

Supplementary Table S2: Patient recruitment pattern in the POPE study

Country	**Pope Study cohort**	
	Patients enrolled in the pulmonologist office	Patients enrolled in hospital based pulmonary outpatient clinics
Austria	0 (0.0%)	283 (100.0%)
Bulgaria	0 (0.0%)	272 (100.0%)
Croatia	0 (0.0%)	331 (100.0%)
Czech Republic	232 (58.1%)	167 (41.9%)
Hungary	254 (70.9%)	104 (29.1%)
Poland	0 (0.0%)	430 (100.0%)
Russia	0 (0.0%)	355 (100.0%)
Serbia	64 (12.4%)	452 (87.6%)
Slovakia	302 (85.6%)	51 (14.4%)
Slovenia	65 (100.0%)	0 (0.0%)
Total	**917 (27.3%)**	**2445 (72.7%)**

Supplementary Table S3 – Characteristics of patients presenting to hospital based outpatient clinics and pulmonologist offices

	Outpatient clinics (N=2445)	Pulmonologist office (N=917)	P-value
Total			
Age	66.0 (51.0; 81.0)	66.0 (53.0; 81.0)	0.203
Number of cigarettes/day	20.0 (10.0; 40.0)	20.0 (8.0; 40.0)	< **0.001**
FEV_1 (%)	50.2 (23.2; 83.9)	56.6 (29.7; 85.5)	< **0.001**
ACOS	N=169	N=62	
Age	61.0 (43.0; 78.0)	65.5 (53.0; 80.0)	< **0.001**
Number of cigarettes/day	20.0 (8.0; 40.0)	20.0 (10.0; 40.0)	0.396
FEV_1 (%)	54.1 (29.0; 86.4)	51.9 (33.1; 83.3)	0.934
NON-AE	N=1434	N=691	
Age	66.0 (52.0; 80.0)	66.0 (53.0; 81.0)	0.435
Number of cigarettes/day	20.0 (10.0; 40.0)	20.0 (8.0; 40.0)	< **0.001**
FEV_1 (%)	53.0 (26.1; 87.3)	59.2 (31.6; 87.1)	< **0.001**
AE NON-CB	N=271	N=48	
Age	65.0 (53.0; 82.0)	67.0 (52.0; 79.0)	0.216
Number of cigarettes/day	20.0 (10.0; 40.0)	20.0 (10.0; 40.0)	0.574
FEV_1 (%)	42.6 (20.5; 73.9)	40.6 (23.1; 67.1)	0.993
AE CB	N=571	N=116	
Age	66.0 (53.0; 81.0)	68.0 (56.0; 81.0)	0.123
Number of cigarettes/day	20.0 (10.0; 40.0)	20.0 (10.0; 40.0)	0.417
FEV_1 (%)	43.4 (19.5; 76.9)	47.1 (25.3; 71.4)	**0.044**

Parameters are described as median (5. ; 95. percentile) and tested by Mann-Whitney test.

NON-AE = Non-exacerbator; AE NON-CB = Exacerbator without CB, AE CB = Exacerbator with CB; ACOS = Asthma - COPD Overlap Syndrome

Supplementary Table S4

Distribution of GOLD classification according to phenotypes (N=3 361)

		Phenotypes				
		NON-AE N=2 125 (a)	**AE NON-CB N=319 (b)**	**AE CB N=687 (c)**	**ACOS N=231 (d)**	**P-value**
GOLD (A-D)	**A**	264 (12.4%)	-	-	23 (10.0%)	0.340
	B	957 (45.1%) [d]	-	-	66 (28.6%) [a]	**< 0.001**
	C	73 (3.4%) [b]	24 (7.5%) [a, c]	16 (2.3%) [b, d]	12 (5.2%) [c]	**0.001**
	D	830 (39.1%) [b, c, d]	295 (92.5%) [a, c, d]	671 (97.7%) [a, b, d]	130 (56.3%) [a, b, c]	**< 0.001**

NON-AE = Non-exacerbator; AE NON-CB = Exacerbator without CB
AE CB = Exacerbator with CB; ACOS = Asthma - COPD Overlap Syndrome
Variables are described by absolute (relative) frequencies.
Differences between phenotypes are tested by Fisher exact test. In variables, where the difference is significant, indexes a, b, c, d show statistically significant difference between two phenotypes (Fisher exact test).

Supplementary Table S5 Prevalence of comorbidities in CEE patients with COPD according to GOLD classification (N=3 361)

	GOLD categories				P-value
	A N=287 (a)	**B N=1 023 (b)**	**C N=125 (c)**	**D N=1 926 (d)**	
Cardiovascular disease*	192 (66.9%) [b, d]	763 (74.6%) [a]	83 (66.4%)	1 409 (73.2%) [a]	**0.025**
Myocardial infarction	17 (5.9%) [b]	108 (10.6%) [a, d]	9 (7.2%)	157 (8.2%) [b]	**0.044**
Congestive heart failure	8 (2.8%) [b, d]	117 (11.4%) [a, c, d]	7 (5.6%) [b, d]	311 (16.1%) [a, b, c]	< **0.001**
Peripheral vascular disease	21 (7.3%) [b, d]	143 (14.0%) [a, c]	9 (7.2%) [b]	229 (11.9%) [a]	**0.005**
Cerebrovascular Disease	10 (3.5%) [b, d]	117 (11.4%) [a, c]	6 (4.8%) [b]	186 (9.7%) [a]	< **0.001**
Coronary Artery Disease	28 (9.8%) [b, d]	239 (23.4%) [a, c]	16 (12.8%) [b, d]	481 (25.0%) [a, c]	< **0.001**
Hypertension	174 (60.6%)	681 (66.6%)	74 (59.2%)	1 218 (63.2%)	0.106
Atrial fibrillation	19 (6.6%)	89 (8.7%)	10 (8.0%)	153 (7.9%)	0.719
Pulmonary embolism	5 (1.7%)	23 (2.2%)	4 (3.2%)	37 (1.9%)	0.648
Peptic ulcer disease	14 (4.9%) [b, d]	95 (9.3%) [a]	6 (4.8%)	169 (8.8%) [a]	**0.039**
Liver disease	8 (2.8%)	41 (4.0%)	2 (1.6%)	96 (5.0%)	0.122
Gastroesophageal reflux Disease	22 (7.7%)	129 (12.6%)	10 (8.0%)	217 (11.3%)	0.075
Renal disease	5 (1.7%)	26 (2.5%)	4 (3.2%)	74 (3.8%)	0.127
Solid tumour	12 (4.2%)	45 (4.4%)	5 (4.0%)	106 (5.5%)	0.535
Diabetes mellitus	38 (13.2%)	171 (16.7%)	13 (10.4%)	315 (16.4%)	0.165
Hyperlipidaemia	72 (25.1%) [c]	286 (28.0%) [c]	19 (15.2%) [a, b, d]	518 (26.9%) [c]	**0.016**
Anaemia	4 (1.4%) [d]	21 (2.1%) [d]	1 (0.8%)	80 (4.2%) [a, b]	**0.001**
Osteoporosis	14 (4.9%) [d]	78 (7.6%) [d]	10 (8.0%)	219 (11.4%) [a, b]	< **0.001**
Depression	12 (4.2%) [d]	73 (7.1%) [d]	3 (2.4%) [d]	256 (13.3%) [a, b, c]	< **0.001**
Anxiety	17 (5.9%) [d]	77 (7.5%) [c, d]	3 (2.4%) [b, d]	212 (11.0%) [a, b, c]	< **0.001**
Insomnia	13 (4.5%) [b, d]	134 (13.1%) [a, c]	7 (5.6%) [b, d]	267 (13.9%) [a, c]	< **0.001**

* If any of the following occurred: myocardial infarction, congestive heart failure, peripheral vascular disease, coronary artery disease, hypertension and/or atrial fibrilation

Categorical variables are described by absolute (relative) frequencies.
Differences between GOLD categories are tested by Fisher exact test.
In variables, where the difference is significant, indexes a, b, c, d show statistically significant difference between two categories (Fisher exact test).

Supplementary Table S6 Inhaler therapy in CEE patients with COPD according to GOLD classification (N=3 361)

	GOLD categories				P-value
	A N=287 (a)	**B N=1 023 (b)**	**C N=125 (c)**	**D N=1 926 (d)**	
Mono-LAMA	73 (25.4%) [b, c, d]	170 (16.6%) [a, c, d]	12 (9.7%) [a, b, d]	93 (4.8%) [a, b, c]	< **0.001**
Mono-LABA	43 (15.0%) [c, d]	132 (12.9%) [c, d]	3 (2.4%) [a, b]	69 (3.6%) [a, b]	< **0.001**
Mono-ICS	1 (0.3%)	8 (0.8%)	1 (0.8%)	14 (0.7%)	0.888
LAMA + LABA	45 (15.7%)	203 (19.8%) [c, d]	14 (11.3%) [b]	241 (12.5%) [b]	< **0.001**
LAMA + ICS	2 (0.7%)	6 (0.6%)	1 (0.8%)	14 (0.7%)	0.863
LABA + ICS	47 (16.4%)	141 (13.8%)	23 (18.5%)	307 (15.9%)	0.285
LAMA + LABA + ICS	48 (16.7%) [b, c, d]	271 (26.5%) [a, c, d]	61 (48.8%) [a, b, d]	1 135 (58.9%) [a, b, c]	< **0.001**
No maintenance inhaler therapy	28 (9.8%) [d]	92 (9.0%) [d]	10 (8.1%) [d]	53 (2.8%) [a, b, c]	< **0.001**

ICS – inhaled corticosteroid; LABA – long –acting Beta-agonist; LAMA – long-acting antimuscarinic agent

Categorical variables are described by absolute (relative) frequencies.
Differences between GOLD categories are tested by Fisher exact test.
In variables, where the difference is significant, indexes a, b, c, d show statistically significant difference between two categories (Fisher exact test).