ONLINE SUPPLEMENT

METHODS

PROMISE study

The study was performed at 11 European tertiary respiratory centers from November 2008 to October 2011, was approved by the corresponding ethical committees and registered as the PROMISE-COPD study (ISRCTN99586989). Written informed consent was obtained from all patients prior to inclusion. Patients were required to: 1) fulfill criteria of the Global Initiative for Chronic Obstructive Lung Disease grade II to IV (post-bronchodilator forced expiratory volume in one second/forced vital capacity < 70% and forced expiratory volume in one second < 80% predicted); 2) be clinically stable for more than four weeks; 3) be at least 40 years of age and 4) have a smoking history of at least 10 pack years. Patients were excluded from the study if: 1) the main respiratory disorder was not COPD; 2) death was expected within 6 months; 3) the patient was immunosuppressed, including human immunodeficiency virus infection, organ transplantation or chronic steroids use (above 20 mg prednisolone equivalent per day) or 4) a musculoskeletal or neuromuscular disorder prevented ambulation. Study visits included a physical examination, registration of vital signs, assessment of a detailed history and questionnaire. Spirometry and six minute walking distance tests were performed according to the American Thoracic Society guidelines (1, 2). The assessment of BODE, mMRC (modified Medical Research Council) dyspnea scale and SGRQ (St. George's Respiratory Questionnaire) were performed as described previously (3, 4). Additional visits were scheduled at every exacerbation and four weeks after the exacerbation. Exacerbations not reported and treated at a different health care facility were registered at every standard study visit. The study protocol did not influence COPD management or any other therapy. Outcomes of interest were confirmed at the time of study visits. The patients were contacted if they did not make it to the scheduled appointment. If multiple attempts failed relatives, physicians or insurance

providers were contacted. Patients included in the study center Basel were approached five years after study inclusion to assess survival status.

PROCOLD study

Patients with hospitalized for AECOPD in the University Hospital Basel (Switzerland) were recruited from November 2003 to March 2005. Patients were included if they 1) met the definition of severe AECOPD, 2) were older than 40 years, 3) met spirometric COPD criteria and 4) provided a written informed consent. Immunosuppressed patients, patients with asthma, cystic fibrosis or radiographic infiltrates were not included. The study was approved by the institutional review board and registered as the PROCOLD study (ISRCTN77261143). The primary study objective was to improve antibiotic prescription at AECOPD as reported previously (5). At study inclusion baseline data, including medical history, clinical assessment, blood tests and lung function were performed. A short-term follow up was performed after 14 to 21 days and a long-term follow up after six months. Two years after study inclusion survival status was assessed.

COCOMICS

The COCOMICS study is a pooled analysis of individual patient-data from 11 Spanish COPD cohorts as reported previously (6). Principal investigators provided data sets from several COPD cohorts (Requena II (7), Sevilla (8), Tenerife (9), Zaragoza (10) and Terrassa I-III (11, 12)) with baseline parameters as well as follow up and outcome of each participating patient.

COMIC

COMIC was a single-center cohort study performed in Enschede (The Netherlands) from December 2005 to April 2010 (13). Patients were included if they met following criteria 1) diagnostic criteria of COPD according to the GOLD guidelines, 2) current or previous smoker, 3) age above 40 years, 4) no other medical condition compromising survival within the three year follow up, 5) no serious psychiatric illness, 6) no other active lung disease, 7) no antibiotic maintenance therapy and 8) ability

to speak Dutch. Patients were enrolled at stable or exacerbated COPD. Baseline characteristics were assessed at study inclusion or in the case of exacerbation as soon as they reached clinical stability.

Copeptin measurements

Copeptin was measured in 50µL serum using a sandwich immunoluminometric assay using 2 polyclonal antibodies to amino acids 132 to 164 of preprovasopressin (CT-proAVP LIA; BRAHMS AG, Henningsdorf/Berlin, Germany). The lower detection limit was 0.4 pmol/L, and the functional assay sensitivity (< 20% interassay coefficient of variation) was less than 1 pmol/L (14, 15). A median copeptin level of 4.2pmol/L (95% confidence interval [CI], 4.0-4.4 pmol/L) was measured in healthy individuals, previously (14).

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E-TABLES

Table E1: Univariate cox regression for predicting 2-year all-cause mortality (PROMISE; n = 460). AECOPD denotes acute exacerbations of COPD, BMI body mass index, CI confidence interval, FEV_1 forced expiratory volume in one second, GOLD Global Initiative for Obstructive Lung Disease, HR hazard ratio, mMRC modified Medical Research Council dyspnea scale, SGRQ St George's Respiratory Questionnaire.

Parameters	HR (95% CI)	p value
Age, years/10	1.52 (1.12-2.07)	**0.007**
Gender, female	1.35 (0.78-2.35)	0.3
BMI, kg/m^2	0.91 (0.86-0.97)	**0.002**
Current smoker	1.54 (0.89-2.66)	0.12
AECOPDs year before inclusion	1.10 (1.00-1.21)	0.055
Severe AECOPDs year before inclusion	2.19 (1.51-3.17)	**< 0.001**
FEV_1, %predicted/10	0.78 (0.66-0.93)	**0.005**
GOLD grade (1, 2, 3, 4)	1.49 (1.06-2.09)	**0.023**
GOLD combined assessment (A, B, C, D)		0.076
mMRC dyspnea score	1.83 (1.45-2.31)	**< 0.001**
6-minute walking distance, m/50	0.94 (0.91-0.96)	**< 0.001**
SGRQ, total score/10	1.38 (1.19-1.59)	**< 0.001**
Copeptin at inclusion, pmol/L/10	1.16 (1.09-1.24)	**< 0.001**

Table E2: Multivariate cox regression models for predicting 2-year all-cause mortality (PROMISE; n = 460). AECOPD denotes acute exacerbations of COPD, BMI body mass index, CI confidence interval, FEV_1 forced expiratory volume in one second, HR hazard ratio, mMRC modified Medical Research Council dyspnea scale.

Parameters	HR (95% CI)	p value	C-statistic
Parameters of the BODE index			
BMI, kg/m^2	0.91 (0.86-0.97)	**0.004**	0.73 (0.64-0.81)
FEV_1, %predicted/10	1.08 (0.88-1.33)	0.5	
mMRC dyspnea score	1.38 (1.01-1.88)	**0.042**	
6-minute walking distance, m/50	0.94 (0.92-0.97)	**< 0.001**	
Parameters of the ADO index			
Age, years/10	1.64 (1.20-2.26)	**0.002**	0.72 (0.64-0.80)
mMRC dyspnea score	1.81 (1.40-2.34)	**< 0.001**	
FEV_1, %predicted/10	0.88 (0.73-1.05)	0.2	
Parameters of the DOSE index			
mMRC dyspnea score	1.82 (1.41-2.35)	**< 0.001**	0.71 (0-63-0.78)
FEV_1, %predicted/10	0.87 (0.73-1.03)	0.11	
Current smoker	1.70 (0.98-2.97)	0.060	
AECOPDs year before inclusion	0.94 (0.79-1.12)	0.5	
Parameters of the B-AE-D-C index			
BMI, kg/m^2	0.90 (0.85-0.96)	**0.001**	0.76 (0.69-0.81)
Severe AECOPDs year before inclusion	1.90 (1.28-2.82)	**0.001**	
mMRC dyspnea score	1.71 (1.34-2.17)	**< 0.001**	

Copeptin at inclusion, pmol/L/10	1.21 (1.12-1.30)	**< 0.001**

Table E3: Performance of B-AE-D and B-AE-D-C parameters plus additional predictors to predict 2-year all-cause mortality (PROMISE; n = 460). Age, gender, smoking status or six minute walking distance was added to the parameters of B-AE-D and B-AE-D-C. The c-statistic of every cox regression model for predicting 2-year all-cause mortality is presented. FEV_1 denotes forced expiratory volume in one second. B-AE-D-C (body mass index, severe exacerbation frequency, dyspnea, copeptin)

	ALONE	+Age	+Gender	+FEV_1, %predicted	+Smoking status	+6-minute walking dist.
B-AE-D	0.725	0.727	0.727	0.727	0.730	0.732
B-AE-D-C	0.763	0.768	0.765	0.764	0.769	0.758

Table E4: Regression coefficients and development of optimized B-AE-D and B-AE-D-C indices (PROMISE; n = 460). Cox regression model for predicting 2-year all-cause mortality. Regression coefficients were multiplied by the factor 5.95. Points were rounded to the next integer. AECOPD denotes acute exacerbations of COPD, BMI body mass index, mMRC modified Medical Research Council dyspnea scale.

	Category	Regression coefficients	Risk score
BMI, kg/m^2	≥21	-	0
	18.5 - 21	0.97	6
	<18.5	1.45	9
Severe AECOPDs, per year	0	-	0
	1	0.45	3
	≥2	1.22	7
mMRC dyspnea score	0 - 2	-	0
	3	0.97	6
	4	1.67	10
Copeptin at inclusion, pmol/L	<20	-	0
	20 - 40	0.50	3
	≥40	1.58	9

Table E5: Baseline characteristics of 530 stable COPD patients (PROMISE). AECOPD denotes acute exacerbations of COPD, BMI body mass index, FEV_1 forced expiratory volume in one second, FVC forced vital capacity, GOLD Global Initiative for Obstructive Lung Disease, mMRC modified Medical Research Council dyspnea scale, NPPV non-invasive positive pressure ventilation, SGRQ St. George's

Respiratory Questionnaire.

Age, years		67 ±10
Gender, female		159 (30%)
Height, cm		168 ±8
Weight, kg		74 ±17
BMI, kg/m^2		26 ±6
Comorbidities		
Congestive heart disease		81 (15%)
Coronary artery disease		125 (24%)
Previous myocardial infarction		55 (10%)
Arterial hypertension		273 (52%)
Peripheral vascular disease		59 (11%)
Cerebrovascular disease		25 (5%)
Gastric ulcer		41 (8%)
Diabetes mellitus		69 (13%)
Renal disease		37 (7%)
Malignancy		24 (5%)
Osteoporosis		63 (12%)
Liver disease		25 (5%)
Pulmonary hypertension		55 (10%)
Depression		81 (15%)
Alcohol abuse		46 (9%)
Adjusted Charlson comorbidity index		4.2 ±1.9
COPD history		
Current smoker		167 (32%)
Pack years smoked		50 ±30
COPD symptoms, months		103 ±88
AECOPDs year before inclusion, numbers		0.90 ±1.4
Severe AECOPDs year before inclusion, numbers		0.5 ±0.8
Lung function parameters		
FEV_1, % predicted		49 ±17
FVC, % predicted		78 ±25
FEV_1/FVC, %		48 ±14
COPD assessment		
GOLD	grade 2	257 (49%)
	grade 3	182 (34%)
	grade 4	88 (17%)
GOLD	combined assessment group A	47 (9%)
	combined assessment group B	162 (31%)
	combined assessment group C	23 (4%)
	combined assessment group D	287 (54%)
mMRC dyspnea score		2.7 ±1.1
6-minute walking distance, m		377 ±108
SGRQ, total score		43 ±19
Copeptin at inclusion, pmol/L		13 ±18
COPD therapy at study inclusion		
Inhaled anticholinergics, short acting		123 (23%)
Inhaled anticholinergics, long acting		358 (68%)
Inhaled β2 agonists, short acting		235 (44%)
Inhaled β2 agonists, long acting		446 (84%)
Inhaled corticosteroids		432 (82%)
Systemic corticosteroids		30 (6%)
Theophylline		51 (10%)
Mucolytics		58 (11%)
Long term oxygen therapy		97 (18%)
Nocturnal NPPV		21 (4%)
Previous lung volume reduction surgery		22 (4%)
Current pulmonary rehabilitation		128 (24%)

Table E6: Characteristics of the validation cohorts PROCOLD, COCOMICS and COMIC. AECOPD denotes acute exacerbations of COPD, BMI body mass index, FEV_1 forced expiratory volume in one second, mMRC modified Medical Research Council dyspnea scale.

	PROCOLD	**COCOMICS**								**COMIC**
		Requena II	Sevilla	Tenerife	Zaragoza II	Terrassa I	Terrassa II	Terrassa III	TOTAL	
Status at inclusion	AECOPD	Stable	Stable	Stable	Stable	AECOPD	AECOPD	AECOPD		Stable
Numbers	160	152	596	214	859	131	60	141	2153	675
Age, years	71 ±10	71 ±9	66 ±10	63 ±9	63 ±10	72 ±9	71 ±9	72 ±9	66 ±10	67 ±10
Gender, female	71 (44%)	1 (1%)	32(5%)	54 (24%)	59 (7%)	11 (8%)	1 (2%)	8 (6%)	157 (7%)	267 (40%)
BMI, kg/m^2	25 ±5	28 ±5	29 ±6	27 ±5	27 ±5	26 ±5	26 ±4	28 ±5	28 ±5	27 ±5
FEV_1, % predicted	41 ±18	43 ±16	44 ±13	54 ±20	62 ±21	42 ±13	31 ±13	45 ±14	52 ±20	53 ±19
mMRC dyspnea score		3.2 ±1.0	2.4 ±1.0	2.1 ±1.2	2.7 ±1.1	3.4 ±1.3	3.0 ±1.0	3.8 ±1.2	2.7 ±1.2	1.8 ±1.3
Severe AECOPDs year before inclusion, numbers	2.0 ±1.3	0.7 ±1.0	1.2 ±1.9	0.4 ±0.7	1.1 ±2.4	1.0 ±1.4	1.8 ±1.3	1.4 ±2.2	1.0 ±2.0	0.18 ±53

Table E7: B-AE-D performance in individual COCOMICS cohorts. B-AE-D (body mass index, severe exacerbation frequency, dyspnea).

C statistic of B-AE-D for predicting	Requena II	Sevilla	Tenerife	Zaragoza II	Terrassa I	Terrassa II	Terrassa III	**TOTAL**
1-year all-cause mortality	0.74	0.59	0.66	0.62	0.74	0.59	0.62	**0.68**
2-year all-cause mortality	0.68	0.58	0.65	0.63	0.69	0.57	0.60	**0.65**
3-year all-cause mortality	0.64	0.56	0.62	0.64	0.67	0.57	0.63	**0.63**

E-FIGURES

Figure E1: Study flow diagram of PROMISE. AECOPD denotes acute exacerbations of COPD, BMI body mass index, mMRC modified Medical Research Council dyspnea scale.

Figure E2: Study flow diagrams of PROCOLD, COCOMICS and COMIC. AECOPD denotes acute exacerbations of COPD, BMI body mass index, mMRC modified Medical Research Council dyspnea scale.