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Therapy with proton-pump inhibitors for gastroesophageal reflux disease does not reduce the risk for severe exacerbations in COPD

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SUMMARY AT A GLANCE

We prospectively evaluated 638 COPD patients and provide evidence that COPD patients receiving anti-acid therapy with PPI for GERD remain at high risk of frequent and severe exacerbations independently of adjusted Charlson score, FEV1% predicted, BODE index, MMRC and medication for comorbidities.

ABSTRACT

Background and objective: Gastroesophageal reflux disease (GERD) symptoms are associated with a higher risk of chronic obstructive pulmonary disease (COPD) exacerbation. We hypothesize that treatment with proton pump inhibitors reduces the risk of exacerbation in patients witii stable COPD.
Methods: A total of 638 patients wim stable COPD for ≥6 weeks, ≥10 pack-years of smoking and Global Initiative for Chronic Obstructive Lung Disease II-IV seeking care in tertiary hospitals in eight European countries in the Predicting Outcome using Systemic Markers in Severe Exacerbations-COPD cohort was prospectively evaluated by us. Comorbidities including associated medical treatment were assessed at baseline, at exacerbation and at biannual visits. Median observation time was 24 months. The primary study outcomes were exacerbation and/or death.
Results: A total of 85 (13.3%) of COPD patients were on anti-GERD therapy. These patients had higher annual and higher severe exacerbation rates ($P = 0.009$ and $P = 0.002$), decreased quality of life (SF-36: activity score $P = 0.004$, St. George's Respiratory Questionnaire: physical functioning $P = 0.013$ and social functioning $P = 0.007$), higher body mass airflow obstruction, dyspnea and exercise capacity index ($P = 0.033$) and Modified Medical Research Council scores ($P = 0.002$), shorter 6-min walking distance ($P = 0.0004$) and a higher adjusted Charlson score ($P < 0.0001$). Anti-GERD therapy was associated with a shorter time to severe exacerbation (HR 2.05 95% CI 1.37-3.08). Using three multivariable Cox-regression models, this association was independent of the following: (i) adjusted Charlson score and FEV1% predicted (HR 1.91 95% CI 1.26-2.90); (ii) adjusted Charlson score, body mass, airflow obstruction, dyspnea and exercise capacity index and Modified Medical Research Council (HR 1.62 95% CI 1.04-2.54); and (iii) adjusted Charlson score, FEV1% predicted and nine classes of medication for comorbidities (HR 1.63 95% CI 1.04-2.53).
Conclusion: These findings suggest that patients with stable COPD receiving acid-suppressive therapy with proton pump inhibitors remain at high risk of frequent and severe exacerbations.

Keywords : anti-gastroesophageal reflux disease therapy ; chronic obstructive pulmonary disease ; chronic obstructive pulmonary disease exacerbations ; gastroesophageal reflux disease ; proton pump inhibitors.

Abbreviations : 6MWD, 6-min walking distance ; AECOPD, acute exacerbations of COPD ; BODE index, body mass, airflow obstruction, dyspnea and exercise capacity inde x; CI, confidence intervals ; COPD, chronic obstructive pulmonary disease ; FEV1, forced expiratory volume in 1 s ; FVC, forced vital capacity ; GERD, gastroesophageal reflux disease ; GOLD, Global Initiative for Chronic Obstructive Lung Disease ; HR, hazard ratio ; MMRC, Modified Medical Research Council ; post-brd, post-bronchodilated ; PPI, proton pump inhibitors

; PROMISE-COPD, Predicting Outcome using Systemic Markers in Severe Exacerbations of Chronic Obstructive Pulmonary Disease Study.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality characterized by airflow limitation that is usually progressive and associated with chronic inflammation in the airways and the lung.[1,2] The accelerated deterioration of pulmonary function in COPD may occur at any stage, and the associated episodes are called acute exacerbations of COPD (AECOPD). Frequent AECOPD hasten lung function decline,[3] reduce quality of life and contribute significantly to mortality and morbidity.[4,5] AECOPD can be triggered by viral or bacterial infections[6,7] and stimulate both airway and systemic inflammatory responses.[8,9]

Chronic obstructive pulmonary disease is associated with a number of comorbidities such as gastroesophageal reflux disease (GERD) with a prevalence of about 10-29% in Western population.[10-13] GERD is denned as a condition of reflux of stomach contents causing symptoms like postprandial heartburn and regurgitation, often occurring at night.[14] A low-lying diaphragm due to hyperinflation,[15] cough and the increased use of abdominal muscles predicts GERD in COPD patients. GERD is associated with extra-oesophageal symptoms of chronic cough, hoarseness, laryngitis and dental erosions. Epidemiologic studies show a moderate association between GERD and a range of pulmonary symptoms.[16]

The prevalence of GERD symptoms in patients with COPD ranges from 16.5-60%.[17-20] Patients with GERD have impaired cough-related quality of life and more COPD symptoms.[21] As COPD is also a common chronic disease, there is a great effort to evaluate the potential association between these two diseases and whether the presence of GERD increases the prevalence of COPD and its exacerbation or vice versa. The recent ECLIPSE study, which included 2138 COPD patients, showed that reflux symptoms are an independent predictor of frequent exacerbations and postulated a phenotype of susceptibility to exacerbation.[22] It is unknown whether treatment of GERD could decrease the susceptibility to AECOPD. We hypothesized that treatment of GERD with proton pump inhibitors (PPI) reduces the risk of exacerbations in stable COPD.

METHODS

Study design

The present study was based on data collected from the Predicting Outcome using Systemic Markers in Severe Exacerbations of Chronic Obstructive Pulmonary Disease cohort (PROMISE-COPD; ISRCTN99586989), which is an investigator-driven, multicenter, longitudinal observational study. The PROMISE-COPD study was approved by the ethics committees of all the participating centres. All patients provided written informed consent for study assessments, and the study was conducted in accordance with the Good Clinical Practice guidelines.

Patients

We consecutively recruited 638 patients with moderate to very severe COPD, who were clinical stable and at least 4 weeks after an exacerbation. All patients were ≥40 years old, current or ex-smokers with a smoking history of ≥10 pack-years. Exclusion criteria were a life expectancy of less than 6 months, pulmonary condition other than COPD, immunosuppression including organ transplantation or chronic steroid use (>20 mg prednisolone equivalent per day) and muscle-skeletal or neuromuscular process preventing ambulation.

At baseline, patients underwent sputum analysis and standard spirometry. The severity of obstruction and condition of the patients was graded according to the stages of disease defined by the Global Initiative for Chronic Obstructive Lung Disease. Each patient underwent 6-min walking distance (6MWD) testing and provided information on quality of life questionnaire (St. George's Respiratory Questionnaire, SF-36). Furthermore, a Modified Medical Research Council dyspnea score (MMRC), body mass, airflow obstruction, dyspnea and exercise capacity (BODE index score)[23] and age-adjusted Charlson score were performed for each patient. Comorbidities including associated medical therapy were assessed at baseline, at exacerbation and at biannual visits. After the baseline visit, patients had scheduled visits every 6 months and unscheduled visits at exacerbation and 4 weeks later. The median follow-up was 24 months.

Reflux was defined as post-prandial heartburn and symptomatic regurgitation. Exacerbations were denned as an

acute event characterized by a worsening of respiratory symptoms leading to a change in medication. Episodes requiring hospitalization were denned as severe exacerbations. The exacerbation frequency was observed over a period of 24 months.

The cohort of 638 patients was divided in two groups. One group included 85 patients (13.3%) with GERD and receiving PPI. The other group included 553 (86.7%) patients that did not meet the criteria of GERD and were not receiving PPI. A total of 75 patients from the first and 500 patients from the second group completed the median follow-up of 2 years (Fig. 1).

Statistical analysis

For data analysis, Statistical Package for Social Sciences (SPSS, Chicago, IL) for Windows, version 21.0, was used.

RESULTS

Patient characteristics

The baseline demographic and clinical characteristics of the patients are shown in Table 1. Most common drugs used for GERD treatment were esomeprazole (45%), pantoprazole (27%) and omeprazole (20%). Most patients receiving GERD treatment at baseline were still receiving the same drugs during the follow-up period of the study. Patients receiving therapy for GERD and patients not receiving therapy for GERD had similar demographic and clinical characteristics. However, the cohort receiving GERD therapy had higher BODE index ($P = 0.033$), higher MMRC scores ($P = 0.002$), a shorter 6MWD ($P = 0.0004$) and higher adjusted Charlson score ($P < 0.0001$).

The majority of patients (62.2%) reported sputum production in most days of the year. Positive sputum bacteriology was identified in 32.2% of the 155 patients that underwent sputum sampling without significant differences between the two groups of patients (Table 1).

Most COPD patients received combined therapy with short acting β 2 agonists and short acting muscarinic antagonists or long acting β *2* agonists and inhaled corticosteroids or long acting muscarinic antagonists. There were no significant differences in the medication between the groups (Table 2).

Cardiovascular diseases, pulmonary hypertension, diabetes mellitus and renal failure were the most common comorbidities (Supplementary Table S1). There was a higher incidence of arterial hypertension, congestive heart failure, diabetes mellitus and renal failure in the group on therapy for GERD, as compared with the non-treatment group. The GERD treatment group had a decreased quality of life (SF-36: activity score $P = 0.004$, St. George's Respiratory Questionnaire: physical functioning $P = 0.013$ and social functioning $P = 0.007$) (Supplementary Table S2).

Figure 1 *Flow chart for the present analysis. COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; PROMISE-COPD, Predicting Outcome using Systemic Markers in Severe Exacerbations of Chronic Obstructive Pulmonary Disease Study.*

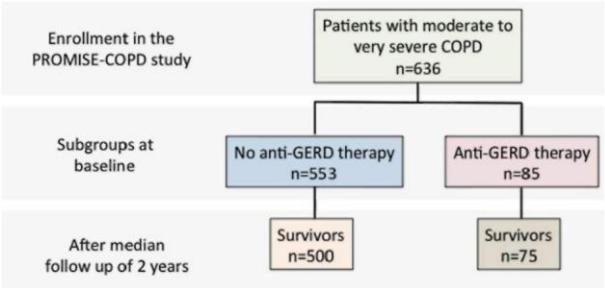

Table 1 *Baseline demographic and clinical characteristics according to the use of PPI in 685 patients with GOLD II—IV, at stable state, included in the PROMISE study*

		Medication for GERD		
Characteristic	All *n* = 638	No (*n* = 553)	Yes (*n* = 85)	*P* value
Age, years	67 (60-74)	67 (60-74)	69 (61.5-76.5)	0.038
Male, *n* (%)	448 (70.2%)	388(70.1%)	60 (70.6%)	1.000
Caucasian, *n* (%)	632 (99.1%)	547 (98.9%)	85 (100%)	1.000
Current smoker, *n* (%)	213 (33.4%)	185 (33.5%)	28 (32.9%)	1.000
Pack-years (mean ± SD)	50.2±29.9	51.2±32.9	53.5±23.3	0.468
Duration of COPD symptoms, months (mean±SD)	104.6±89	106.6±87.4	74±62.4	0.925
Time elapse since diagnosis, months (mean±SD)	80.9±76.3	81.9±74.4	108.2±95.5	0.749
BMI (kg/m^2) (mean±SD)	26.6±5.5	26.6±5.8	25.0±27.6	0.113
MMRC grade	2 (1-3)	1 (1-2)	2 (1-3)	0.002
6MWD (m) (mean±SD)	379±105	378±109	338±109	0.005
BODE index	3 (1-4)	3 (1-4)	4 (2-6)	0.033
Age-adjusted Charlson score	4 (3-5)	4 (3-5)	4 (3-6)	<0.001
GOLD grade, *n* (%)				
II	303 (47.5%)	269 (48.6%)	34 (40%)	0.294
III	217 (34%)	184 (33.3%)	33 (38.8%)	
IV	101 (15.8%)	84 (15.2%)	1 7 (20%)	
FVC, post-brd, % predicted	77.0±24	78.5 ±24.5	78.2±24.7	0.119
FEV1, post-brd, % predicted	48.9±18.2	48.0±18.7	44.0±17.6	0.061
FEV1/FVC post-brd %	48.5±14.0	47.9±14	42.6±12.1	0.046
Bronchitic phenotype *n* (%)	397 (62.2%)	346 (62.6%)	51 (61.4%)	0.719
Positive sputum bacteriology *n* (%)	50/155 (32.2%)	40/134 (29.9%)	10/21 (47.6%)	0.132

6MWD, 6-min walking distance; BMI, body mass index; BODE index, body mass, airflow obstruction, dyspnea and exercise capacity index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MMRC, Modified Medical Research Council; PPI, proton pump inhibitor; post-brd, post-bronchodilated; PROMISE, Predicting Outcome using Systemic Markers in Severe Exacerbations; SD, standard deviation.

Clinical outcome

Within the 2 years follow-up period, significantly more patients in the group receiving therapy for GERD had exacerbations ($P = 0.009$), severe exacerbations per year ($P = 0.002$) and more frequent severe exacerbations ($P = 0.014$) (Table 3). Using univariate Cox-regression analysis, we observed that anti-GERD therapy was associated with a significant ($P < 0.0001$) shorter time to severe exacerbation, with a hazard ratio of 2.05 (95% CI: 1.37-3.08) (Table 4). Furthermore, several factors such as BODE index ($P < 0001$), its subdomains' MMRC grade ($P = 0.001$), 6MWD ($P < 0.001$), a history of lung volume reduction procedures ($P = 0.017$), congestive heart failure ($P = 0.013$) and a lower FEV1/FVC % ratio post-bronchodilatation ($P = 0.002$) were associated with a shortened time to severe AECOPD.

Multivariate Cox-regression analysis revealed that anti-GERD therapy was significantly associated with time to severe exacerbation in COPD, independently of BODE index, supervised rehabilitation, lung volume reduction procedure and congestive heart failure (HR 1.58, 95% CI: 1.01-2.47); adjusted Charlson score and FEV1% predicted (HR 1.91, 95% CI: 1.26-2.91); and adjusted Charlson score, FEV1% predicted and nine classes of medication for comorbidities (HR 1.63, 95% CI: 1.04-2.53) in three multivariable Cox-regression models (Table 5).

Table 2 *COPD-specific treatment according to the use of PPI in 685 patients with GOLD II—IV, at stable state, included in the PROMISE study*

	All (*n* = 638)	Medication for GERD		*P* value
		No (*n* = 553)	Yes (*n* = 85)	
Pharmacological treatment				
SABA/SAMA	115 (18.0%)	105 (18.9%)	10 (11.8%)	0.129
LABA/ICS	450 (70.5%)	388 (70.2%)	62 (72.9%)	0.702
SABA	183 (28.7%)	156 (28.2%)	27 (31.8%)	0.520
LAMA	423 (66.3%)	362 (64.5%)	61 (71.8%)	0.270
ICS	72 (11.3%)	64 (11.6%)	8 (9.4%)	0.713
Methylxanthines	66 (10.3%)	59 (10.7%)	7 (8.2%)	0.571
Mucolytics/antioxidants	74 (11.6%)	60 (10.8%)	14 (16.5%)	0.145
Non-pharmacological treatment				
Supervised rehabilitation	150 (23.5%)	122 (22.1%)	28 (32.9%)	0.038
Oxygen therapy	123 (19.3%)	102 (18.4%)	21 (24.7%)	0.184
Non-invasive ventilation	27 (4.2%)	21 (3.8%)	6 (7.0%)	0.156

COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long acting β 2 agonists; LAMA, long acting muscarinic antagonists; PPI, proton pump inhibitor; PROMISE, Predicting Outcome using Systemic Markers in Severe Exacerbations; SABA, short acting β 2 agonists; SAMA, short acting muscarinic antagonists.

Table 3 *Clinical outcomes according to the use of PPI in 685 patients with GOLD II—IV, at stable state, included in the PROMISE study in COPD patients*

		Medication for GERD		*P*
Clinical outcome	All (*n* = 638)	No (*n* = 553)	Yes (*n* = 83)	value
Exacerbations per year median (interquartile range)	0.72 (0-1.8)	0.67 (0-1.8)	1.03 (0-3.4)	0.009
Severe exacerbation per year median (interquartile range)	0 (0-0)	0 (0-0)	0 (0-0.5)	0.002
Time to exacerbation median (interquartile range)	338 (135-697)	336 (133-392)	310 (135-730)	0.484
Time to severe exacerbation median (interquartile range)	701 (342-748)	710 (364-749)	518 (187-748)	0.014
Time to death median (interquartile range)	722 (395-762)	725 (393-763)	719 (418-758)	0.708

COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PPI, proton pump inhibitor; PROMISE, Predicting Outcome using Systemic Markers in Severe Exacerbations.

DISCUSSION

In the present study, we included 638 COPD patients enrolled in the large observational PROMISE cohort, to examine the potential association of anti-GERD therapy on AECOPD. We report that therapy for GERD is an independent factor associated with shorter time to severe exacerbation in COPD patients.

Acute exacerbations of COPD impact on patient morbidity and mortality[2] and pose a considerable economic burden for healthcare systems. Despite the negative impact of AECOPD on the natural course of the disease, there is inadequate information regarding their causes. Recent studies suggest the main determinants for AECOPD are the severity of the disease, previous history of exacerbations and the presence of comorbidities such as congestive heart failure, coronary artery disease, chronic renal/liver failure and GERD.[24] A 'frequent exacerbator phenotype' has been described, which is independent of disease severity and associated with a poorer health outcome with former exacerbations being the strongest trigger for AECOPD.[25] A higher exacerbation rate in patients with GERD symptoms has been shown in a North American cohort,[26] an observation that was also confirmed in two prospective Japanese studies[20,27] and a Chinese study[28] These findings were found to be independent of other triggers for AECOPD, such as respiratory infection, airway obstruction and congestive heart failure.

Should GERD be a major trigger for AECOPD, one would expect that treatment with PPI would reduce exacerbations in COPD patients. Yet in our study, patients on anti-GERD therapy with PPI had higher annual exacerbation rates, as well as higher severe exacerbation rates. Our findings are in accordance with a

retrospective population-based study, which demonstrated that newly diagnosed GERD is an independent risk factor for AECOPD in the first 12 months and despite treatment, these patients are at higher risk of AECOPD-related emergency consultations and hospitalizations.[29] If treatment was efficacious, a possible explanation of our findings might be that PPI do not stop reflux; rather, they render reflux non-acidic or weakly acidic, which has been shown to contribute to pulmonary symptoms.[30] Patients with asthma had more regurgitation-related symptoms than those with COPD, whereas patients with COPD had more dysmotility-related symptoms than those with asthma.[31]

Table 4 *Crude hazard ratio for time to next severe exacerbation in 685 patients with GOLD II—IV, at stable state, included in the PROMISE study*

Characteristics	HR (95% CI)	*P* value
Anti-GERD therapy	2.05 (1.37-3.08)	<0.001
Age, years	1.02 (1.00-1.93)	0.058
Current smoking	1.25 (0.85-1.82)	0.257
MMRC grade	1.28 (1.11-1.48)	0.001
6MWD	0.99 (0.99-0.99)	<0.001
BODE index	1.20 (1.11-1.30)	<0.001
Supervised rehabilitation	1.46 (1.02-2.10)	0.041
Volume reduction therapy	2.19 (1.15-4.11)	0.017
Adjusted Charlson score	1.07 (0.98-1.15)	0.169
Arterial hypertension	1.13 (0.81-1.57)	0.489
Congestive heart failure	1.68 (1.12-2.53)	0.013
Malignancy	1.28 (0.60-2.73)	0.528
Diabetes mellitus	1.57 (0.39-6.37)	0.524
Renal failure	1.76 (1.00-3.12)	0.052
Acetosalicylic acid/clopidogrel	1.24 (0.88-1.74)	0.218
Diuretics	1.53 (1.08-2.16)	0.016
ACE-inhibitors/AT-ll antagonists	1.12 (0.80-1.58)	0.511
β-blockers	1.28 (0.87-1.89)	0.215
Antidepressives	1.38 (0.86-2.21)	0.188
FEV1/FVC% post-brd, %	0.98 (0.76-0.99)	0.002

6MWD, 6-min walking distance; anti-GERD therapy, proton pump inhibitors; BODE, body mass, airflow obstruction, dyspnea and exercise capacity; CI: confidence intervals; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; MMRC: Modified Medical Research Council; PPI, proton pump inhibitors; post-brd, post-bronchodilated; PROMISE, Predicting Outcome using Systemic Markers in Severe Exacerbations.

Table 5 *Multivariate Cox-regression analysis for time to next severe exacerbation in 685 patients with GOLD II—IV, at stable state, included in the PROMISE study*

Model 1 -LLH 1468χ^2 36.23 5 *df*	HR (95% CI)	*P* value
Anti-GERD therapy	1.58 (1.01-2.47)	0.044
BODE index	1.18 (1.09-1.27)	<0.001
Supervised rehabilitation	1.15 (0.77-1.71)	0.503
Lung volume reduction procedure	1.42 (0.71-2.81)	0.320
Congestive heart failure	1.48 (0.95-2.30)	0.083
Model 2 - LLH 1649χ^2 22.5 *3df*		
Anti-GERD therapy	1.91 (1.26-2.91)	0.002
Adjusted Charlson score	1.04 (0.96-1.13)	0.370
FEV1, % predicted	0.99 (0.98-0.995)	0.002
Model 3-LLH 1605χ^2 24.89 1*2df*		
Anti-GERD therapy	1.63 (1.04-2.53)	0.032
Adjusted Charlson score	0.99 (0.90-1.010)	0.882
FEV1, % predicted	0.99 (0.98-0.99)	0.002
Medication for comorbidities		
Aspirin	1.04 (0.70-1.55)	0.838
Statins	0.998 (0.65-1.54)	0.991
Diuretics	1.45 (0.98-2.13)	0.061

ACE-inhibitors/AT-ll antagonists	1.04 (0.71-1.54)	0.829
Ca-antagonists	0.97 (0.61-1.52)	0.879
β-blockers	1.25 (0.83-1.89)	0.292
Antidepressives	1.29 (0.79-2.11)	0.306
Oral antidiabetics	1.01 (0.55-1.84)	0.975
Insulin	0.93 (0.37-2.35)	0.879

Anti-GERD therapy, proton pump inhibitors; BODE index, body mass, airflow obstruction, dyspnea and exercise capacity index; CI: confidence intervals; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; post-brd, post-bronchodilated; PROMISE, Predicting Outcome using Systemic Markers in Severe Exacerbations.

Another hypothesis, explaining how airway obstruction may predispose to GERD, was described using Boyle's Law and Bernoulli's Principle.[32] Boyle's Law predicts that the oesophagus is kept collapsed by the maximal negative thoracic pressure during end-inspiration and consecutively, on the other side of the diaphragm, abdominal pressure is increased. In airways obstruction, more negative thoracic pressure is required for inspiration resulting in positive abdominal pressure. Therefore, increased intra-abdominal pressure might compromise the anti-reflux barrier by forcing stomach contents through the lower oesophageal sphincter, which is relaxed during swallowing in response to pharyngeal and oesophageal distension.[33] This effect might be aggravated by a decreased low-oesophagus sphincter pressure because of β agonists.[34] Gadel *et al.*[35] measured a high prevalence of oesophageal motility disorders in COPD patients and found a negatively correlation of upper and lower oesophageal sphincter pressure to indices of hyperinflation. Furthermore, Turbyville[32] suggested that Bernoulli's Principle in upper airway obstruction may be the cause of air shunting into the oesophagus and compromising the anti-reflux barrier from above by a suction effect.

Treating GERD with acid reduction can be beneficial to control symptoms. However, GERD is not only caused by acid over-production but it is also associated with a mechanical breach and physical effect of the anti-reflux barrier. The aforementioned hypothesis may explain why COPD can predispose to GERD, and once GERD develops, the risk for AECOPD persists even after anti-reflux therapy is started.[35] Thus, as long as patients remain obstructive, they will have reflux, and that is why anti-GERD therapy may not be the final solution to emerge reflux in airway obstruction.

It remains unclear if there is a causative mechanism involving micro aspiration of stomach contents, leading to increased airway inflammation and AECOPD. Interestingly, patients receiving treatment for GERD did not have a higher colonization rate in sputum samples, indicating that bacterial colonization does not seem to be a major factor contributing to AECOPD in patients on anti-GERD therapy. Another hypothesis suggests that the vagal-mediated oesophago-bronchial reflux may provoke bronchoconstriction[36], but as mentioned, GERD may be the result of other causes than acid effect. Alternatively, the use of PPI could be a marker of disease severity, its comorbidities and/or related medication. This hypothesis is less convincing because the association of PPI with exacerbation remained significant after adjusting for multiple characteristics of severity in COPD. However, in the absence of randomized data, it cannot be fully refuted. Hyperinflation is a factor that can intensify GERD symptoms, but after adjustment for lung volume reduction procedures, anti-GERD therapy remained significantly associated with a shorter time to severe AECOPD. Further investigations are required to explore how non-acid (laryngeal) reflux and dynamic lung hyperinflation influence AECOPD.

In a randomized, single-blind, non-placebo controlled trial involving 100 elderly ex-smokers without GERD, treatment with lansoprazole was associated with a significant decrease in AECOPD within a period of 12 months.[37] However, in asthma patients with GERD, treatment with esomeprazole once or twice daily did not improve asthma outcomes.[38] Furthermore, it has been shown that in patients with duodenal ulcer disease infected with *Helicobacter pylori*, treatment with omeprazole decreased significantly the production of proinflammatory and inflammatory cytokines in PHA-cultured peripheral blood lymphocytes.[39] In a recent study, it has been shown that patients with COPD and GERD, who did not use acid inhibitory treatment regularly, had an increased risk of COPD exacerbations during follow-up as compared with those who used acid inhibitory treatment regularly.[40] However, in this study, the authors used questionnaires to define GERD and AECOPD were denned by the use of corticosteroids alone or in combination with antibiotics. Furthermore, comparison was made between patients with COPD and GERD without treatment with PPI and patients with COPD and GERD receiving treatment with PPI, while in our study, we compared time to severe exacerbations between COPD patients and COPD patients with GERD treated with PPI.

Our study has a few limitations. It was not placebo controlled, and anti-GERD therapy was decided according to

clinical findings. GERD was not objectively diagnosed by 24-h oesophageal pH-monitoring, which is the Global Initiative for Chronic Obstructive Lung Disease standard to diagnose acid regurgitation. We may have missed reflux in the control group, because many episodes of reflux are asymptomatic and are only detected by oesophageal manometry.[41] It would be interesting to use laryngeal pH-metry in combination with manometry to prospectively select asymptomatic patients with COPD having reflux for future intervention studies. We believe, however, that potentially, patients with a more severe disease (i.e. symptomatic reflux) would tend to benefit more from therapy than those with subclinical or minimal disease. Our study can be seen as a hypothesis generating analysis of a cohort study specifically designed to assess factors associated with exacerbation risk in COPD. Due to study design, the two groups of patients were not matched in size, COPD severity, comorbidities and concomitant therapies. Thus, a prospective, placebo-controlled design would be the preferable design to answer if PPI reduce the frequency of exacerbations in COPD patients with GERD symptoms.

Study strengths include its prospective design, a full characterization of the patient population and the long-term follow-up. Furthermore, we assessed many measurable parameters that may influence the main finding, which is the association of anti-GERD therapy with a shorter time to severe exacerbation in patients with stable COPD, like the following: (i) quality of life including activity score, physical functioning and social functioning; (ii) BODE index; (iii) MMRC scores; (iv) 6-min walking distance; (v) adjusted Charlson score (i.e. age and 22 comorbidities); and (vi) medication for the treatment of the comorbidities. We have analysed the aforementioned parameters with three multivariable Cox-regression models and concluded that the association of anti-GERD therapy with a shorter time to severe exacerbation was independent of the parameters included in the three models. Even if we cannot exclude that other unknown factors, associated with the exacerbation rate, may have influenced our results, we believe that it is fair to state that we have excluded a high number of confounding that could have accounted for the findings in our study by adjusting for known COPD characteristics associated with exacerbation risk and exploring different statistical models, which adjusted for those characteristics. However, these adjustments, by far, do not allow for the degree of certainly provided by a randomized controlled trial.

In conclusion, the findings suggest that patients with stable COPD receiving acid-suppressive therapy with a PPI are at high risk of frequent and severe exacerbations. However, due to study design, our conclusions should be consciously interpreted and confirmed with a randomized, placebo-control study.

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Supplementary Information

Additional Supplementary Information can be accessed via the *html* version of this article at the publisher's website:

Table S1 Comorbidities according to the use of PPI in 685 patients with GOLD ll-IV, at stable state, included in the PROMISE study.

Table S2 Health status according to the use of PPI in 685 patients with GOLD ll-IV, at stable state, included in the PROMISE study.