CARDIOVASCULAR DISEASE DOES NOT PREDICT EXACERBATION RATE OR MORTALITY IN COPD

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To the Editor

Cardiovascular disease (CVD) is common in patients with chronic obstructive pulmonary disease (COPD) (1-4), yet it is unclear whether its presence increases the incidence of acute exacerbations (AECOPD) or the risk of death. Observational studies have shown that COPD is associated with a 2-5 times higher risk of ischaemic heart disease (IHD), cardiac dysrhythmia, heart failure, diseases of the pulmonary circulation, and diseases of the arteries, compared with non-COPD populations (4,5). A prospective evaluation of COPD exacerbations in patients with comorbid IHD from the London COPD Cohort reported longer duration but not an increased frequency of AECOPD in patients with IHD (6).

This prospective study was designed to test the hypothesis that the presence of CVD increases the risk of AECOPD and/or death in COPD patients recruited in a primary care setting.

Methods

The ACCESS study (Assessment of Comorbidities in COPD in European Symptomatic Subjects; NCT01516528; 115058 study) was a prospective, longitudinal, observational, non-drug interventional, two-year study in COPD patients enrolled from primary care in Belgium, France, Germany, the Netherlands, Poland, and Spain. Patients, visiting their general practitioner (GP) for any reason, were invited to participate if they were ≥40 years old, current or ex-smoker (smoking history of ≥10 pack-years), a minimum of 12 months of prior history of COPD, and a forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) post-bronchodilator ratio <0.70. Patients with a primary diagnosis of asthma, pulmonary fibrosis, asbestosis, any cancer or clinically significant bronchiectasis were excluded.

Patients were followed up for 27 months through clinic visits at screening (-3 months), baseline (0 months), 12 months and 24 months, and by phone at 3, 6, 9, 15, 18 and 21 months. Written informed consent was obtained from all subjects and the study was approved by independent ethics committees as per the requirements in each country.

The prevalence of CVD at baseline was defined using a composite measure with previously published criteria (7). The primary outcome was the annual rate of moderate-severe AECOPD during the 24-month follow-up period. Moderate AECOPD was defined as a worsening of symptoms that required oral corticosteroids and/or antibiotics, whilst severe exacerbations were defined as those that included hospitalization. Mortality was a secondary outcome; details of patient deaths were obtained from the GP.

To derive event rates and test associations, we applied multivariable negative binomial regression and Cox proportional hazards regression models, respectively. All analysis was pre-specified except hospitalizations and mortality outcome modeling which were post-hoc.

Results

2,887 evaluable patients were included in this analysis. Their mean age was 66 years, 70% were male, and 47% were current smokers with a mean post-bronchodilator FEV_1% predicted of approximately 60% (Table 1). The mean number of moderate-severe AECOPD episodes in the previous year was 0.61 (95% CI: 0.57, 0.64); for severe AECOPD: 0.08 (95% CI: 0.07, 0.09). At baseline, COPD patients with CVD (1375, 48%) were older and more likely to be ex-smokers, but had similar airflow limitation and history of exacerbations to those without CVD.

Over 24 months, there was no difference in the annualized rate of AECOPD between those with or without CVD (adjusted rate per patient: 0.63 (95% CI: 0.57, 0.69) vs. 0.63 (95% CI: 0.58, 0.69); the Rate Ratio was 0.99 (95% CI: 0.88,1.11) (Table 2). Male sex, lower post-bronchodilator FEV_1 % predicted, and higher CAT score, but not older age, were significantly independently associated with a higher overall rate of exacerbations. Addition of history of AECOPD events in the 12 months prior to study baseline into models was significantly associated with the rate during the study, but it didn't change the effect of CVD on this outcome (Rate Ratio: 1.01 [95% CI: 0.90,1.12]). Additionally, a sensitivity analysis for each CVD diagnosis from the composite CVD definition, did not show any relationship between individual CV diseases and the incidence of AECOPD.

The unadjusted annual rate of severe exacerbations (requiring hospitalization) was 51% higher in patients with CVD than those with no CVD (Rate Ratio 1.51 [95% CI: 1.16; 1.97], p=0.003)). In the adjusted multivariable model, this trend was not statistical significant (Rate Ratio 1.14 (95% CI: 0.87; 1.50) (Table 2).

The crude mortality rate was greater in patients with CVD compared with no CVD (3.0 events per 100 patient years [95% CI: 2.3, 3.6] vs. 1.5 [95% CI: 1.1, 2.0]), however, this association was attenuated in the multivariable model (Hazard Ratio in patients with/without CVD: 1.26 (95% CI: 0.85, 1.87) due to statistically significant effects of age, gender and COPD clinical characteristics.

Discussion:

This is the first large scale study to prospectively evaluate the relationship between CVD and exacerbation rates and mortality in a well characterized cohort of COPD patients. Although, on average, the patients were relatively mild in terms of lung function, CAT score and exacerbation rate, the cohort did contain the whole range of

disease severity. We found that the presence of CVD was not independently associated with an increased risk of exacerbations or death. This finding was not expected in view of prior evidence that there was a link (8-10). There are at least two reasons to explain this difference. Some earlier studies had methodological limitations, for example, two were retrospective and used data extracted from routine electronic medical records. Furthermore, it is also important to understand temporal associations and mechanisms of causality. For example, patients hospitalized for AECOPD are at increased risk of myocardial infarction following admission (11,12), and case series data provide evidence of a link through viral infections, which may trigger both AECOPD and vascular events (13,14).

It is conceivable that within this primary care population, there was an insufficient number of patients of a particular phenotype in whom a link does exist, or patients did not have sufficiently severe COPD to demonstrate the link, but the sample was large and the rate ratio was very close to 1.0, so the likelihood of this being a factor is low. We conclude that there is little or no evidence that the presence of CVD in COPD patients increases the risk of exacerbations or death, but it may increase the risk of hospitalization.

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REFERENCES

1. From the *Global Strategy for the Diagnosis, Management and Prevention of COPD*, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://www.goldcopd.org/.

2. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. Chest 2005;128:2640–2646.

3. Agarwal S, Rokadia H, Senn T, Menon V. Burden of cardiovascular disease in chronic obstructive pulmonary disease. Am J Prev Med 2014;47(2):105–114.

4. Müllerova H, Agusti A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD. Systematic literature review. Chest 2013;144(4):1163–1178.

5. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Lancet Respir Med 2015;3:631–39.

6. Patel ARC, Donaldson GC, Mackay AJ, Wedzicha JA, Hurst JR. The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD. Chest 2012;141:851–857.

7. Vestbo J, Anderson J, Brook RD, Calverley PMA, Celli BR, Crim C, Martinez FJ, Yates J, Newby DE, on behalf of the SUMMIT Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. The Lancet 2016;387:1817-1826.

8. Dalal AA, Shah M, Lunacsek O, Hanania NA. Clinical and economic burden of patients diagnosed with COPD with comorbid cardiovascular disease. Respir Med 2011;105:1516-1522.

9. McGarvey L, Lee AJ, Roberts J, Gruffydd-Jones K, McKnight E, Haughney J.

Characterisation of the frequent exacerbator phenotype in COPD patients in a large UK primary care population. Respir Med 2015;109:228-237.

10. Niewoehner DE, Lokhnygina Y, Rice K, Kuschner WG, Sharafkhaneh A, Sarosi GA, Krumpe P, Pieper K, Kesten S. Risk Indexes for Exacerbations and Hospitalizations Due to COPD. Chest 2007;131:20–28.

11. McAllister DA, Maclay JD, Mills NL, Leitch A, Reid P, Carrutherse R, O'Connore J, McAlpine L, Chalmers G, Newby DE, Clark E, Macfarlane PW, MacNee W. Diagnosis of myocardial infarction following hospitalisation for exacerbation of COPD. Eur Respir J 2012;39:1097–1103.

12. Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. Chest 2010;137(5):1091–1097.

13. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med 2004;351:2611-8.

14. Clayton TC, Capps NE, Stephens NG, Wedzicha JA, Meade TW. Recent respiratory infection and the risk of myocardial infarction. Heart 2005;91:1601–1602.

Table 1: Baseline characteristics at the screening visit

	Patients with CVD (N=1375)	Patients without CVD (N=1512)	Total (N=2887)
Age (years), mean (SD)	69.7 (8.7)	62.9 (9.9)	66.1 (10.0)
Male, n (%)	1050 (76)	964 (64)	2014 (70)
Body mass index, mean kg/m^2 (SD)	27.9 (5.1)	26.5 (5.3)	27.2 (5.2)
Current smoker, n (%)	534 (39)	820 (54)	1354 (47)
CAT score*, mean (SD)	15.6 (7.7)	14.5 (7.7)	15.0 (7.7)
Mean post-bronchodilator FEV_1 % predicted (SD)	58.8 (19.1)	60.0 (19.8)	59.4 (19.5)
GOLD grade airflow limitation			
1 - mild	183 (13.3)	238 (15.7)	421 (14.6)
2 - moderate	736 (53.5)	779 (51.5)	1515 (52.5)
3 - severe	376 (27.3)	393 (26.0)	769 (26.6)
4 - very severe	80 (5.8)	102 (6.7)	182 (6.3)
GOLD 2016 group†, n (%)			
A – low symptom/low risk	228 (17)	337 (22)	565 (20)
B – high symptom/low risk	548 (40)	549 (37)	1097 (38)
C – low symtoms/high risk	91 (7)	119 (8)	210 (7)
D – high symptom/high risk	505 (37)	497 (33)	1002 (35)
COPD exacerbations in12 months prior to baseline			
Moderate-severe			
N (%) patients with ≥1 event	516 (38)	570 (38)	1086 (38)
Mean (95% CI)	0.60 (0.54;0.65)	0.61 (0.56;0.66)	0.61 (0.57;0.64)
Events requiring hospitalization			
N (%) patients with ≥1 event	113 (8)	68 (4)	181 (6)
Mean (95% CI)	0.11 (0.09;0.14)	0.05 (0.04;0.07)	0.08(0.07;0.09)

*CAT was assessed at the baseline visit; †Combined assessment based on CAT as a symptom measure according to GOLD 2016. CVD: cardiovascular disease; CAT: COPD Assessment Test; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 sec; GOLD: Global Initiative for Chronic Obstructive Lung Disease; SD: standard deviation; CI: confidence interval

Table 2: Adjusted annual rate of moderate-severe COPD exacerbations and hospitalizations due to COPD after 24 months of follow-up - Negative binomial regression analysis including covariates

	CVD (N=1375)	No CVD (N=1512)
Adjusted annual rate per patient of moderate-severe exacerbations (95% CI)	0.63 (0.57;0.69)	0.63 (0.58;0.69)
Rate Ratio in patients with CVD / without CVD (95% CI)	0.99 (0.88;1.11)	
Effect of covariates; parameter estimate (p-value):		
Age	0.0057 (0.074)	
Gender (female)	0.1788 (0.004)	
Smoking status (current smoker)	- 0.0997 (0.093)	
Post-bronchodilator FEV_1 % predicted	- 0.0142 (<0.001)	
CAT score	0.0368 (<0.001)	
Adjusted annual rate per patient of hospitalizations due to COPD (95% CI)	0.05 (0.04;0.06)	0.04 (0.04;0.06)
Rate Ratio in patients with CVD / without CVD (95% CI)	1.14 (0.87;1.50)	
Effect of covariates (p-value)		
Age	0.0395 (<0.001)	
Gender (female)	0.2738 (0.059)	
Smoking status (current smoker)	0.0416 (0.767)	
Post-bronchodilator FEV_1 % predicted	-0.0381 (<0.001)	
CAT score	0.0725 (<0.001)	

Models were also adjusted for the country effect.
CVD: cardiovascular disease; CAT: COPD Assessment Test; FEV_1: forced expiratory volume in 1 sec; CI: confidence interval