Mortality after admission with pneumonia is higher than after admission with an exacerbation of COPD

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To the Editor:

Patients with COPD often experience exacerbations and pneumonia that are occasionally severe and lead to hospital admission [1–3]. The risk of pneumonia is further increased by treatment with inhaled corticosteroids (ICS) [4–6]. Although potentially difficult to distinguish [7], there could be differences in the risk of death associated with these events that need to be taken into account when planning management and clinical follow-up. The Salford Lung Study was set up to evaluate the effectiveness and safety of the once-daily inhaled combination of fluticasone furoate and vilanterol (FF/VI; in ELLIPTA dry powder inhaler) compared with existing maintenance therapy (usual care) in a large, real-world population of patients with COPD in conditions of normal care [8]. Strengths of the study include the relatively unselected patient population, the completeness of follow-up using a joint electronic record system and the fact that all patients were provided usual standard of care for their exacerbations and during admissions. We used this study database to examine mortality after an admission with a severe exacerbation or pneumonia, and the impact of classification of these events.

A total of 2799 patients who were 40 years or older, had a documented diagnosis of COPD made by a general practitioner and ⩾1 COPD exacerbations in the past 3 years were recruited from general practice for the Salford Lung Study [8]. All patients were on regular maintenance inhaler therapy.

The study has been described in detail previously [8]. Mean age was 67 years, mean FEV_1 1.62 L and 49% were women. In the analyses for this substudy, we have pooled all ICS patients to be able to jointly analyse a sufficient number of events. We reviewed narratives of all deaths as well as all chest radiographs available in the study period for patients being admitted with either a severe exacerbation or pneumonia. Radiographs were ordered at the clinicians' discretion. For this study, the radiographs were all read by three specialist radiologists independently and unaware of the physicians' diagnoses. In case of disagreement, consensus was found through discussion.

To ensure sufficient follow-up after events, we included events up to 184 days after randomisation in order to have 6 months of follow-up. A severe exacerbation was defined as hospital admission and a diagnosis of an exacerbation. An admission with pneumonia was based on the initial diagnosis made by the treating physician. For our additional classification analysis, we assigned a diagnosis based on the radiologist's evaluation of the chest radiograph, *i.e.* presence *versus* absence of a new lung infiltrate; pneumonia *versus* exacerbation. We used first hospital admission for either of these events. For this, we had access to 121 chest radiographs, all evaluated by three radiologists.

Of the 2799 patients who underwent randomisation, 111 patients experienced a hospital admission with an initial diagnosis of a COPD exacerbation; 86 were hospitalised with an initial diagnosis of pneumonia. Patients admitted were older (pneumonia: 70.2 years; COPD exacerbation: 69.3 years) than those not admitted (66.4 years). Patients admitted with pneumonia were more often men and less often current smokers when comparing with patients admitted for a COPD exacerbation or not admitted with either. Of those admitted with COPD, 60% had severe or very severe COPD; this was the case for 47% of those admitted with pneumonia and 27% among those not admitted. Both a history of >2 exacerbations during

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Mortality after an admission for pneumonia is considerably higher than for an admission for an exacerbation in COPD patients recruited from usual clinical practice. A proper diagnosis in acute worsenings of symptoms in COPD is therefore important. https://bit.ly/3LyhnnC

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the year prior to randomisation and cardiac comorbidity were more frequent for those admitted with COPD (77% and 47%) compared to those with pneumonia (53% and 42%) and those not admitted (48% and 30%).

Of the 111 with a hospitalised exacerbation, eight (7%) died during the 6-month follow-up, whereas this was the case for 14 (16%) of the 86 with a pneumonia admission. In a Cox regression model with age, sex, exacerbation history, use of ICS at study entry, score from the COPD Assessment Test, and smoking status as covariates, hazard ratios for mortality within 30 days of being hospitalised were 29.6 (95% CI 12.5–69.9) and 176.8 (95% CI 102.6–304.7) for an exacerbation admission and a pneumonia admission, respectively. In a similar model analysing mortality 31–180 days following hospital admission, hazard ratios were 0.85 (95% CI 0.1–6.2) and 11.6 (95% CI 5.1–26.3), respectively. Exacerbation history prior to admission did not differ among those dying from an exacerbation or a pneumonia.

There was a substantial discrepancy between events diagnosed as a pneumonia by the admitting physician and the subsequent classification of events based on a blinded specialist radiologists' evaluation of a chest radiograph. Radiologists agreed on the presence of pneumonia in only 61% of cases and 10 cases clinically classified an acute exacerbation of COPD were reclassified as pneumonia. Radiologist reclassification of the presence or absence of pneumonia had a significant impact on the risk of death after discharge (figure 1).

Interpretation of mortality following an admission comes with caveats. Many deaths occurred months following the index hospitalisation, something that is well known from previous studies of pneumonia. However, the risk of death continued to rise for approximately 3 months. We had 6 months follow-up and it is possible that longer follow-up may have added additional excess deaths. Malignancies were frequent in this patient group, as in COPD in general, and we cannot preclude the possibility that some of the pneumonias were the first impact of a subsequently fatal malignancy. It is, nevertheless, noteworthy that a persistent elevated risk of mortality after 30 days was only observed in patients when independent radiological assessment confirmed the diagnosis of pneumonia. The impact of a radiologist's diagnosis of an infiltrate consistent with pneumonia was significant and important for prognosis. This has implications for clinical care, as the importance of a distinction between an exacerbation and a pneumonia is rarely highlighted [1] and is a salient lesson for interpreting past and future studies of pneumonia in the setting of COPD.

Approximately 90% of patients in our substudy were treated with ICS due to the study design [8]. We could therefore not assess the added risk from ICS; however, the risk of pneumonia associated with ICS use is well documented [9]. The aim of treating with ICS is to reduce exacerbations requiring treatment with systemic corticosteroids, a treatment in itself associated with an increased risk of severe pneumonia [10]. This invariably complicates the assessment of risk/benefit for ICS for the clinician.

Our study included an unselected population of patients with a diagnosis of COPD, likely representing up to 50% of all COPD patients in Salford. In a pragmatic setting, a number of uncertainties exist: varying

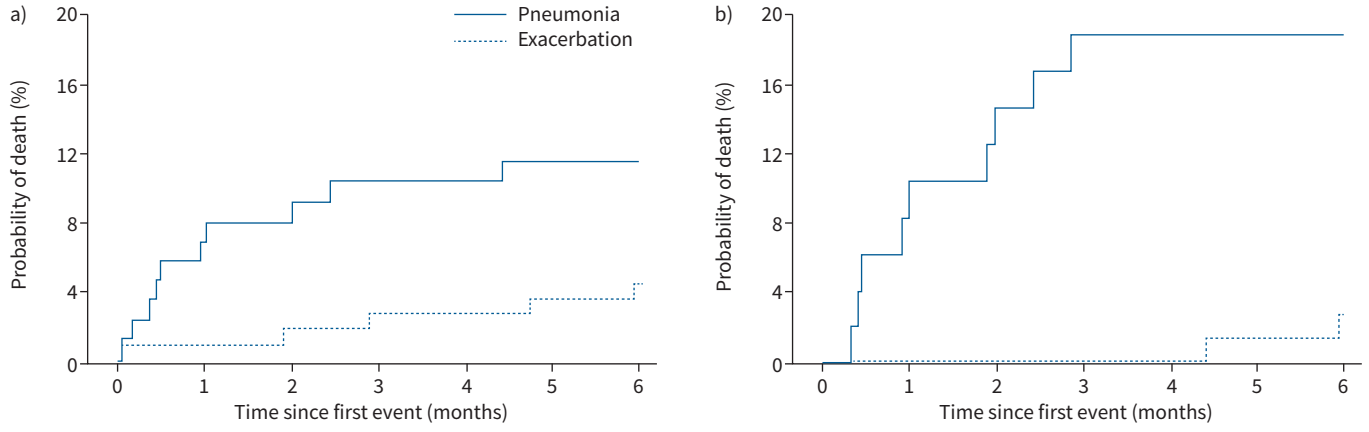

FIGURE 1 Time to death following a hospital admission for an exacerbation or pneumonia for diagnoses according to a) study reporting and b) radiologist reporting.

use of diagnostic procedures, variation in clinicians' diagnostic evaluation, effect of subsequent readmissions, *etc*. However, this real-world data is important because interpretation of the risks associated with pneumonia in the setting of ICS treatment in randomised controlled trials is potentially misleading as patients who may be at the highest risk of pneumonia (very low lung function, very low body mass index, significant comorbidities) are often excluded. Our data strongly suggests that in an unselected group of patients with COPD, the weighting given to pneumonia events in deciding whether to use ICS or not may be different in some groups of patients, especially those who would typically be excluded from randomised controlled trials.

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The Salford Lung Study trial registration number is NCT01551758. Information on GlaxoSmithKline's data sharing commitments and requesting access to anonymised individual participant data and associated documents can be found at www.clinicalstudydatarequest.com

Conflict of interest: J. Vestbo received personal fees from GlaxoSmithKline plc., Chiesi Pharmaceuticals, Boehringer Ingelheim, Novartis and AstraZeneca, congress attendance from Chiesi and holds a grant from Boehringer Ingelheim. G. Waterer received personal fees from GlaxoSmithKline plc. N. Diar Bakerly received grants and personal fees from GlaxoSmithKline plc., Novartis and Almirall/AstraZeneca, and congress attendance from Boehringer Ingelheim. I. Satia received personal fees from GlaxoSmithKline plc., consulting and speaker fees from AstraZeneca and Merck, grants from Merck, GlaxoSmithKline plc, fellowship from ERS Marie-Curie Award, E.J. Moran Campbell Early Career Award, Department of Medicine, McMaster, outside the submitted work. A. Woodcock received speaker fees and expenses from Boehringer Ingelheim, Chiesi, GlaxoSmithKline and Novartis; is chairman/shareholder of Reacta Healthcare and Axalbion, and Chairman of the Medicines Evaluation Unit. D. Leather, L. Frith, L. Jacques and C. Harvey are employees of GlaxoSmithKline plc. and hold shares in the company. C. Crim was an employee of GlaxoSmithKline plc. at the time of the study.

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