

C-reactive protein as a biomarker of response to inhaled corticosteroids among patients with COPD



Olorunfemi A. Oshagbemi^{a,b,c,d,e,g}, Frits M.E. Franssen^{d,e}, Emiel F.M. Wouters^{d,e,g}, Anke H. Maitland-van der Zee^{c,f}, Johanna H.M. Driessen^{a,b,c}, Anthonius de Boer^c, Frank de Vries^{a,b,c,*}

^a Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre, Maastricht, the Netherlands

^b Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, the Netherlands

^c Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Utrecht, the Netherlands

^d CIRO, Horn, the Netherlands

^e Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands

^f Department of Respiratory Medicine, Academic University Medical Centre, University of Amsterdam (UvA) Amsterdam, the Netherlands

^g Department of Epidemiology, Care and Public Health Research Institute (CAPHR), Maastricht University, the Netherlands

ARTICLE INFO

Keywords:

Chronic obstructive pulmonary disease
C-reactive protein
Exacerbations
Inhaled corticosteroids

ABSTRACT

Aims: C-reactive protein (CRP) is an important biomarker in systemic inflammation in COPD; reports have suggested inhaled corticosteroids (ICS) attenuate CRP levels. We evaluated the risk of moderate-to-severe exacerbations, severe exacerbations and all-cause mortality among patients with COPD currently exposed to Inhaled corticosteroids (ICS) stratified by CRP levels compared to never ICS users with low CRP levels.

Methods: We included subjects age 40 or more who had a diagnosis of COPD from January 1, 2005 to January 31, 2014 from the UK Clinical Practice Research Datalink (CPRD). ICS exposure was determined time-dependently, as current, recent, past or never users. We evaluated the risk of moderate-to-severe exacerbations, severe exacerbations and all-cause mortality among ICS users stratified by CRP levels.

Results: 17,722 subjects diagnosed with COPD met the inclusion criteria. Among current or never ICS with elevated CRP levels we found, no significantly reduced risk of moderate-to-severe or severe exacerbations. For patients currently exposed ICS with CRP levels ≥ 8 mg/L there was no reduced risk of moderate-to-severe exacerbations (adjusted hazard ratio [adj. HR] 0.99; 95% confidence interval [CI] 0.76–1.31) or severe exacerbations (adj.HR 1.52; 95% CI 0.71–3.27). However, we found an increased risk of all-cause mortality among COPD patients with CRP levels ≥ 8 mg/L irrespective of ICS exposure.

Conclusion: We did not find a reduced risk of moderate and/or severe COPD exacerbations among COPD patients with varying CRP levels currently exposed to ICS. However, low-grade systemic inflammation was associated with all-cause mortality among COPD patients.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide [1] and is projected to be the third leading cause of death by the year 2030 [2]. Due to the heterogeneity of COPD, there is a growing interest in biomarkers and their potential to guide therapy among sub-groups of patients with COPD [3]. Inhaled corticosteroids (ICS) are additionally used to suppress inflammation and reduce exacerbation risk in patients unresponsive to bronchodilators. Hurst and colleagues assessed 36 biomarkers with the potential for

diagnosis and management of COPD, one of which was C-reactive protein (CRP) [4]. CRP is an acute-phase protein synthesised predominantly by the hepatocytes and acts by binding to receptors of the phagocytes and impacting on apoptosis and necrosis [5]. The ECLIPSE study illustrated that after 3 years of follow-up, all-cause mortality and exacerbation frequency was higher in persistently inflamed COPD patients (as measured by an increase in various biomarkers including CRP) compared to non-inflamed patients [6]. COPD is not an isolated condition with pathological mechanisms specifically localised in the lungs, but a heterogeneous disease with chronic inflammatory

* Corresponding author. Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, the Netherlands.

E-mail address: f.devries@uu.nl (F. de Vries).

<https://doi.org/10.1016/j.pupt.2019.101870>

Received 22 September 2019; Received in revised form 13 November 2019; Accepted 25 November 2019

Available online 27 November 2019

1094-5539/ © 2020 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

processes in various tissues accompanied by changes in various biomarkers [3].

Reports from clinical studies have suggested that ICS attenuate CRP levels among patients with moderate to severe COPD [7–9] and elevated CRP levels have been linked with increased risk of severe exacerbations and mortality [10,11]. The Copenhagen City Heart Study followed COPD patients, a small proportion of whom were exposed to ICS over a period of 8 years, and reported that patients with elevated CRP levels in combination with other biomarkers were at increased risk of severe exacerbations [12]. A randomised controlled trial (RCT) that enrolled more than 6,000 COPD patients over a 3-year period found that ICS exposure reduced COPD exacerbations but not all-cause mortality [13]. Furthermore, a meta-analysis of 15 studies showed that high baseline CRP was associated with a higher risk of mortality among COPD patients [11]. The use of ICS has been reported to significantly reduce CRP levels [7–9], hence we speculate that this attenuation of CRP will result in decreased risk of exacerbations and mortality. Biomarker guided therapy has the potential to help reduce the risk of fractures and pneumonia associated with ICS exposure by identifying patients groups more likely to benefit from ICS treatment [3]. No longitudinal study has yet evaluated the role of CRP in guiding ICS therapy among patients with COPD in a large general practice setting. Therefore, the aim of this study was to evaluate the risk of moderate-to-severe exacerbations, severe exacerbations and all-cause mortality among patients with COPD currently exposed to ICS and never ICS users stratified by CRP categories compared to never ICS users with the lowest CRP categories.

2. Methods

2.1. Data source

Data for this study were obtained from the Clinical Practice Research Datalink (CPRD). CPRD holds computerised medical records of 674 primary care practices in the United Kingdom. The database provides detailed information on drug prescriptions, clinical events, demographics, specialist referrals, and hospital admissions [14]. In addition, laboratory test results are available, including biomarker information. Data collection began in January 1987 and over 11 million persons are currently included [15]. This database has been used in various studies among COPD patients [16–18]. Approval for this study was obtained from the Independent Scientific Adversary Committee (ISAC) of the Medicines and Healthcare product Regulatory Authority (protocol no: 18_323R).

2.2. Study population

For this study we selected all newly diagnosed COPD subjects aged 40 years and older as recorded by a first read code during our study period January 1, 2005 (after the introduction of the Quality Outcome Framework (QOF)) to the January 31, 2014. Subjects were followed from the date of their COPD diagnosis (index date) until the end of data collection, date of death, and end of study or when the outcome of interest occurred, whichever came first. Subjects needed to have at least one CRP measurement before the index date to be included in the study. Subjects with a history of asthma at baseline were excluded. Subjects with acute exacerbations of COPD or oral glucocorticoid use within 30 days prior to index date were excluded.

2.3. Exposure

Each patient's follow-up time was divided into fixed periods of 90 days. Exposure to ICS was determined time-dependently during follow-up. Prior to the start of each interval, ICS exposure was determined based on the time since the most recent prescription, and classified as current (1–30 days), recent (31–60 days), past (> 60 days) or never

use. Never users of ICS comprised of patients without ICS exposure during follow-up. Subjects could move between exposure groups over time. Our exposure groups of interest included current users (subjects exposed to ICS within the first 30 days to the start of an interval) and never users (subjects with no ICS use within an interval). Current and never users of ICS were further stratified by the most recent CRP measurements, with the CRP levels classified into categories (category 1 (0–3 mg/L), category 2 (4–7 mg/L) and category 3 (≥ 8 mg/L)). We derived CRP categories by splitting the CRP distribution at the 33.3rd and 66.7th centiles using the PROC univariate procedure (SAS 9.4). CRP values were assessed time-dependently. We introduced a 12 months look-back period to determine CRP levels during follow-up; this choice was based on the mechanistic plausibility for ICS to attenuate CRP over this time period, hence we also provided a missing CRP category [9]. Patients with missing CRP measurements were classified into a separate category. When two or more CRP measurements were recorded on the same date, the mean CRP value was calculated. We used the term “elevated CRP” levels to refer to CRP levels > 3 mg/L in this work.

2.4. Outcome

The primary outcome of interest was moderate-to-severe exacerbation, which was defined using validated definitions (H312200, H3y1.00) for acute exacerbations of COPD from the clinical and referral files [19]. The secondary outcome was a severe exacerbation, defined as a COPD-related hospitalisation/accident and emergency visit using read codes (8H2R.00, 66Yi.00) from either the clinical or referral files or the read codes (H312200, H3y1.00) for acute exacerbations from the referral file. This definition of severe exacerbations is based on the fact that about 93% of patients with acute exacerbation of COPD reporting to the emergency department in the UK end up being hospitalised, with an average length of hospital stay of 1.25 days, which qualifies as a severe exacerbation [20]. The primary and secondary outcomes were not fully mutually exclusive. We also evaluated the risk of all-cause mortality. Referral files contain referral details recorded by general practitioners (GPs) while the clinical file contains all medical data entered by the GP [21].

2.5. Covariates

Potential confounders were assessed time-dependently with the exception of gender, smoking status, alcohol use, and body mass index, which were determined at baseline. The following covariates were considered as potential confounders, and identified at the start of each interval: a history of congestive heart failure, ischemic heart disease, anxiety, chronic liver disease, cancer excluding non-melanoma skin cancer, stroke, rheumatoid arthritis, diabetes mellitus, hypertension, inflammatory bowel disease, solid organ transplant, atopic dermatitis, renal dialysis, human immunodeficiency virus or osteoporosis. In addition, the use of the following drugs within 6 months prior to the start of an interval were considered as potential confounders: antihistamines, proton pump inhibitors, antipsychotics, or antidepressants [22–25]. We statistically adjusted our analyses for proxy indicators of the severity of obstructive airway disease, as previously defined as use of short- and long-acting beta-agonists, short- and long-acting anti-muscarinic agents, xanthine derivatives, oxygen use or oral corticosteroids [26,27]. In addition, the use of antibiotics for COPD exacerbations in the month prior to an interval was considered as a potential confounder [28].

2.6. Statistical analysis

We evaluated the risk of moderate-to-severe exacerbations, severe exacerbations and all-cause mortality stratified by ICS use and CRP levels using Cox regression analysis (SAS 9.4). Current and never ICS users were stratified by CRP levels. Categories were made to reduce the

impact of outlying values and to account for the positively skewed distribution of CRP. The reference category for this study included patients who were never exposed to ICS with the lowest CRP levels (0–3 mg/L). Furthermore, we compared the risk of study outcomes between never users in category 2 (4–7 mg/L) and current ICS users in category 2 (4–7 mg/L), never ICS users in category 3 (≥ 8 mg/L) and current ICS users category 3 (≥ 8 mg/L) using Wald test and we only reported any significant differences the groups in our fully-adjusted analyses p-values less than 0.05. Potential confounders were included in the final model if they changed the beta-coefficient for the association between current ICS and never use and the outcome of interest by at least 5% or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from literature. For the baseline characteristics ICS exposure status was determined prior to the start of follow-up (index date) as ICS users were patients with an ICS prescription ever before, and non-using patients as all patients without a record of ICS ever before.

2.7. Sensitivity analysis

We repeated the above-mentioned analyses but broke down the highest CRP level category into patients with a serum CRP level 8–19 mg/L and those with values ≥ 20 mg/L. We chose this threshold because we felt that it may better reflect the acute phase inflammatory process [29].

3. Results (588)

We identified 213,561 patients with COPD, 17,722 patients met the inclusion criteria (Fig. 1). Table 1 shows the baseline characteristics of all COPD patients. At baseline 5162 COPD patients were exposed to ICS and 12,560 were not. Over half of the ICS users were females, with a mean age of 69.1 years. At baseline, the mean CRP levels were 12.9 (± 29.0) mg/L for ICS users with COPD and 12.4 (± 30.0) mg/L COPD patients who had not used ICS. About 29.3% of ICS users were obese versus 24.1% of ICS non-using subjects, 35.6% of ICS users were current smokers compared to 45.0% among subjects not exposed to ICS.

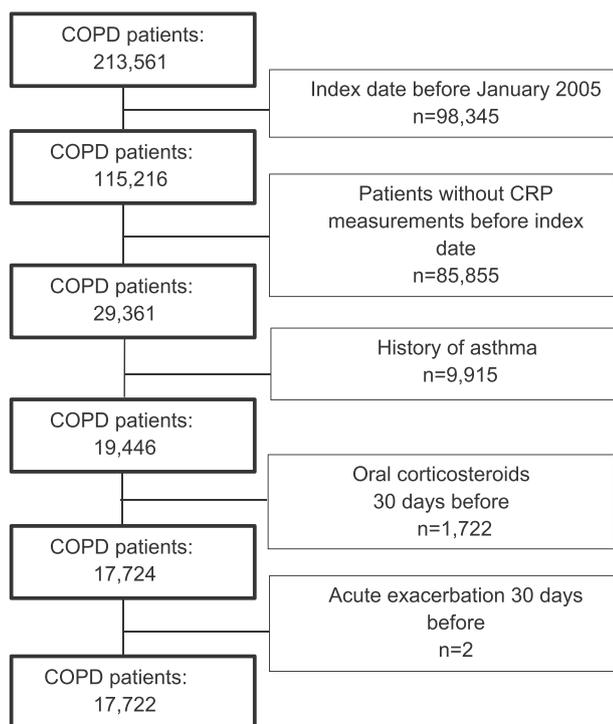


Fig. 1. Flow chart showing the selection of eligible patients.

Table 1
Baseline characteristic of COPD patients.

	ICS ^b		ICS non-users ^b	
	n = 5162	%	n = 12,560	%
Females	2688	52.1	5981	47.6
Mean age (years, SD)	69.1	11.7	68.2	11.0
Mean follow-up (years, SD)	3.0	2.2	3.0	2.2
Age category (years)				
40–59	1069	20.7	2766	22.0
60–79	3030	58.7	7659	61.0
80+	1063	20.6	2135	17.0
BMI (kg/m ²) ^b in the past 6 months				
Underweight (BMI < 18.5 kg/m ²)	264	5.1	797	6.3
Normal weight (BMI 18.5–24.9 kg/m ²)	1640	31.8	4498	35.8
Overweight (BMI 25.0–29.9 kg/m ²)	1596	30.9	3905	31.1
Obese (BMI ≥ 30.0 kg/m ²)	1512	29.3	3029	24.1
Missing	150	2.9	331	2.6
Mean CRP (mg/L, SD)	12.9	29.0	12.4	30.0
Median CRP (mg/L, IQR)	5.0	7.1	5.0	7.0
CRP ≤ 8.0 mg/L	3535	68.4	8862	70.5
Blood eosinophil counts > 300 cell/ μ L ^a	972	18.8	2077	16.5
Smoking status at index date				
Never	737	14.3	1211	9.6
Current	1839	35.6	5656	45.0
Former	2581	50.0	5688	45.3
Missing	5	0.1	5	0.1
Drug use (in the past 6 months)				
SABAs	3375	65.4	4168	32.2
LABAs	2304	44.6	388	3.1
SAMAs	500	9.7	619	4.9
LAMAs	1010	19.6	673	5.4
Xanthine derivatives	43	0.8	12	0.1
Antipsychotics	63	1.2	133	1.1
History of co-morbidities				
Cardiovascular disease	1232	23.9	2610	20.8
Diabetes Mellitus	726	14.1	1439	11.5
Anxiety	953	18.5	2187	17.4
Osteoporosis	443	8.6	943	7.5
Any cancer (except non-melanoma skin cancer)	922	17.9	2186	17.4
Chronic liver disease	16	0.3	62	0.5

Abbreviations: SD, standard deviation; COPD, chronic obstructive pulmonary disease; BMI, body mass index; CRP, C-reactive protein; SABAs, short-acting beta-2 agonists; LABAs, long-acting beta-2 agonists; SAMAs, short-acting muscarinic antagonists; ICS, inhaled corticosteroids; LAMAs, long-acting muscarinic antagonists; n, number; %, percentage.

**All medications were assessed 6 months prior to index date and comorbidities were assessed ever before index date.

^a Measured in the year prior to index.

^b ICS exposure status was determined prior to start of follow-up (index date) as ICS users were patients with an ICS prescription ever before and non-using patients as all patients without a record of ICS ever before.

3.1. Moderate-to-severe and severe exacerbations

Table 2 shows that the risk of moderate-to-severe exacerbations was not different between COPD patients who were current ICS users with CRP levels of 0–3 mg/L compared to never ICS users with low CRP serum (0–3 mg/L, adjusted hazard [adj.] ratio [HR] 0.95 95% confidence interval [CI] 0.70–1.27 (4–7 mg/L or ≥ 8 mg/L), Wald tests showed that the risk of moderate-to-severe COPD exacerbations was not different between ICS users and never users with COPD. Regardless of ICS exposure status, risk of moderate-to-severe COPD exacerbations was not statistically different between different CRP categories (0–3 mg/L vs 4–7 mg/L vs or ≥ 8 mg/L). Table 3 shows that these findings were largely similar for the risk of severe COPD exacerbations.

3.2. All-cause mortality

All-cause mortality among COPD patients with low CRP levels (0–3 mg/L) was not different between current ICS users and never

Table 2
Risk of moderate-to-severe exacerbations among never and current ICS user stratified by CRP levels.

	Moderate-to-severe (n = 1530) ^b	IR (/1000PY)	Age and sex adjusted HR (95% CI)	Adjusted HR (95% CI) ^a
ICS use				
Never	380	47.4		
By CRP levels (mg/L)				
0-3	132	54.9	Reference	Reference
4-7	97	49.1	0.90(0.69–1.17) ^c	0.88(0.68–1.14)
≥8	151	64.7	1.19 (0.94–1.51) ^d	1.11(0.88–1.40)
Current	221	95.6		
By CRP levels (mg/L)				
0-3	72	91.3	1.65(1.24–2.19)	0.95(0.70–1.27)
4-7	56	82.4	1.50(1.10–2.05) ^c	0.83(0.60–1.14)
≥8	93	103.9	1.92(1.47–2.50) ^d	0.99(0.76–1.31)

Abbreviations: ICS, Inhaled corticosteroids; IR, incidence rate; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; PY, person-years.

Recent ICS users had 285 moderate-to-severe exacerbations; Past ICS users had 644 moderate-to-severe exacerbations.

^a Adjusted for age, sex, smoking status, body mass index, alcohol use, history of heart failure, chronic liver disease, ischemic heart disease, recent ICS use, past ICS use, use of antipsychotic, antidepressants, atopic dermatitis, use of oxygen, short-acting beta-2 agonists, long-acting beta-2 agonists, short-acting muscarinic antagonists, long-acting muscarinic antagonists, xanthine derivatives and oral corticosteroid 6 months prior and use of antibiotics 1 month prior.

^b 2781 moderate-to-severe exacerbations were recorded among 17,722 patients with COPD.

^c Wald test showed that these categories were statistically significantly different, despite overlapping confidence intervals.

^d Wald test showed that these categories were statistically significantly different, despite overlapping confidence intervals.

users, adj. HR please add (Table 4). This finding was consistent when ICS use was compared with never use in other CRP categories (4–7 mg/L or ≥8 mg/L). However, all-cause mortality among COPD patients with CRP levels ≥8 mg/L showed approximately three-fold significantly increased as compared to COPD patients with low CRP serum levels (0–3 mg/L) adj. HR 2.81; 95% CI 2.20–3.58 for ICS non-using COPD patients.

3.3. Sensitivity analysis

In the sensitivity analysis, never or current use of ICS among COPD patients with CRP levels of ≥20 mg/L was not associated with a significant reduction in the risk of moderate-to-severe or severe COPD exacerbations compared to never ICS users with low CRP serum levels (0–3 mg/L, Tables S1 and S2). However, we found that the risk of all-cause mortality among COPD patients with CRP levels ≥20 mg/L was 3.5-4-fold increased among ICS and ICS non-using patients, adj. HR 4.03; 95% CI 3.11–5.22, among never users of ICS.

Table 3
Risk of severe exacerbations among never and current ICS user stratified by CRP levels.

	Severe exacerbations (n = 211) ^b	IR (/1000PY)	Age and sex adjusted HR (95% CI)	Adjusted HR (95% CI) ^a
ICS use				
Never	42	5.1		
By CRP levels (mg/L)				
0-3	13	5.2	Reference	Reference
4-7	12	5.8	1.11(0.51–2.43) ^c	1.08(0.49–2.37)
≥8	17	6.9	1.34(0.65–2.76) ^d	1.24(0.60–2.56)
Current	35	11.0		
By CRP levels (mg/L)				
0-3	7	7.3	1.35(0.54–3.38)	0.83(0.32–2.13)
4-7	12	14.4	2.64(1.21–5.79) ^c	1.60(0.71–3.60)
≥8	16	14.3	2.64(1.27–5.50) ^d	1.52(0.71–3.27)

Abbreviations: ICS, Inhaled corticosteroids; IR, incidence rate; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; PY, person-years.

Recent ICS users had 39 severe exacerbations; Past ICS users had 95 severe exacerbations.

Missing CRP category not included.

^a Adjusted for age, sex, smoking status, body mass index, alcohol use, history of heart failure, chronic liver disease, diabetes mellitus, ischemic heart disease, osteoporosis, recent ICS use, past ICS use, use of proton-pump inhibitors, antidepressants, oxygen, antipsychotics, statins, short-acting beta-2 agonists, long-acting beta-2 agonists, short-acting muscarinic antagonists, long-acting muscarinic antagonists, xanthine derivatives and oral corticosteroids in the 6 months prior and use of antibiotics specific for COPD 1 month prior.

^b 367 severe exacerbations were recorded among 17,722 patients with COPD.

^c Wald test showed that these categories were statistically significantly different, despite overlapping confidence intervals.

^d Wald test showed that these categories were statistically significantly different, despite overlapping confidence intervals.

Table 4
Risk of all-cause mortality among never and current ICS user stratified by CRP levels.

	All-cause mortality (n = 1756) ^b	IR (/1000PY)	Age and sex adjusted HR (95% CI)	Adjusted HR (95% CI) ^a
ICS use				
Never	459	47.0		
By CRP levels (mg/L)				
0-3	84	33.6	Reference	Reference
4-7	84	40.5	1.17(0.86–1.58)	1.21(0.89–1.63)
≥8	291	117.3	3.11(2.44–3.96)	2.81(2.20–3.58)
Current	235	62.4		
By CRP levels (mg/L)				
0-3	37	37.9	1.08(0.74–1.59)	0.81(0.55–1.20)
4-7	35	41.2	1.18(0.80–1.76)	0.90(0.60–1.34)
≥8	163	142.5	3.59(2.75–4.67)	2.38(1.81–3.13)

Abbreviations: ICS, Inhaled corticosteroids; IR, incidence rate; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; PY, person-years.

Recent ICS users had 264 deaths; Past ICS users had 798 deaths.

Missing CRP category not included.

^a Adjusted for age, sex, smoking status, body mass index, alcohol use, history of heart failure, chronic liver disease, ischemic heart disease, atopic dermatitis, diabetes mellitus, cancer, recent ICS use, past ICS use, use of oxygen, statins, short-acting beta-2 agonists, long-acting beta-2 agonists, short-acting muscarinic antagonists, long-acting muscarinic antagonists, xanthine derivatives and oral corticosteroid use in the 6 months prior and use of antibiotics specific for COPD 1 month prior.

^b 2839 deaths were recorded among 17,722 patients with COPD.

investigators evaluated each elevated biomarker alone (including CRP), no significantly increased risk of frequent exacerbations was found, in line with our findings. It is important to note that the authors stated that the use of ICS was “relatively rare” among the patients enrolled and might have affected their findings (with only 3% of the study population was exposed to ICS at baseline) [31]. In our study, we noted an increased risk of moderate and/or severe exacerbations when we adjusted only for age and sex (Table 2), following adjustments for all possible confounders the risk disappeared. This is the first study to specifically evaluate the risk of moderate-to-severe, severe exacerbations and all-cause mortality among COPD patients currently exposed to ICS stratified by CRP levels. A randomised controlled trial conducted across 11 centres among 289 COPD patients treated with ICS, with or without LABA, found no reduction in CRP levels although serum protein D levels decreased, suggesting that ICS treatment affects lung-specific biomarkers rather than systemic inflammatory markers [8]. Furthermore, ECLIPSE investigators found that elevated levels of CRP, fibrinogen and leucocyte counts were associated with the occurrence of exacerbations in the first year in a univariate analysis [32]. However, the effect disappeared following multivariate adjustments except for leucocyte counts. Approximately 30% of patients with COPD exacerbations have been reported to have normal CRP levels [33], which questions the validity of CRP as a robust biomarker. Furthermore, De Torres et al., [34] reported that current exposure to glucocorticoids did not influence CRP levels, contrary to previous reports [7]. Consistent with our study, there was a huge variation in CRP levels across the mean, suggesting that CRP cannot be used as a clinical biomarker [35]. The exact mechanism by which ICS interact with CRP in COPD remains unclear. However, interleukin 6, a potent regulator of CRP generation known to be present in high concentrations in the serum and expiratory condensates of patients with COPD, can be down-regulated by corticosteroids [36].

All-cause mortality is an important end-point, which is seldom assessed among COPD patients mostly due to the short duration of patient follow-up in most studies. In our study we found an increased risk of all-cause mortality among COPD patients with elevated CRP levels (8 mg/L) compared to patients with low CRP. Consistent with our finding, the Lung Heart Study which enrolled over 4800 patients with mild to moderate COPD stratified by CRP quartiles reported that patients with elevated CRP levels were at increased risk of all-cause mortality [37]. Similarly, a cohort study of 1302 patients with airflow limitation with a median follow-up of 8-years in Denmark, reported a greater risk of COPD deaths among patients with high CRP levels compared to patients

with lower CRP levels [12]. However, a multi-center study with 218 patients with stable COPD found that elevated CRP levels did not increase the risk of all-cause mortality [34]. This might be due to the low statistical power of their study. More recently, a meta-analysis and systematic review of 15 studies, which included 11,180 COPD patients, found that higher baseline CRP was associated with a higher risk of mortality [11]. Cardiovascular events and cancers accounted for most deaths [11,38]. With no clear CRP cut-off, researchers have called for the adoption of a clearly defined threshold for clinical and observational studies, in order to truly reveal the potential of CRP in COPD management [39].

The heterogeneity of systemic inflammation has been recognised in patients with COPD. These include high heterogeneity in serum CRP, fibrinogen, and TNF, which are largely attributed to host or disease-related factors [40]. Elevated CRP levels have been reported in obese patients and epidemiological data shows an age-related increase in inflammatory biomarkers [40]. In general population a dose-related effect has been reported between cigarette smoking and increased levels of CRP and fibrinogen [41,42] and CRP levels remained elevated for approximately two decades after smoking cessation [43]. Although, better understanding of the effects of confounders on CRP levels exist, CRP stability and variability of remains critical to its relevance as a guide for therapeutic interventions in COPD. The ECLIPSE study reported CRP as the least stable biomarker assessed, with only 21% of patients having a 3-months measurement within 25% of baseline values [44]. Furthermore, CRP is known to have a half-life in plasma of 19 h and the National Health and Nutrition Examination Survey (NHANES) observed significant short-term variability (approximately 2.5 weeks) in CRP levels, particularly at high values [45]. These factors make CRP a poor biomarker for personalised management of COPD.

A major strength of this study was the inclusion of patients from one of the world's largest primary care databases, thus providing a large population-based cohort of COPD patients with CRP measurements followed over time with fair recording of all-cause mortality [46,47]. Second, in our study we used validated definitions for moderate and/or severe exacerbations of COPD, using read codes reported having a 96% positive predictive value of identifying an acute exacerbation within the CPRD [19]. Nevertheless, we may have missed considerable numbers of exacerbations, which may be miscoded e.g. as respiratory tract infections such as pneumonia. Third, time-varying classification of exposure to ICS, CRP and covariates allowed us to conduct an “on-treatment analysis”, which results in less non-differential misclassification of exposure than in an ‘intention to treat analysis’ which ignores ICS

exposure during follow-up. Lastly, data on confounding factors such as smoking status, BMI, comorbidities, and drugs prescribed were available and as such these covariates were adjusted for in our models.

Limitations to our study include, a potential for confounding by disease severity as we lacked information on COPD disease stage. Confounding by disease severity is a multifactorial phenomenon that may act in different directions. Although we did not use information on disease severity, we adjusted for proxies of COPD disease severity. While we excluded asthma patients, it was impossible to rule out the inclusion of patients with reversible airflow limitation. CRP measurements are not routinely collected as part of diagnosis of COPD; they are most likely requested by the GP in suspicion of bacterial infections and might have introduced misclassification bias. We expect this bias to be non-differential among COPD patients exposed to ICS and ICS never users leading to biased estimates towards the null. While this might have masked the true risk of moderate and/or severe exacerbations among patients with elevated CRP levels, we found significant associations among patients with elevated CRP levels for all-cause mortality, suggesting that our results could not have been affected by this bias. Furthermore, because ICS use is associated with pneumonia, these patients might have a higher CRP level among the ICS users potentially resulting in differential misclassification. This will lead to bias estimates towards or away from the null. However, considering the similarities in mean CRP levels between “ever before” ICS users and ICS non-using patients, it is less likely that this bias had a huge impact on our estimates. We had a significant amount of patients with missing CRP serum levels during follow-up; this was due to the choice of a 1-year look-back period for CRP assessment. We could not determine cause-specific death such as COPD-related mortality, considering that only approximately 58% of general practices are consented to required linkage [15], which will substantially diminish the power of our study to accurately detect study outcomes. We could not determine the criteria for ICS prescription in this study as a significant dissociation exist between clinical recommendation/guidelines and actual prescribing practice by GPs [48]. While the choice of this look back window results in missing CRP counts, this choice was rightly made considering the mechanistic plausibility of ICS to attenuate CRP and exacerbations over this period [9]. The choice of a longer period would have resulted in less missing CRP counts during follow-up but will not be realistically plausible in clinical settings.

4.2. Key message

In conclusion, we did not find a reduced risk of moderate and/or severe COPD exacerbations among COPD patients with varying CRP levels currently exposed to ICS. However, we found an increased risk of all-cause mortality among patients with elevated (≥ 8 mg/L) CRP levels irrespective of ICS use. There is tremendous enthusiasm and effort to improve precision medicine using biomarkers in COPD. While CRP might be a useful biomarker for COPD prognosis, it does not seem to have the potential to guide ICS therapy in COPD management.

Authors contributions

O.A.O, F.V, E.W and F.F initiated the study and wrote the initial draft of the manuscript. O.A.O and J.H.M were responsible for the data analysis. AB gave critical analyses and contributions to the project. All authors made contributions to the interpretation of the results and the revision of the manuscript. F.V, E.W and F.F supervised the study.

What is known about this subject

1. Reports from clinical studies have suggested that ICS attenuate CRP levels among patients with moderate to severe COPD.
2. Elevated CRP has been associated with an increased risk of moderate-and-severe exacerbations and mortality

3. ICS helps to improve exacerbation outcomes among patients with COPD.

What this study adds

1. Irrespective of ICS exposure patients with persistently elevated CRP levels had an increased risk of mortality.
2. Among patients with persistently elevated CRP, current ICS exposure did not reduce the risk of moderate-to-severe or severe exacerbations.

Data availability statement

Research data are not shared as they belong to the CPRD in the UK and only licensed institutions are given access to the data.

Declaration of competing interest

All authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pupt.2019.101870>.

References

- [1] GOLD, Global strategy for the prevention, diagnosis and treatment of chronic obstructive pulmonary disease (2019 Report), <https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf>, (2018), Accessed date: 15 November 2018.
- [2] GBD 2010 Mortality and Causes of Death Collaborators, Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010, *Lancet* 380 (9859) (2012) 2095–2128.
- [3] O.A. Oshagbemi, A.M. Burden, D.C.W. Braeken, et al., Stability of blood eosinophils in patients with chronic obstructive pulmonary disease and in control subjects, and the impact of sex, age, smoking, and baseline counts, *Am. J. Respir. Crit. Care Med.* 195 (10) (2017).
- [4] J.R. Hurst, G.C. Donaldson, W.R. Perera, et al., Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease, *Am. J. Respir. Crit. Care Med.* 8 (2006) 867–874.
- [5] P.J. Barnes, B. Chowdhury, S.A. Kharitonov, et al., Pulmonary biomarkers in chronic obstructive pulmonary disease, *Am. J. Respir. Crit. Care Med.* 174 (1) (2006) 6–14.
- [6] A. Agustí, L.D. Edwards, S.I. Rennard, et al., Persistent systemic inflammation is associated with poor clinical outcomes in copd: a novel phenotype, *PLoS One* 7 (5) (2012) e37483.
- [7] D.D. Sin, P. Lacy, E. York, S.F.P. Man, Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease, *Am. J. Respir. Crit. Care Med.* 170 (7) (2004) 760–765.
- [8] D.D. Sin, S.F.P. Man, D.D. Marciniuk, et al., The effects of fluticasone with or without salmeterol on systemic biomarkers of inflammation in chronic obstructive pulmonary disease, *Am. J. Respir. Crit. Care Med.* 177 (11) (2008) 1207–1214.
- [9] Y.-H. Lin, X.-N. Liao, L.-L. Fan, Y.-J. Qu, D.-Y. Cheng, Y.-H. Shi, Long-term treatment with budesonide/formoterol attenuates circulating CRP levels in chronic obstructive pulmonary disease patients of group D, *PLoS One* 12 (8) (2017) e0183300.
- [10] A. Comes, E.S. Ianosi, Gabriela Jimborean, Inflammatory biomarkers in chronic obstructive pulmonary disease, *J. Interdiscip. Med.* 1 (2016) 12.
- [11] G. Leuzzi, C. Galeone, F. Taverna, P. Suatoni, D. Morelli, U. Pastorino, C-reactive protein level predicts mortality in COPD: a systematic review and meta-analysis, *Eur. Respir. Rev.* 26 (143) (2017).
- [12] M. Dahl, J. Vestbo, P. Lange, S.E. Bojesen, A. Tybjaerg-Hansen, B.G. Nordestgaard, C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease, *Am. J. Respir. Crit. Care Med.* 175 (3) (2007) 250–255.
- [13] P.M.A. Calverley, J.A. Anderson, B. Celli, et al., Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease, *N. Engl. J. Med.* 356 (8) (2007) 775–789.
- [14] J.K. Quint, H. Müllerova, R.L. DiSantostefano, et al., Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD), *BMJ Open* 4 (7) (2014).
- [15] E. Herrett, A.M. Gallagher, K. Bhaskaran, et al., Data resource profile: clinical practice Research Datalink (CPRD), *Int. J. Epidemiol.* 44 (3) (2015) 827–836.
- [16] M.F. Barakat, H.I. McDonald, T.J. Collier, L. Smeeth, D. Nitsch, J.K. Quint, Acute kidney injury in stable COPD and at exacerbation, *Int. J. Chronic Obstr. Pulm. Dis.* 10 (1) (2015) 2067–2077.
- [17] H. Mullerova, A. Shukla, A. Hawkins, J. Quint, Risk factors for acute exacerbations

- of COPD in a primary care population: a retrospective observational cohort study, *BMJ Open* 4 (12) (2014) e006171.
- [18] K.E. Wurst, A. Shukla, H. Muellerova, K.J. Davis, Respiratory pharmacotherapy use in patients newly diagnosed with chronic obstructive pulmonary disease in a primary care setting in the UK: a retrospective cohort study, *COPD* 11 (5) (2014) 521–530.
- [19] K.J. Rothnie, H. Müllerová, J.R. Hurst, et al., Validation of the recording of acute exacerbations of COPD in UK primary care electronic healthcare records, *PLoS One* 11 (3) (2016).
- [20] D. Neville, T. Jones, E. Lanning, T. Brown, B. Green, A. Chauhan, COPD attendances in a busy emergency department; frequency and timing, *Eur. Respir. J.* 48 (Suppl 60) (2016).
- [21] S. Padmanabhan, CPRD GOLD data specification, Published https://www.ed.ac.uk/files/atoms/files/cprd_gold_full_data_specification.pdf, (2015), Accessed date: 15 May 2018.
- [22] W.M. Chatila, B.M. Thomashow, O.A. Minai, G.J. Criner, B.J. Make, Comorbidities in chronic obstructive pulmonary disease, *Proc. Am. Thorac. Soc.* 5 (4) (2008) 549–555.
- [23] R.W. Dal Negro, L. Bonadiman, P. Turco, Prevalence of different comorbidities in COPD patients by gender and GOLD stage, *Multidiscip. Respir. Med.* 10 (1) (2015) 24.
- [24] F.M.E. Franssen, C.L. Rochester, Comorbidities in patients with COPD and pulmonary rehabilitation: do they matter? *Eur. Respir. Rev.* 23 (131) (2014) 131–141.
- [25] M. Divo, C. Cote, J.P. De Torres, et al., Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease, *Am. J. Respir. Crit. Care Med.* 186 (2) (2012) 155–161.
- [26] M.N. de Melo, P. Ernst, S. Suissa, Inhaled corticosteroids and the risk of a first exacerbation in COPD patients, *Eur. Respir. J.* 23 (5) (2004) 692–697.
- [27] P. Ernst, A.V. Gonzalez, P. Brassard, S. Suissa, Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia, *Am. J. Respir. Crit. Care Med.* 176 (2) (2007) 162–166.
- [28] NICE, Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing, <https://www.nice.org.uk/guidance/ng114>, (2018).
- [29] H. Melbye, D. Hvidsten, A. Holm, S.A. Nordbø, J. Brox, The course of C-reactive protein response in untreated upper respiratory tract infection, *Br. J. Gen. Pract.* 54 (506) (2004) 653–658.
- [30] J.A. Wedzicha, T.A. Seemungal, COPD exacerbations: defining their cause and prevention, *Lancet* 370 (9589) (2007) 786–796.
- [31] M. Thomsen, T.S. Ingebrigtsen, J.L. Marott, et al., Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease, *JAMA, J. Am. Med. Assoc.* 309 (22) (2013) 2353–2361.
- [32] J.R. Hurst, J. Vestbo, A. Anzueto, et al., Susceptibility to exacerbation in chronic obstructive pulmonary disease, *N. Engl. J. Med.* 363 (12) (2010) 1128–1138.
- [33] N. Weis, T. Almdal, C-reactive protein—can it be used as a marker of infection in patients with exacerbation of chronic obstructive pulmonary disease? *Eur. J. Intern. Med.* 17 (2) (2006) 88–91.
- [34] J.P. de Torres, V. Pinto-Plata, C. Casanova, et al., C-reactive protein levels and survival in patients with moderate to very severe COPD, *Chest* 133 (6) (2008) 1336–1343.
- [35] A. Agusti, D.D. Sin, Biomarkers in COPD, *Clin. Chest Med.* 35 (1) (2014) 131–141.
- [36] S.F.P. Man, D.D. Sin, Effects of corticosteroids on systemic inflammation in chronic obstructive pulmonary disease, *Proc. Am. Thorac. Soc.* 2 (1) (2005) 78–82.
- [37] S.F.P. Man, J.E. Connett, N.R. Anthonisen, R.A. Wise, D.P. Tashkin, D.D. Sin, C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease, *Thorax* 61 (10) (2006) 849–853.
- [38] V.M. Pinto-Plata, H. Müllerova, J.F. Toso, et al., C-reactive protein in patients with COPD, control smokers and non-smokers, *Thorax* 61 (1) (2006) 23–28.
- [39] B. Müller, M. Tamm, Biomarkers in acute exacerbation of chronic obstructive pulmonary disease: among the blind, the one-eyed is king, *Am. J. Respir. Crit. Care Med.* 174 (8) (2006) 848–849.
- [40] M. Breyer, E.P.A. Rutten, M. Spruit, W.C.J. Hop, S.D. Postma, E. Wouters, Systemic inflammation in patients with chronic obstructive pulmonary disease: results from the cosmic study, *Open J. Respir. Dis.* 2 (3) (2012) 66–72.
- [41] W.B. Kannel, R.B. D'Agostino, A.J. Belanger, Fibrinogen, cigarette smoking, and risk of cardiovascular disease: insights from the Framingham study, *Am. Heart J.* 113 (4) (1987) 1006–1010.
- [42] L.A. Bazzano, J. He, P. Muntner, S. Vupputuri, P.K. Whelton, Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States, *Ann. Intern. Med.* 138 (11) (2003) 891–897.
- [43] S.G. Wannamethee, G.D.O. Lowe, A.G. Shaper, A. Rumley, L. Lennon, P.H. Whincup, Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease, *Eur. Heart J.* 26 (17) (2005) 1765–1773.
- [44] J.A. Dickens, B.E. Miller, L.D. Edwards, et al., COPD association and repeatability of blood biomarkers in the ECLIPSE cohort, *Respir. Res.* 12 (1) (2011) 146.
- [45] J.K. Bower, M. Lazo, S.P. Juraschek, E. Selvin, Within-person variability in high-sensitivity C-reactive protein, *Arch. Intern. Med.* 172 (19) (2012) 1519–1521.
- [46] K. Haynes, Mortality: the final outcome, *Pharmacoepidemiol. Drug Saf.* 28 (5) (2019) 570–571.
- [47] A.M. Gallagher, D. Dedman, S. Padmanabhan, H.G.M. Leufkens, F. de Vries, The accuracy of date of death recording in the Clinical Practice Research Datalink GOLD database in England compared with the Office for National Statistics death registrations, *Pharmacoepidemiol. Drug Saf.* 28 (5) (2019) 563–569.
- [48] J.D. Chalmers, A. Tebbboth, A. Gayle, A. Ternouth, N. Ramscar, Determinants of initial inhaled corticosteroid use in patients with GOLD A/B COPD: a retrospective study of UK general practice, *NPJ Prim. Care Respir. Med.* 27 (2017) 43.