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Early View

Original research article

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Please cite this article as: Ashdown HF, Smith M, McFadden E, *et al*. Blood eosinophils to guide inhaled maintenance therapy in a primary care COPD population. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00606-2021).

Blood eosinophils to guide inhaled maintenance therapy in a primary care COPD population

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Take home message:
ICS-naïve COPD patients who are initiated on ICS and whose most recent blood eosinophil count is <150/µL have a 15% higher risk of future exacerbation compared to those with a count ≥150/µL. ICS should be reserved for those with higher blood eosinophils.

Abstract

Blood eosinophils are a potentially useful biomarker for guiding inhaled corticosteroid (ICS) treatment decisions in COPD. We investigated whether existing blood eosinophil counts predict benefit from initiation of ICS compared to bronchodilator therapy.

We used routinely collected data from UK primary care in the Clinical Practice Research Datalink. Participants were ≥40 years with COPD, ICS-naïve and starting a new inhaled maintenance medication (intervention group: ICS; comparator group: long-acting bronchodilator, non-ICS). Primary outcome was time-to-first exacerbation, compared between ICS and non-ICS groups, stratified by blood eosinophils ("high" (≥150/µL) and "low" (<150/µL) groups).

Of 9,475 eligible patients, 53.9% initiated ICS and 46.1% non-ICS treatment with no difference in eosinophils between treatment groups (P=0.71). Exacerbation risk was higher in patients prescribed ICS than non-ICS, but with a lower risk in those with "high" eosinophils (hazard ratio 1.04, 95% CI 0.98 to 1.10) than "low" eosinophils (1.19, 95% CI 1.09 to 1.31) (P value for interaction=0.01). Risk of pneumonia hospitalisation with ICS was greatest in those with "low" eosinophils (hazard ratio 1.26, 95% CI 1.05 to 1.50; P value for interaction=0.04). Results were similar whether the most recent blood eosinophil count or the mean of blood eosinophil counts was used.

In a primary care population, the most recent blood eosinophil count could be used to guide initiation of ICS in COPD patients. We suggest that ICS should be considered in those with higher eosinophils and avoided in those with lower eosinophils (<150/µL).

Introduction

Guidelines for pharmacological management of chronic obstructive pulmonary disease (COPD) recommend addition of inhaled corticosteroids (ICS) to bronchodilator therapy for worsening symptoms (frequent exacerbations or persistent breathlessness) [1]. Although there is some benefit in reducing exacerbations, long-term effects of ICS on lung function decline and mortality are unclear. ICS use is associated with adverse effects including pneumonia and osteoporotic fractures, as well as being cumulatively expensive [2, 3]. ICS compounds are nevertheless widely used in clinical practice [4]. In UK primary care, almost 2 in 5 patients prescribed an ICS did not meet criteria for this treatment [3]. There is therefore an urgent need to improve clarity around when ICS should be prescribed.

Blood eosinophil count has gained interest as a biomarker for identifying COPD patients more likely to benefit from ICS treatment. Many post-hoc analyses, using various eosinophil count thresholds, have shown greater response to ICS-containing preparations in patients with a higher baseline blood eosinophil count [5]. There have also been recent prospective evaluations of ICS-response and peripheral blood eosinophil count [6, 7]. However, patients included in such trials are not representative of the real-world population as inclusion is centred around patients already established on inhaled maintenance medication. This is especially important in primary care where patients are often diagnosed and where step-up or initiation of ICS therapy is most often considered [8, 9].

General practice research databases, which routinely collect anonymised information from patient consultations and are linked at patient level with hospital and national statistics, provide an efficient

and well-validated way of answering clinical questions relevant to primary care involving large sample sizes [10].

Using the Clinical Practice Research Datalink (CPRD), we investigated whether the most recent peripheral blood eosinophil count at the point of an inhaled treatment step-up or initiation decision could predict treatment outcomes, in a COPD ICS-naïve primary care population from 2005-2015.

Methods

Study design

We used a new-user active-comparator study design [11] and compared time-to-first exacerbation of those commencing inhaled maintenance medication containing an ICS (ICS group) with those not containing an ICS (non-ICS group), looking for effect modification by baseline blood eosinophil count. Additional methods are presented in the online supplement.

Data source and included population

The CPRD, a large database of UK general practice clinical records, individually linked with Hospital Episode Statistics records, was used. Included patients were those with data linkage aged ≥40 years with a COPD diagnosis code, a valid blood eosinophil count (see below for definition), a history of current/past smoking and spirometry diagnostic of COPD (FEV_1/FVC ratio <0.7), who were starting a new inhaled maintenance medication for COPD in the period 1st January 2005-31st August 2015 (index date). Our range of index dates were chosen to be after introduction of Quality and Outcomes Framework (QOF) targets in UK primary care which improved coding of COPD and spirometry [12], but before blood eosinophils were promoted as a potential biomarker, which might have influenced

prescribing choices. Recruited patients were also ICS-naïve, due to concern that steroid treatment might suppress blood eosinophil values, [13] which was defined as no ICS prescriptions and fewer than three oral corticosteroid prescriptions in the previous 12 months. Excluded patients were those with a diagnosis of bronchiectasis, alpha-1 anti-trypsin deficiency, interstitial lung disease or cystic fibrosis. Those with an active diagnosis of asthma (coded in last two years vs. a historical code on the medical records) were excluded from the primary analysis. Follow-up continued until the earliest of the date the practice stopped providing data to CPRD, the patient died or left the practice, or 29th February 2016. Eligible patients were required to have at least 24 months continuous data, 6 months before and after the index date, to ensure adequate recording of baseline covariates and outcomes.

Exposures

The exposure was a new ICS-containing inhaled maintenance medication (ICS, ICS/LABA (long-acting beta-2 agonist), or ICS/LAMA (long-acting muscarinic antagonist)), compared with a non-ICS treatment (LABA, LAMA, or LAMA/LABA). A new inhaled maintenance medication was defined as a prescription for that drug category that had not been issued in the previous 12 months. Those commencing triple therapy were also excluded to enable a better comparison between ICS and non-ICS therapies, and to minimize confounding, as in similar studies.[14] While outside guidelines, prescriptions for ICS monotherapy were included as this is a common initial treatment for COPD in other database studies [15] and we wanted to reflect real-life practice. Designated prescriptions had to be continued for a minimum of 6 months after the index date (for the primary analysis). Continuous use was defined as treatment duration totalling at least 90 days' supply, similar to methods used in a previous study of ICS in COPD [14]. Patients that had a change or addition of another inhaled medication within 30 days of the index date which would result in a change of

comparator group were excluded. Sensitivity analyses (see supplement) explored the effect on results of managing medication adherence and changes of drug class.

To examine a potential dose-response relationship in ICS-containing medications, the strength of ICS prescribed on the index date was stratified into low, medium and high (corresponding to estimated equivalent daily doses of beclomethasone dipropionate (BDP-CFC) of ≤500µg, >500-1000µg and >1000µg respectively), as used elsewhere [14], but higher than standard clinical categorisations for asthma [16].

Covariates

Baseline information included demographic, disease and general health characteristics. A valid blood eosinophil count was the most recently recorded value in the two years prior to the index date, based on simplicity of use for primary care clinicians. For the primary analysis, eosinophil values within two weeks of an exacerbation, pneumonia episode or elevated C-reactive protein (>100mg/L) were excluded as these would not reflect baseline state. An eosinophil threshold of <150 cells/µL was used to categorise patients into the low eosinophil group and ≥150 cells/ µL for the high eosinophil group. This primary threshold was chosen in response to unpublished work at the time of study set up [17] but with multiple alternative secondary thresholds assessed.

Outcomes

The primary outcome was time-to-first exacerbation following the index date, which was selected as the outcome of most relevance to patients [18]. Exacerbations were defined as any of the following: code for COPD exacerbation; code for lower respiratory tract infection; prescription of exacerbation-specific antibiotic e.g. amoxicillin/macrolide/doxycycline and oral steroid for 5-14

days; symptom of exacerbation (cough, breathlessness or sputum) plus prescription of exacerbation-specific antibiotic or oral steroid; hospital admission with COPD or acute respiratory cause as the primary cause of hospitalisation, or a COPD exacerbation code within a hospitalisation episode. Exacerbation events defined by prescriptions alone and occurring on the same date as spirometry, or a code implying rescue pack administration, were excluded as this suggested a visit for annual COPD review with provision of standby medication, rather than an exacerbation.

Secondary outcomes analysed were pneumonia episodes, and hospitalisations and death due to COPD, pneumonia or any cause (all time-to-event following index date). A pneumonia episode was defined as a CPRD code for pneumonia, hospital admission with an ICD-10 pneumonia code, or a death certificate with pneumonia listed as a cause.

All outcome events occurring within two weeks of a previous episode, were counted as the same event. Events within 30 days of the index date were excluded to reduce protopathic bias, as in other studies [14].

Missing data

Handling of missing data is detailed in the supplement.

Statistical analysis

Stata (Release SE13 64-bit) was used for all analysis. Data are presented as mean with standard deviation (SD), median with interquartile range (IQR) or hazard ratios (HR) with 95% confidence intervals (CI). Cox proportional hazards models assessed disease outcomes after index date, by drug group (ICS vs. non-ICS) groups. Inclusion of an interaction term looked for effect modification by

blood eosinophils (due to the difference in response to treatment between eosinophil groups being more relevant than the effect size itself). Covariates were adjusted for if significant (P<0.10) in univariate Cox analysis, to reduce confounding by indication in terms of ICS vs. non-ICS group.

Pre-specified subgroup analyses by baseline exacerbation frequency, ICS dose, and history of asthma were performed (and by smoking status post-hoc). A history of frequent exacerbations was defined as ≥2 in year prior to index date and less frequent exacerbations defined as <2 in year prior to index date (exacerbations included hospitalisations for exacerbations, as defined above). Multiple sensitivity analyses explored whether different ways of defining the population (e.g. inclusion/exclusion of those with asthma and atopy) and alternative methods for handling medication adherence and outcome timing, had any impact on overall results (full details in supplement).

Results

Characteristics of included population

There were 30,378 eligible patients, of whom 18,235 (60.0%) had a valid eosinophil count in primary care records. A further 8,760 met exclusion criteria, leaving 9,475 patients for analysis (Supplementary Figure 1).

Table 1 shows baseline characteristics and distribution of patients between ICS and non-ICS treatment groups. Patients were more likely to be prescribed ICS therapy if they were younger, female, had previous asthma, more severe airflow limitation, or with a higher baseline exacerbation frequency, oral steroid use or hospital admissions (Supplementary Table 1). There were 4,371 (46%) patients in the non-ICS group (prescribed LABA 19%, LAMA 77%, LAMA/LABA 4%) and 5,104 in the

ICS group (prescribed ICS 36%, ICS/LABA 62%, ICS/LAMA 3%). Prescriptions for ICS decreased by 81.6% over the decade of the study, whereas non-ICS prescriptions remained constant. A high eosinophil (≥150cells/μL) occurred in 69.0%. There was no difference in treatment distribution between the ICS and non-ICS groups by eosinophil group (P=0.71).

Primary analysis

468 patients experienced an exacerbation in the first month after initiating treatment (58.1% in ICS group) and were excluded from the primary analysis. The remaining 9007 patients provided 38,421 years of follow-up (median 3.8 years per patient (IQR 2.1 to 6.0; range 0.5 to 11.1), of whom 6,478 (71.9%) experienced an exacerbation during follow-up. The median time-to-first exacerbation was 645 (95% CI 615 to 686) days in the non-ICS group and 512 (95% CI 483 to 541) days in the ICS group (unadjusted HR ICS vs. non-ICS 1.17, 95% CI 1.12 to 1.23; P<0.001; adjusted HR 1.08, 95% CI 1.03-1.14); P=0.002, Figure 1A). Following stratification for baseline eosinophils, the adjusted HR was 1.19 (95% CI 1.09 to 1.31; P<0.001, Figure 1B) in the low eosinophils group and 1.04 (95% CI 0.98 to 1.10; P=0.23, Figure 1C) in the high eosinophils group (15% absolute difference; interaction of eosinophil group with treatment group 0.87, 95% CI 0.78 to 0.97, P=0.01, see figure 1).

Subgroup and sensitivity analyses of primary analysis

Risk of exacerbations on ICS was lower in those with high eosinophils and history of frequent exacerbations compared to those with low eosinophils and less frequent exacerbations (0.94, 95% CI 0.82 to 1.07, P=0.34 vs. 1.21, 95% CI 1.10 to 1.34, P=0.001 respectively, Table 2). Multiple sensitivity analyses including using the eosinophil count average of the most recent two, three, or all, eosinophil counts instead of the most recent value, excluding the highest values (≥500 cells/μL),

and including eosinophil values close to acute events, made no difference to overall results (Supplementary Table 2).

Analysis with different eosinophil thresholds

Using a threshold of 340 cells/μL [19, 20] instead of 150 cells/μL, the number of patients in the 'high eosinophil' group decreased from 69.0% to 19.4% (Supplementary Table 3). Decreasing HR for ICS treatment as eosinophil count increased was found with increasing eosinophil thresholds, categories, and in continuous analysis (Supplementary Table 4), and ICS only reduced exacerbations at much higher eosinophil counts (≥450 cells/μL) (Figure 2).

Secondary outcomes

At eosinophil levels <150 cells/μL, ICS use was associated with pneumonia, with significant interaction in pneumonia hospitalisations (HR in low eosinophil group 1.26, 95% CI 1.05-1.50; P value for interaction P=0.04) (Table 3). Time-to-event analyses for different eosinophil thresholds for the pre-specified secondary outcomes are presented in Supplementary Table 5.

Discussion

Summary of main findings

In this real-world study comparing ICS with non-ICS treatment in patients with COPD, there was a statistically significant interaction between ICS treatment and baseline blood eosinophil count. This translated as a 15% lower absolute risk of subsequent exacerbations in patients with higher baseline eosinophil counts who were prescribed an ICS treatment, compared with patients with lower eosinophils who were prescribed ICS. In patients prescribed an ICS there was an eosinophil dose-response with risk of subsequent exacerbation greatest in those with lower eosinophil counts (i.e., <150 cells/µL). Results were unchanged when mean of eosinophil counts was used instead of most recent values, or when those taken close to an acute illness were included. In secondary analyses, there was a higher risk of pneumonia hospitalisation in patients receiving ICS treatment with eosinophil counts less than 150 cells/µL.

Contrary to national and international COPD guidelines, almost 1 in 5 patients were initiated on ICS monotherapy for their COPD [21, 22], but this has been replicated in other real-life database studies [23, 24]. We found that those prescribed ICS had more 'asthma-like' features (e.g. younger, female, previous asthma or oral steroid use, which could suggest that patients with ongoing asthma might be included in the cohort. However, these patients had been coded as COPD and had spirometry diagnostic of COPD, and sensitivity analyses excluding or including all patients with asthma did not change results.

Strengths and weaknesses

We included a large number of patients exposed to routine primary care rather than a highly-selected trial population [8]. Other strengths include the new-user cohort study design which avoids

immortal time bias that may be present in pharmaco-epidemiological studies; [25] evaluation of steroid-naïve patients, as ICS treatment can affect blood eosinophil values [13]; and use of key variables of interest such as blood results and prescriptions which are generally inputted automatically and so should have virtually complete coverage and accuracy. In this study, missing information is likely to be equally distributed between the eosinophil and treatment groups and should therefore not impact findings.

There is a risk of residual confounding by indication i.e. there may be unmeasured differences between treatment groups which have not been accounted for. This may partly explain the worse outcome seen with ICS treatment in this study compared to in trials, which have in general found either no or a small benefit of ICS on exacerbation outcomes,[2, 26-28] including 'real-life' trials in primary care, such as the Salford Lung Study.[29] However, it is the difference in treatment effect size between eosinophil groups, rather than the absolute values, which are important for assessing the role of eosinophils in predicting ICS responsiveness. Importantly, there was no difference in treatment distribution between the ICS and non-ICS groups by eosinophil group.

Our choice of primary eosinophil count threshold of 150 cells/µL is lower than in other studies and is not the threshold for considering initiation in global guidelines[1]. However, this was a pre-specified cut-off based on data available during protocol development.Our observed eosinophil-treatment association was consistent across repeated different thresholds in addition to methodological sensitivity analyses, whilst a dose-response relationship was seen using continuous analysis of eosinophils.

Our sample size was reduced by almost half due to discontinuation of the new inhaled treatment within 6 months. This may be because of a conscious trialling of medication, a change to an alternative, or the patient failing to request prescriptions. However, sensitivity analysis using the full intention-to-treat population, as well as complete on-treatment analysis, made minimal difference to results. Other sensitivity analyses including inclusion of those with an outcome in the first month, and inclusion of covariates with large amounts of missing data, made minimal difference to overall findings.

Comparison with other studies

A systematic review and meta-analysis [5] including eleven post-hoc analyses of RCTs, and five retrospective observational studies, found a relative risk (RR) of ICS on reducing exacerbation risk of 0.65 (0.52-0.79) with eosinophil counts >150 cells/μL and RR 0.87 (0.79-0.95) <150 cells/μL (four studies used this threshold), and a dose-response of increasing benefit with increasing eosinophil count. However, four of the five observational studies showed no association. Similar findings have been found in continuous eosinophil analysis of previous trials, except that the benefit of ICS was seen at lower eosinophil counts of 100[30] and 180[31] cells/μL. Non-ICS treatment appears more favourable in the lowest eosinophil groups.[32]. These differences in findings between observational studies and RCTs may be explained by patients who are more unwell being commenced on ICS vs. non-ICS treatment, and indeed this was confirmed in the differences between the two groups at baseline, which may relate to other unknown confounders.

Two other studies also used CPRD data to address the same objective. Oshagbemi et al found a similar hazard ratio of exacerbations in patients prescribed ICS vs. non-ICS treatment, but that stratification of ICS use by either absolute or relative eosinophil counts did not identify significant

differences in risk.[33] However, they excluded all patients with asthma and those who had had any exacerbations in the baseline period. Suissa et al[34] was a new-user cohort study but directly comparing LABA-ICS with LAMA, which found a slightly lower HR for exacerbations than in our study (0.95 (95% CI 0.90 to 1.01) vs. 1.08 (95% CI 1.03 to 1.14)), but a higher HR for pneumonia risk (HR 1.37 (95% CI 1.17 to 1.60 vs. 1.06 (95% CI 1.00 to 1.13)). Despite a number of differences in the methods between our studies, they found a similar association but with the benefit of ICS seen at lower eosinophil counts.

Our secondary outcomes investigated the relationship of pneumonia events, including severe hospitalised events and pneumonia mortality. We confirm a higher risk of pneumonia in patients with COPD receiving ICS therapy with eosinophils <150 cells/µL. This risk was greatest and significant in severe pneumonia events. These findings have been demonstrated before [34, 35] and may relate to an increased bacterial load in ICS-treated patients who have lower (≤2%) blood eosinophils [36].

Application

Our study findings suggest that eosinophil count can be used to predict risk-benefit of ICS treatment: at lower eosinophil levels (especially <150 cells/µL) there is a much higher risk of exacerbations and pneumonia hospitalisation with ICS treatment. In this cohort, benefit of ICS treatment was only seen in those with baseline eosinophil counts ≥450 cells/µL, and suggests that ICS treatment should particularly be avoided in those with low eosinophil counts. This fits with current GOLD recommendations [37] and NICE guidelines [38].

It is not clear whether one or more eosinophil count estimation is required to guide ICS initiation in patients with COPD in clinical practice where often many results are available. [39, 40] Our sensitivity analyses demonstrated that decisions to initiate ICS could be made irrespective of whether the last recorded eosinophil value or an average of multiple results were used.

Conclusions

We recommend considering a more limited approach to ICS prescribing and advise against ICS treatment initiation at low blood eosinophil levels (<150 cells/μL), where there is a lower likelihood of treatment benefit and potential harms.

Acknowledgements

Thanks to David McCartney (University of Oxford) for assisting with refining code lists; Rebecca Fortescue (St George's, University of London) for support; Dan Lasserson (University of Warwick), Mike Thomas (University of Southampton), David Mant (University of Oxford) and John Stradling (University of Oxford) for input and feedback at the study design stage. We thank the patients who were involved in setting research priorities and input into study design, particularly the Banbury Breathe Easy group.

Ethical approval

The protocol was reviewed and approval for access to the data was obtained from the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare Products Regulatory Agency (MHRA) (protocol number 16_094) and the approved protocol made available to the journal and reviewers during peer review. Ethical approval for observational research using the CPRD with approval from ISAC has been granted by a National Research Ethics Service committee (Trent MultiResearch Ethics Committee, REC reference number 05/MRE04/87).

Patient and public involvement

We consulted with a local patient group (a British Lung Foundation Breathe Easy group) and subsequently appointed a specific patient advisor. We sought patient input at the time of funding application for defining the research questions of importance to patients, and in the study design in discussion of outcome measures (particularly the decision to use exacerbations as the primary outcome as this was most relevant to patients).

Contributor and guarantor information

HFA, DL, IDP, CCB and MB conceived the idea for the study and designed the project, with substantial input from EM to study design. MS acquired the data and managed it, with some input from HFA. Analysis was mainly done by HFA with advisory input from MS and EM. Interpretation of the data was done by all authors. HFA drafted the manuscript for submission and received critical input from all authors. HFA is guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding

This work was funded by a personal fellowship from the National Institute for Health Research (NIHR) awarded to HFA (DRF 2014-07-052). MS and IDP are supported by the NIHR Oxford Biomedical Research Centre.

The funder had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. The funder will approve the manuscript before publication. The researchers are independent from funders and all authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. This work uses data provided by patients and collected by the NHS as part of their care and support and would not have been possible without access to this data. The NIHR recognises and values the role of patient data, securely accessed and stored, both in underpinning and leading to improvements in research and care.

This study is based in part on data from the Clinical Practice Research Datalink (CPRD) obtained under licence from the UK Medicines and Healthcare products Regulatory Agency (MHRA). The data are provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone.

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare:

HFA's academic department has received money from Boehringer Ingelheim for her role in a collaborative project and participation in a discussion forum.

MS has no conflicts of interest.

EM has no conflicts of interest.

IP has received speaker's honoraria for speaking at sponsored meetings from Astra Zeneca, Boehringer Ingleheim, Aerocrine, Almirall, Novartis, Teva, Chiesi, Sanofi/Regeneron and GSK and payments for organising educational events from Astra Zeneca, GSK, Sanofi/Regeneron and Teva. He has received honoraria for attending advisory panels with Genentech, Sanofi/Regeneron, Astra Zeneca, Boehringer Ingelheim, GSK, Novartis, Teva, Merck, Circassia, Chiesi and Knopp and payments to support FDA approval meetings from GSK. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, Astra Zeneca, Teva and Chiesi. He has received a grant from Chiesi to support a phase 2 clinical trial in Oxford. He is co-patent holder of the rights to the Leicester Cough Questionnaire and has received payments for its use in clinical trials from Merck, Bayer and Insmed. In 2014-5 he was an expert witness for a patent dispute involving Astra Zeneca and Teva.

CB is an NIHR Senior Investigator, and Clinical Director of the University of Oxford Primary Care and Vaccines Clinical Trials Collaboration, and the NIHR Oxford Community Medical technology and Invitro diagnostics Co-operative, and he receives funding from the NIHR Health Protection Research Unit (HPRU) in Healthcare Associated Infections and Antimicrobial Resistance at the University of Oxford, Oxford, UK, in partnership with Public Health England. He has received fees from Roche Molecular Diagnostics for participating in an Advisory Board about point of care testing; held a grant form Roche Molecular Diagnostics to evaluate the analytic performance of a point of care testing device; and is part of publicly funded research consortia that include industrial partners.

MB has received honoraria from AstraZeneca, Boehringer-Ingelheim, Cipla, Chiesi, Roche and GSK, grants from AstraZeneca, and support for attending meetings from AZ and Chiesi.

There are no other relationships or activities that could appear to have influenced the submitted work.

Data sharing statement

Requests for data should be directed to the corresponding author; we are happy to share anonymised data within the confines of what is permitted by the CPRD and MHRA.

References

1. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Criner GJ, Frith P, Halpin DMG, Han M, Lopez Varela MV, Martinez F, Montes de Oca M, Papi A, Pavord ID, Roche N, Sin DD, Stockley R, Vestbo J, Wedzicha JA, Vogelmeier C. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: The GOLD Science Committee Report 2019. *The European respiratory journal* 2019.
2. Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. *The Cochrane database of systematic reviews* 2014: 3: CD010844.
3. White P, Thornton H, Pinnock H, Georgopoulou S, Booth HP. Overtreatment of COPD with inhaled corticosteroids--implications for safety and costs: cross-sectional observational study. *PloS one* 2013: 8(10): e75221.
4. Wurst KE, Punekar YS, Shukla A. Treatment evolution after COPD diagnosis in the UK primary care setting. *PloS one* 2014: 9(9): e105296.
5. Harries TH, Rowland V, Corrigan CJ, Marshall IJ, McDonnell L, Prasad V, Schofield P, Armstrong D, White P. Blood eosinophil count, a marker of inhaled corticosteroid effectiveness in preventing COPD exacerbations in post-hoc RCT and observational studies: systematic review and meta-analysis. *Respiratory research* 2020: 21(1): 3.
6. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA, Martinez FJ, Singh D, Tabberer M, Wise RA, Pascoe SJ, Investigators I. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *The New England journal of medicine* 2018: 378(18): 1671-1680.
7. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, Trivedi R, St Rose E, Ballal S, McLaren J, Darken P, Aurivillius M, Reisner C, Dorinsky P, Investigators E. Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. *The New England journal of medicine* 2020: 383(1): 35-48.
8. Kruis AL, Stallberg B, Jones RC, Tsiligianni IG, Lisspers K, van der Molen T, Kocks JW, Chavannes NH. Primary care COPD patients compared with large pharmaceutically-sponsored COPD studies: an UNLOCK validation study. *PloS one* 2014: 9(3): e90145.
9. Herland K, Akselsen JP, Skjonsberg OH, Bjermer L. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? *Respiratory medicine* 2005: 99(1): 11-19.
10. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *British journal of clinical pharmacology* 2010: 69(1): 4-14.
11. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol* 2015: 11(7): 437-441.
12. Smith CJ, Gribbin J, Challen KB, Hubbard RB. The impact of the 2004 NICE guideline and 2003 General Medical Services contract on COPD in primary care in the UK. *QJM* 2008: 101(2): 145-153.
13. Kreindler JL, Watkins ML, Lettis S, Tal-Singer R, Locantore N. Effect of inhaled corticosteroids on blood eosinophil count in steroid-naive patients with COPD. *BMJ Open Respir Res* 2016: 3(1): e000151.
14. DiSantostefano RL, Sampson T, Le HV, Hinds D, Davis KJ, Bakerly ND. Risk of pneumonia with inhaled corticosteroid versus long-acting bronchodilator regimens in chronic obstructive pulmonary disease: a new-user cohort study. *PloS one* 2014: 9(5): e97149.
15. Brusselle G, Price D, Gruffydd-Jones K, Miravitlles M, Keininger DL, Stewart R, Baldwin M, Jones RC. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. *International journal of chronic obstructive pulmonary disease* 2015: 10: 2207-2217.
16. Beasley R, Harper J, Bird G, Maijers I, Weatherall M, Pavord ID. Inhaled Corticosteroid Therapy in Adult Asthma. Time for a New Therapeutic Dose Terminology. *American journal of respiratory and critical care medicine* 2019: 199(12): 1471-1477.

17. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *The Lancet Respiratory medicine* 2015.
18. Zhang Y, Morgan RL, Alonso-Coello P, Wiercioch W, Bala MM, Jaeschke RR, Styczen K, Pardo-Hernandez H, Selva A, Ara Begum H, Morgano GP, Waligora M, Agarwal A, Ventresca M, Strzebonska K, Wasylewski MT, Blanco-Silvente L, Kerth JL, Wang M, Zhang Y, Narsingam S, Fei Y, Guyatt G, Schunemann HJ. A systematic review of how patients value COPD outcomes. *The European respiratory journal* 2018: 52(1).
19. Oshagbemi OA, Burden AM, Braeken DCW, Henskens Y, Wouters EFM, Driessen JHM, Maitland-van der Zee AH, de Vries F, Franssen FME. 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. *American journal of respiratory and critical care medicine* 2017: 195(10): 1402-1404.
20. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. *American journal of respiratory and critical care medicine* 2016: 193(9): 965-974.
21. National Institute for Health and Clinical Excellence Guidance. Management of chronic obstructive pulmonary disease in adults in primary and secondary care [CG101]. 2010.
22. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2013). 2013.
23. Price D, Miravitlles M, Pavord I, Thomas M, Wedzicha J, Haughney J, Bichel K, West D. First maintenance therapy for COPD in the UK between 2009 and 2012: a retrospective database analysis. *NPJ primary care respiratory medicine* 2016: 26: 16061.
24. Chalmers JD, Tebboth A, Gayle A, Ternouth A, Ramscar N. Determinants of initial inhaled corticosteroid use in patients with GOLD A/B COPD: a retrospective study of UK general practice. *NPJ primary care respiratory medicine* 2017: 27(1): 43.
25. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* 2008: 167(4): 492-499.
26. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews* 2012: 9: CD006829.
27. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews* 2012: 7: CD002991.
28. Nannini LJ, Poole P, Milan SJ, Holmes R, Normansell R. Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews* 2013: 11: CD003794.
29. Vestbo J, Leather D, Diar Bakerly N, New J, Gibson JM, McCorkindale S, Collier S, Crawford J, Frith L, Harvey C, Svedsater H, Woodcock A, Salford Lung Study I. Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice. *The New England journal of medicine* 2016: 375(13): 1253-1260.
30. Bafadhel M, Peterson S, De Blas MA, Calverley PM, Rennard SI, Richter K, Fageras M. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *The Lancet Respiratory medicine* 2018: 6(2): 117-126.
31. Siddiqui SH, Guasconi A, Vestbo J, Jones P, Agusti A, Paggiaro P, Wedzicha JA, Singh D. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. *American journal of respiratory and critical care medicine* 2015: 192(4): 523-525.
32. Roche N, Chapman KR, Vogelmeier CF, Herth FJF, Thach C, Fogel R, Olsson P, Patalano F, Banerji D, Wedzicha JA. Blood Eosinophils and Response to Maintenance Chronic Obstructive Pulmonary Disease Treatment. Data from the FLAME Trial. *American journal of respiratory and critical care medicine* 2017: 195(9): 1189-1197.
33. Oshagbemi OA, Franssen FME, Braeken DCW, Henskens Y, Wouters EFM, Maitland-van der Zee AH, Burden AM, de Vries F. Blood eosinophilia, use of inhaled corticosteroids, and risk of COPD exacerbations and mortality. *Pharmacoepidemiology and drug safety* 2018.

34. Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study. *The Lancet Respiratory medicine* 2018: 6(11): 855-862.
35. Pavord ID, Lettis S, Anzueto A, Barnes N. Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis. *The Lancet Respiratory medicine* 2016: 4(9): 731-741.
36. Contoli M, Pauletti A, Rossi MR, Spanevello A, Casolari P, Marcellini A, Forini G, Gnesini G, Marku B, Barnes N, Rizzi A, Curradi G, Caramori G, Morelli P, Papi A. Long-term effects of inhaled corticosteroids on sputum bacterial and viral loads in COPD. *The European respiratory journal* 2017: 50(4).
37. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2019 report). 2019.
38. National Institute for Health and Clinical Excellence Guidance. Chronic obstructive pulmonary disease in over 16s: diagnosis and management [NG115]. 2018.
39. Brusselle G, Pavord ID, Landis S, Pascoe S, Lettis S, Morjaria N, Barnes N, Hilton E. Blood eosinophil levels as a biomarker in COPD. *Respiratory medicine* 2018: 138: 21-31.
40. Celli BR, Criner GJ. Using the Peripheral Blood Eosinophil Count to Manage Patients with Chronic Obstructive Pulmonary Disease. *Annals of the American Thoracic Society* 2019: 16(3): 301-303.
41. Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC family practice* 2010: 11: 1.

Table 1: Distribution of patients between ICS and non-ICS groups by baseline characteristics

Baseline variable	Overall n=9,475	Non-ICS group n=4,371	ICS group n=5,104
Age, mean (SD), years	69.7 (10.0)	70.0 (9.7)	69.4 (10.2)
Female, n (%)	4,111 (43.4)	1,809 (41.4)	2,302 (45.1)
Current smoker,[a] n (%)	3,946 (41.8)	1,836 (42.1)	2,110 (41.6)
Airflow limitation severity (most recent FEV_1 % predicted),[b] n (%)			
Mild (≥80%)	838 (11.9)	401 (11.3)	437 (12.5)
Moderate (50-80%)	3,878 (55.0)	2,110 (59.4)	1,768 (50.6)
Severe (30-50%)	2,010 (28.5)	914 (25.7)	1,096 (31.4)
Very severe (<30%)	322 (4.6)	127 (3.6)	195 (5.6)
Asthma >2 years previously, n (%)	1,098 (11.6)	269 (6.2)	829 (16.2)
History of atopy,[c] n (%)	2,493 (26.3)	1,107 (25.3)	1,386 (27.2)
Exacerbations in previous year, n (%)			
0	4,887 (51.6)	2,433 (55.7)	2,454 (48.1)
1	2,829 (29.9)	1,250 (28.6)	1,579 (30.9)
2	1,165 (12.3)	466 (10.7)	699 (13.7)
3 or more	594 (6.3)	222 (5.1)	372 (7.3)
Pneumonia episodes in previous year, n (%)			
0	7,484 (79.0)	3,514 (80.4)	3,970 (77.8)
1	1,500 (15.8)	660 (15.1)	840 (16.5)
2 or more	491 (5.2)	197 (4.5)	294 (5.8)
Theophylline in two previous years, n (%)	97 (1.0)	17 (0.4)	80 (1.6)
Oxygen use ever, n (%)	46 (0.5)	19 (0.4)	27 (0.5)
Nebulisers in two previous years, n (%)	157 (1.7)	48 (1.1)	109 (2.1)
Non-elective hospitalisations[d] in previous year, n (%)			
0	7,767 (82.0)	3,663 (83.8)	4,104 (80.4)
1	1,277 (13.5)	529 (12.1)	748 (14.7)
2 or more	431 (4.6)	179 (4.1)	252 (4.9)
GP consultations in previous year, n (%)			
0-3	2,699 (28.5)	1,280 (29.3)	1,419 (27.8)
4-7	3,381 (35.7)	1,586(36.3)	1,795 (35.2)
8 or more	3,395 (35.8)	1,505 (34.4)	1,890 (37.0)
Influenza vaccination in previous year, n (%)	6,710 (70.8)	3,106 (71.1)	3,604 (70.6)
Blood eosinophil count (cells/μL)			
Geometric mean	200	200	201
Median (IQR)	200 (100-300)	200 (100-300)	200 (100-300)

Percentages are column percentages. [a] n=9,442 for smoking status (only past or current smokers included). [b] n=7,048 for airflow limitation severity. [c] Atopy defined using presence of codes for allergy, eczema or hay fever. [d] for any cause.

Table 2: Subgroup analysis of ICS vs. non-ICS treatment, stratified by blood eosinophil group and by baseline exacerbation frequency

n=9,007	Low eosinophil group (<150)	High eosinophil group (>=150)	Interaction HR and P Value
Low exacerbation rate (0 or 1)	1.21 (1.10 to 1.34) P=0.001 n=2,299	1.07 (1.00 to 1.15) P=0.06 n=5,068	0.88 (0.78 to 0.99), P=0.04
Higher exacerbation rate (≥2)	1.18 (0.97 to 1.44) P=0.11 n=498	0.94 (0.82 to 1.07) P=0.34 n=1,102	0.79 (0.62 to 1.00), P=0.06

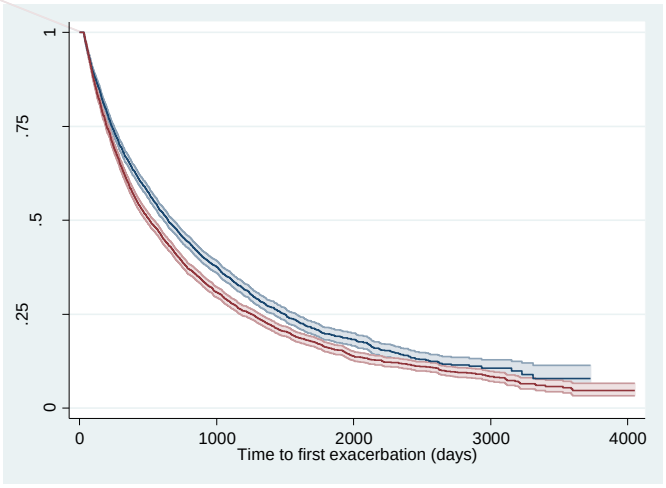
Hazard ratios (HR) are for time-to-first exacerbation after treatment initiation, for ICS vs. non-ICS treatment. Hazard ratios are from Cox regression including the interaction term and adjusted for covariates as listed in Figure 1 legend.

Table 3: Pneumonia outcomes stratified by baseline blood eosinophil group

	Low eosinophil group (<150 cells/µL)	High eosinophil group (>=150 cells/µL)	Interaction HR and P Value
Pneumonia episodes	1.10 (0.99 to 1.24) P=0.09 n=2,832	1.05 (0.97 to 1.13) P=0.24 n=6,321	0.95 (0.83 to 1.08), P=0.44
Hospitalisation due to pneumonia	1.26 (1.05 to 1.50) P=0.01 n=2,910	1.00 (0.88 to 1.14) P>0.99 n=6,499	0.80 (0.64 to 0.99), P=0.04
Death due to pneumonia	1.19 (0.50 to 2.84) P=0.70 n=2,918	0.53 (0.27 to 1.05) P=0.07 n=6,517	0.44 (0.65 to 4.42, P=0.14

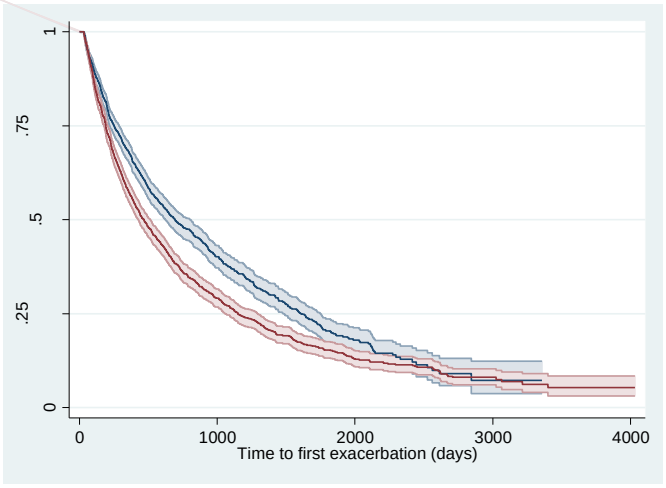
Hazard ratios are for time-to-first event after treatment initiation, for ICS vs. non-ICS treatment. Hazard ratios are from Cox regression including interaction term and adjusted for covariates as detailed in Figure 1 legend.

Figure 1: Kaplan-Meier curves for time-to-first exacerbation in ICS (red) vs. non-ICS (blue) groups, A) overall and B) C) stratified by baseline blood eosinophil group (95% CI shaded)



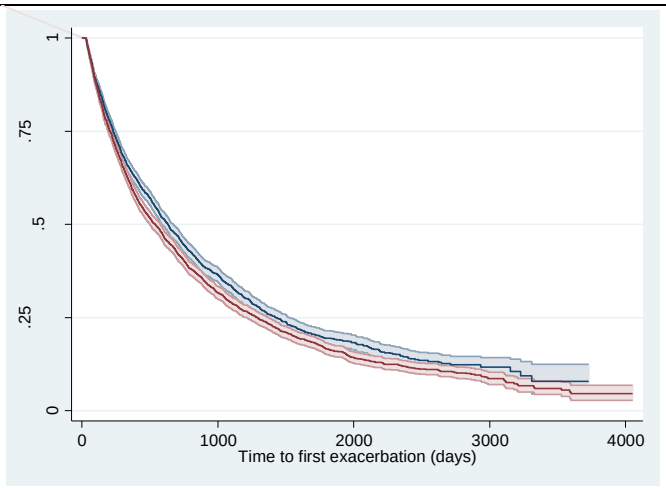
A) Whole group

Adjusted hazard ratio
1.08 (95% CI 1.03-1.14)
p=0.002
n=8,967



B) Low eosinophil group (<150 cells/µL)

Adjusted hazard ratio
1.19 (95% CI 1.09-1.31)
p<0.001
n=2,797

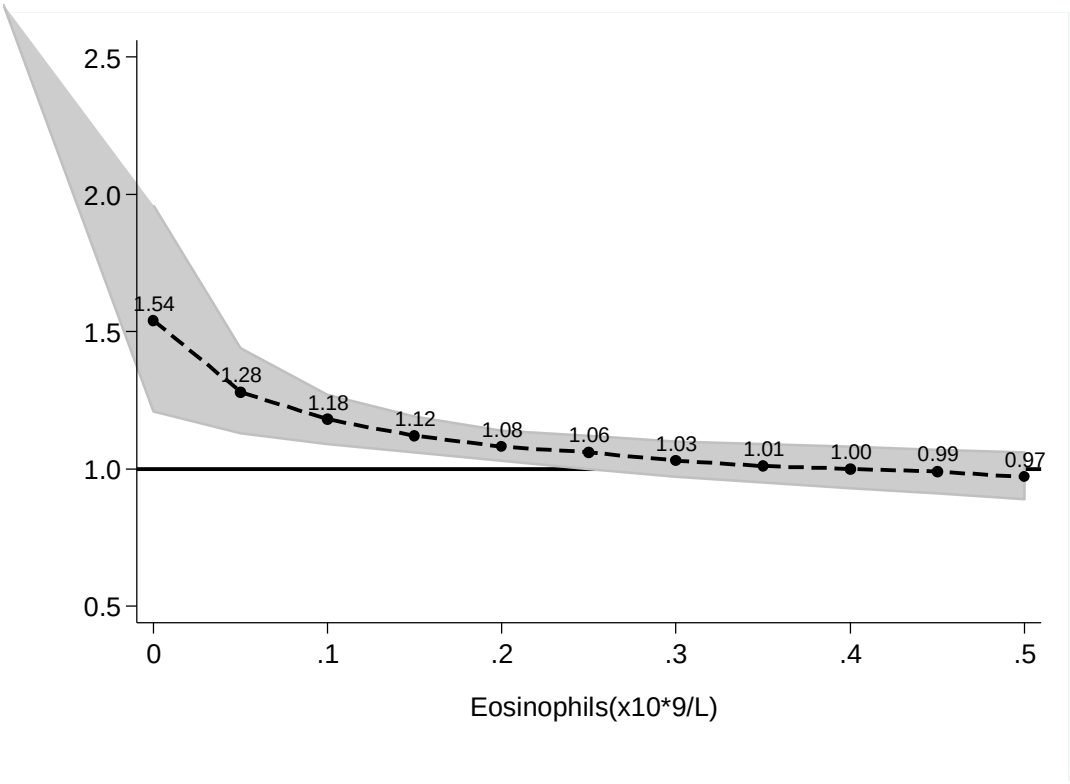


C) High eosinophil group (≥150 cells/µL)

Adjusted hazard ratio
1.04 (95% CI 0.98-1.1)
p=0.23
n=6,170

The interaction between the two eosinophils groups was significant (interaction of eosinophil group with treatment group 0.87, 95% CI 0.78 to 0.97, P=0.01, 15% absolute difference). Hazard ratios are from Cox regression including the interaction term and adjusted for covariates as follows: age category, sex, smoking status, year of index prescription, socio-economic status, history of atopy, history of asthma, exacerbations in previous year, pneumonia episodes in previous year, oral steroid prescriptions in previous year, salbutamol inhaler prescriptions in previous year, theophylline in previous two years, oxygen use ever, nebulised therapies in previous two years, non-elective hospitalisations in previous year, GP consultations in previous year, Charlson comorbidity index [41], influenza vaccination in previous year, pneumococcal vaccination in previous five years.

Figure 2: Graph showing hazard ratios for time-to-first exacerbation for ICS vs. non-ICS treatment, at different eosinophil counts



Eosinophil threshold (cells/µL)	Adjusted hazard ratio (95% CI, p-value)
10	1.54 (1.21-1.96), p<0.001
50	1.28 (1.13-1.44), p<0.001
100	1.18 (1.09-1.27), p<0.001
150	1.12 (1.06-1.19), p<0.001
200	1.08 (1.03-1.14), p=0.002
250	1.06 (1.00-1.12), p=0.05
300	1.03 (0.97-1.10), p=0.29
350	1.01 (0.95-1.09), p=0.67
400	1.00 (0.93-1.08), p=0.98
450	0.99 (0.91-1.07), p=0.73
500	0.97 (0.89-1.06), p=0.55

Hazard ratios are from Cox regression including the interaction term and adjusted for covariates as detailed in Figure 1 legend, but with eosinophils in the model as a continuous variable (logarithmically transformed). The interaction of eosinophils with ICS treatment group was significant in this model (P=0.004). Deviation of the association from log-linearity was assessed by a likelihood ratio test comparing models with categorical eosinophils (P=0.23). Shaded area shows 95% confidence intervals.

Online data supplement

Contents

Supplementary Methods: Further details of methods

Data source

In the UK, 98% of the population are registered with a National Health Service (NHS) general practitioner (GP). GPs are the primary contact for the majority of health-related issues, and the gatekeepers for accessing secondary care, with the majority of COPD management taking place in primary care. Information is recorded routinely on computers using a coding system combined with free text, and using a unique NHS number, which remains with the patient if they move GPs [1].

The CPRD is a primary care database of anonymised medical records from GPs, with 14.5 million patients included (CPRD August 2016 release). Patients in the CPRD are broadly representative of the UK general population in terms of age, sex and ethnicity. GPs are the gatekeepers of primary care and specialist referrals in the UK. The CPRD is therefore a rich source of health data for research, including data on demographics, symptoms, tests, diagnoses and therapies prescribed [1]. Approximately half of the data is linked with other datasets: in this study we obtained linkage with Hospital Episode Statistics (HES) which gives information on hospitalisations and diagnoses, Index of Multiple Deprivation (IMD) (deprivation score) and Office for National Statistics data on causes of death.

For all code lists used to determine diagnoses, therapies or tests, we used search terms combined with QOF code lists, which were then independently selected by two clinicians (HFA and DMcC) and any disagreements discussed and adjudicated by a third clinician (MB). We used previously validated code lists where available [2, 3].

Exposure definition

In the UK, blood eosinophil count is provided automatically as part of a request for a full blood count. Blood eosinophil readings were transformed from other units or percentage values to cells/µL. Values of zero or ≥1500 cells/µL, or where the total white cell count was outside of the range 3-15 $x10^9$/L, were excluded, as they were felt more likely to be a data error (missing values may be entered as zero), or a haematopoietic problem and not truly representative of baseline state. We also calculated season of eosinophil test in case of variation of values throughout the year.

Sensitivity and subgroup analyses

We planned sensitivity analyses as follows: different thresholds for blood eosinophil counts (100, 200, 300, 340 (post-hoc) [4, 5], 400 and 500 cells/µL, percentage eosinophils (<2%, ≥2-<4% and ≥4%)) and continuously (which tells us if there is a linear effect for presence or absence of association which is most useful to look at for overall association; log-transformed data were used as eosinophils are non-normally distributed); using mean of blood eosinophils over prior two years, rather than most recent value before index date; including patients with currently active asthma (coded in the last two years); excluding patients with any history of asthma (coded ever); excluding patients with a history of atopy; including blood eosinophil values close to an acute event (exacerbation/pneumonia episode or raised CRP); and including those who experienced an event in the first month after index date. Post-hoc sensitivity analyses mainly responded to unforeseen issues with the data: including those who remained on their index medication for less than 6 months; censoring by duration of index

medication; censoring by time to initiation of a new drug from the alternative drug class (i.e. change of category ICS to non-ICS or vice versa); censoring by duration of medication and time to initiation of new drug (whichever occurred earlier); including season of blood test in the model; excluding those with the highest eosinophils (≥500 cells/μL); including airflow limitation severity and MRC breathlessness scale in the model; and using mean of the most recent two or three eosinophil counts rather than the single most recent.

The main subgroup analysis was by baseline exacerbation frequency, and we also planned stratification by ICS dose. Following recent publication of post-hoc analysis of trials suggesting that current smokers particularly benefit from ICS [6], we conducted a post-hoc subgroup analysis by smoking status. We also conducted post-hoc analysis stratifying eosinophils into low (<150), medium (150-<340) and high (≥340) groups.

Missing data

For the assessment of clinical diagnosis and outcomes, we assumed that absence of any relevant medical code meant true absence of disease. We expected age, sex and prescriptions to be well recorded in the cohort and so planned a complete case analysis. Spirometry was poorly coded and so we used standard formulae [7] to calculate percentage predicted FEV_1 from data available. Where height was missing, we used the mean height of that sex and 10-year age category in the cohort. Nonetheless, FEV_1 percentage predicted remained missing for a quarter of the population and therefore we did not include this in the main analysis, but conducted a sensitivity analysis to assess the effect of incorporating it into the model. The same was true for MRC breathlessness score, which was missing for approximately half of patients. We did not perform multiple imputation because the assumption that the missing data were missing completely at random or missing at random may not have been realistic [8], indeed in early analyses there were significant differences between groups. It was not possible due to limitations in what had been coded to confirm whether spirometry was pre- or post-bronchodilator.

Supplementary Table 1: Logistic regression for distribution of patients between ICS and non-ICS groups by baseline characteristics

Baseline variable n=9,475	**Unadjusted odds ratio for ICS vs. non-ICS group (95% CI, P Value)**	**Adjusted odds ratio for ICS vs. non-ICS group[a] (95% CI, P Value)**
Age group in years		
40-49	1.92 (1.47-2.50) P<*0*.001	1.92 (1.45-2.55) P<0.001
50-59	1.14 (1.00-1.30) P=0.06	1.10 (0.95-1.27) P=0.20
60-69	1.10 (1.00-1.22) P=0.06	1.14 (1.03-1.27) P=0.01
70-79 (ref)		
80-89	1.16 (1.03-1.32) P=0.01	1.17 (1.03-1.33) P=0.02
>=90	0.92 (0.60-1.39) P=0.06	0.90 (0.58-1.41) P=0.66
Female	1.16 (1.07-1.26) P<0.001	1.11 (1.02-1.21) P=0.02
Current smoker[b]	0.98 (0.90-1.06) P=0.61	
History of atopy	1.10 (1.00-1.20) P=0.04	1.04 (0.95-1.15) P=0.40
Asthma >2 years previously	2.96 (2.56-3.42) P<0.001	2.64 (2.27-3.07) P<0.001
Airflow limitation severity (most recent FEV_1 % predicted)[c]		
Mild (≥80%) (ref)		
Moderate (50-80%)	0.77 (0.66-0.89) P=0.001	
Severe (30-50%)	1.10 (0.94-1.30) P=0.25	
Very severe (<30%)	1.41 (1.08-1.83) P=0.01	
MRC breathlessness scale[c]		
1 (least severe) (ref)		
2	0.70 (0.58-0.85) P<0.001	
3	0.69 (0.57-0.84) P<0.001	
4	0.89 (0.71-1.13) P=0.34	
5 (most severe)	1.12 (0.70-1.78) P=0.64	
Exacerbations in previous year		
0 (ref)		
1	1.25 (1.14-1.37) P<0.001	1.22 (1.10-1.37) P<0.001
2	1.49 (1.31-1.69) P<0.001	1.46 (1.24-1.72) P<0.001
3 or more	1.66 (1.39-1.98) P<0.001	1.51 (1.20-1.90) P<0.001
Pneumonia episodes in previous year		
0 (ref)		
1	1.13 (1.00-1.26) P=0.04	0.89 (0.77-1.01) P=0.08
2 or more	1.32 (1.10-1.59) P=0.003	0.85 (0.67-1.07) P=0.17
Oral steroids in previous year		
0 (ref)		
1	1.48 (1.32-1.65) P<0.001	1.39 (1.22-1.57) P<0.001
2	1.76 (1.45-2.13) P<0.001	1.55 (1.25-1.91) P<0.001
Salbutamol inhalers in previous year		
0 (ref)		
1	0.90 (0.80-1.01) P=0.08	0.88 (0.78-0.99) P=0.04
2	1.05 (0.91-1.22) P=0.50	0.91 (0.78-1.07) P=0.26
3-5	1.18 (0.95-1.22) P=0.26	0.89 (0.78-1.02) P=0.09
6 or more	1.25 (1.12-1.40) P<0.001	0.95 (0.84-1.07) P=0.36
Theophylline in two previous years	4.08 (2.41-6.89) P<0.001	2.61 (1.51-4.53) P=0.001
Oxygen use ever	1.22 (0.68-2.19) P=0.51	
Nebulisers in two previous years	1.97 (1.40-2.77) P<0.001	1.25 (0.87-1.81) P=0.23
Charlson comorbidity index[d]		
0 (ref)		
1	0.96 (0.86-1.08) P=0.50	0.96 (0.85-1.08) P=0.49
2 or more	0.83 (0.76-0.91) P<0.001	0.90 (0.81-1.00) P=0.05

Supplementary Table 1 (continued)		
Baseline variable n=9,475	**Unadjusted odds ratio for ICS vs. non-ICS group (95% CI, P Value)**	**Adjusted odds ratio for ICS vs. non-ICS group[a] (95% CI, P Value)**
Non-elective hospitalisations in previous year		
0 (ref)		
1	1.26 (1.12-1.42) P<0.001	1.20 (1.05-1.36) P=0.006
2 or more	1.26 (1.03-1.53) P=0.02	1.20 (0.97-1.48) P=0.09
GP consultations in previous year		
0-3 (ref)		
4-7	1.02 (0.92-1.13) P=0.69	0.97 (0.87-1.08) P=0.54
8 or more	1.13 (1.02-1.25) P=0.02	1.01 (0.90-1.12) P=0.91
Influenza vaccination in previous year	0.98 (0.90-1.07) P=0.63	
Pneumococcal vaccination in previous 5 years	1.12 (1.03-1.22) P=0.007	0.96 (0.87-1.05) P=.37

[a] Odds ratio calculated using logistic regression. Adjusted odds ratios include baseline variables significant *P*<0.10 in univariate analysis.

[b] n=9,442 for smoking status; reference group was ex-smokers.

[c] Due to large amounts of missing data for airflow limitation severity (n=7,048) and MRC breathlessness score (n=4,272) these were not included in the multivariate analysis.

[d] Charlson comorbidity index gives categories of comorbid disease and provides a summary of disease burden for individual patients [9].

Supplementary Table 2: Sensitivity and subgroup analyses for time-to-first exacerbation ICS vs. non-ICS and interaction with blood eosinophil count

Groups as applicable	150 cells/μL eosinophil threshold		340 cells/μL eosinophil threshold		Continuous eosinophils[a]
	Hazard ratio in low group[b]	Interaction[c]	Hazard ratio in low group[b]	Interaction[c]	Interaction[c]
Main					
(n=9,007)	1.19 (1.09-1.31) P<0.001	0.87 (0.78-0.97) P=0.01	1.09 (1.03-1.16) P=0.002	0.95 (0.84-1.08) P =0.43	0.89 (0.82-0.96) P=0.004
Smoking status (post-hoc subgroup analysis)					
Ex-smokers (n=5,261)	1.15 (1.02-1.30) P=0.02	0.91 (0.79-1.05) P=0.22	1.09 (1.01-1.18) P=0.02	0.95 (0.80-1.12) P=0.52	0.92 (0.83-1.03) P=0.14
Current smokers (n=3,779)	1.24 (1.09-1.43) P=0.002	0.83 (0.70-0.97) P=0.02	1.10 (1.01-1.20) P=0.03	0.96 (0.79-1.18) P=0.73	0.85 (0.76-0.96) P=0.009
Asthma status (main analysis excludes asthma coded in previous two years but includes those with history of asthma)					
Excluding any asthma (n=7,981)	1.21 (1.10-1.33) P<.001	0.85 (0.76-0.96) P=0.006	1.09 (1.02-1.15) P=0.007	0.98 (0.85-1.12) P=0.74	0.88 (0.81-0.96) P=0.004
Including active asthma (n=9,326)	1.20 (1.10-1.31) P<.001	0.87 (0.78-0.96) P=0.008	1.10 (1.04-1.16) P=0.001	0.94 (0.83-1.06) P=0.31	0.88 (0.82-0.95) P=0.002
Atopy (main analysis includes those with atopy)					
Excluding any atopy (n=6,648)	1.19 (1.07-1.33) P=0.001	0.88 (0.78-1.00) P=0.04	1.09 (1.02-1.17) P=0.009	1.00 (0.86-1.16) P=0.98	0.92 (0.83-1.01) P=0.07
Dose of ICS (subgroup analysis)					
≤500μg BDP equivalent (n=5,921)	1.14 (1.01-1.29) P=0.03	0.89 (0.77-1.03) P=0.11	1.09 (1.01-1.18) P=0.02	0.83 (0.70-0.99) P=0.03	0.86 (0.77-0.95) P=0.004
500-1000 μg BDP equivalent (n=5,552)	1.22 (1.08-1.40) P=0.002	0.79 (0.68-0.93) P=0.003	1.04 (0.96-1.13) P=0.36	1.02 (0.85-1.23) P=0.80	0.90 (0.80-1.01) P=0.08
>1000 μg BDP equivalent (n=5,095)	1.29 (1.11-1.50) P=0.001	0.91 (0.77-1.09) P=0.31	1.20 (1.09-1.32) P<0.001	1.04 (0.85-1.28) P=0.69	0.92 (0.81-1.05) P=0.22
Including severity and MRC breathlessness scale (not included in main analysis due to large amounts of missing data)					
Including severity and MRC (n=3,706)	1.17 (1.01-1.36) P=0.04	0.85 (0.72-1.02) P=0.08	1.05 (0.96-1.16) P=0.29	1.00 (0.81-1.23) P=0.98	0.91 (0.79-1.04) P=0.15
Protopathic bias (main analysis excludes those with exacerbation in first month after treatment initiation)					
Including outcome in first month (n=9,475)	1.19 (1.09-1.30) P<0.001	0.87 (0.78-0.96) P=0.007	1.10 (1.04-1.16) P=0.001	0.92 (0.81-1.04) P=0.17	0.88 (0.81-0.95) P=0.001
Intention-to-treat (main analysis only includes those who stayed on their new medication for at least 6 months) (post-hoc)					
Including <6m treatment duration (n=15,941)	1.13 (1.05-1.21) P=0.001	0.91 (0.84-0.99) P=0.026	1.07 (1.02-1.18) P=0.003	0.93 (0.84-1.02) P=0.14	0.93 (0.87-0.99) P=0.02

Censoring by initiation of new drug in alternative treatment group (ICS or non-ICS) (post-hoc)					
Censoring by time to new drug (n=9,007)	1.31 (1.17-1.46) P<0.001	0.82 (0.72-0.93) P=0.002	1.17 (1.09-1.25) P<0.001	0.87 (0.75-1.01) P=0.07	0.85 (0.77-0.94) P=0.001
Censoring by duration of time on new medication (post-hoc)					
Excluding <6m treatment duration (n=9,007)	1.24 (1.12-1.37) P<0.001	0.87 (0.77-0.98) P=0.02	1.13 (1.06-1.21) P<0.001	0.97 (0.84-1.11) P=0.63	0.89 (0.82-0.97) P=0.01
Including <6m treatment duration (n=15,941)	1.23 (1.11-1.36) P<0.001	0.88 (0.79-0.99) P=0.04	1.14 (1.07-1.22) P<0.001	0.94 (0.82-1.07) P=0.35	0.89 (0.82-0.97) P=0.008
Censoring by initiation of new drug in alternative treatment group (ICS or non-ICS) or duration of time on new medication (earlier date where both apply) (post-hoc)					
Excluding <6m treatment duration (n=9,007)	1.33 (1.18-1.49) P<0.001	0.82 (0.72-0.94) P=0.005	1.19 (1.10-1.28) P<0.001	0.89 (0.76-1.05) P=0.17	0.86 (0.77-0.95) P=0.004
Including <6m treatment duration (n=15,941)	1.30 (1.16-1.46) P<0.001	0.85 (0.74-0.97) P=0.02	1.20 (1.11-1.28) P<0.001	0.87 (0.74-1.02) P=0.08	0.86 (0.78-0.95) P=0.003
Eosinophil means (main analysis uses most recent eosinophil result)					
Using mean of all previous results (n=9,007)	1.18 (1.07-1.30) P=0.001	0.89 (0.79-0.99) P=0.03	1.10 (1.04-1.16) P=0.002	0.94 (0.83-1.07) P=0.36	0.90 (0.83-0.98) P=0.01
Using mean of last two results (n=9,007)	1.20 (1.08-1.32) P<0.001	0.88 (0.78-0.98) P=0.02	1.10 (1.04-1.17) P=0.001	0.93 (0.83-1.05) P=0.25	0.90 (0.83-0.98) P=0.01
Using mean of last three results (n=9,007)	1.19 (1.08-1.31) P<0.001	0.88 (0.78-0.98) P=0.02	1.10 (1.03-1.16) P=0.002	0.95 (0.84-1.08) P=0.42	0.90 (0.82-0.97) P=0.009
Including season of eosinophil test as variable in model (post-hoc)					
Including eosinophil test season (n=9,007)	1.19 (1.09-1.30) P<0.001	0.87 (0.78-0.97) P=0.01	1.10 (1.03-1.16) P=0.002	0.95 (0.84-1.08) P=0.45	0.89 (0.82-0.96) P=0.004
Excluding those with eosinophils ≥500 cells/μL (post-hoc)					
Excluding eosinophils ≥500 cells/μL	1.18 (1.08-1.30) P<0.001	0.87 (0.78-0.97) P=0.01	1.09 (1.03-1.15) P=0.004	0.93 (0.79-1.09) P=0.41	0.86 (0.78-0.94) P=0.002
Including eosinophil values close to acute events (exacerbation/pneumonia/episode/C-reactive protein >100mg/L) which main analysis excludes					
Including eosinophils close to acute event (n=9,007)	1.18 (1.08-1.29) P<0.001	0.89 (0.80-0.99) P=0.03	1.10 (1.03-1.16) P=0.002	0.95 (0.84-1.08) P=0.46	0.90 (0.83-0.97) P=0.007

BDP, beclomethasone dipropionate estimated equivalent - [a] Continuous eosinophils were logarithmically transformed for analyses. [b] Hazard ratios are for time-to-first exacerbation comparing ICS with non-ICS treatment groups (hazard ratio >1 favours non-ICS treatment), in the low eosinophil group. Model is including the interaction term and adjusted for covariates as listed in Figure 1. Analyses are sensitivity analyses except where stated as subgroup analyses. [c] Interaction is the hazard ratio for the interaction of baseline blood eosinophils with treatment group, describing magnitude of difference (hazard ratio <1 describes reduced overall hazard ratio in ICS group, with higher eosinophils). Hazard ratio in the high eosinophil group can be calculated by multiplying the hazard ratio in the low group by the interaction term. 95% confidence intervals and P Values are given.

Supplementary Table 3: Distribution of patients between ICS and non-ICS groups by different blood eosinophil thresholds

Eosinophil threshold (cells/µL)	Overall n=9,475 n (%)	Non-ICS group n=4,371 n (%)	ICS group n=5,104 n (%)	Unadjusted odds ratio ICS vs. non-ICS group (95% CI, P Value)	Adjusted odds ratio ICS vs. non-ICS group (95% CI, P Value)
≥100	8,954 (94.5)	4,140 (94.7)	4,814 (94.3)	0.93(0.78-1.11) P=0.40	
≥150	6,535 (69.0)	3,023 (69.2)	3,512 (68.8)	0.98 (0.90-1.07) P=0.71	
≥200	5,924 (62.5)	2,741 (62.7)	3,183 (62.4)	0.99 (0.91-1.07) P=0.73	
≥300	3,144 (33.2)	1,438 (32.9)	1,706 (33.4)	1.02 (0.94-1.12) P=0.59	
≥340	1,842 (19.4)	807 (18.5)	1,035 (20.3)	1.12 (1.01-1.24) P=0.03	1.15 (1.04-1.29) P=0.01
≥400	1,574 (16.6)	687 (15.7)	887 (17.4)	1.13 (1.01-1.26) P=0.03	1.16 (1.04-1.31) P=0.01
≥500	815 (8.6)	359 (8.2)	456 (8.9)	1.10 (0.95-1.27) P=0.21	
Continuous (log scale)				1.02 (0.96-1.09) P=0.57	

Odds ratio calculated using logistic regression including baseline covariates significant P<0.10 in univariate analysis. Percentages are column percentages of those above the eosinophil threshold.

Supplementary Table 4: Outcomes and interactions for different eosinophil thresholds and subgroups

	Hazard ratio for ICS vs non-ICS (95% confidence interval, P Value)	Interaction hazard ratio of eosinophils with treatment group (95% confidence interval, P Value)
Eosinophil thresholds (sensitivity analysis)		
100 cells/μL	1.25 (1.00-1.55), P=0.05	0.86 (0.69-1.08), P=0.19
150 cells/μL (main analysis)	1.19 (1.09-1.31), P<0.001	0.87 (0.78-0.97), P=0.01
200 cells/μL	1.17 (1.08-1.27), P<0.001	0.88 (0.80-0.98), P=0.02
300 cells/μL	1.12 (1.05-1.19), P<0.001	0.90 (0.81-1.01), P=0.06
340 cells/μL (post-hoc)	1.09 (1.03-1.16), P=0.002	0.95 (0.84-1.08), P=0.43
400 cells/μL	1.09 (1.03-1.15), P=0.002	0.96 (0.84-1.10), P=0.53
500 cells/μL	1.08 (1.03-1.15), P=0.003	0.98 (0.82-1.18), P=0.83
Eosinophil categorical analysis (subgroup analysis)		
<150 cells/μL (n=2,819)	1.19 (1.09-1.31), P<0.001	1.15 (1.02-1.29), P=0.01
≥150-<340 cells/μL* (n=4,451)	1.04 (0.97-1.12) P=0.29	
≥340 cells/μL (n=1,737)	1.04 (0.93-1.17) P=0.50	1.00 (0.88-1.15), P=0.98
Eosinophils as continuous variable (logarithmically transformed) (sensitivity analysis)		
Continuous	1.18 (1.09-1.27), P<0.001	0.89 (0.82-0.96), P=0.004
Eosinophil percentages† (subgroup analysis)		
<2% (n=2,811)	1.17 (1.07-1.28) P=0.001	1.08 (0.96-1.21), P=0.21
2-4% (n=3,795)*	1.08 (1.00-1.17) P=0.04	
≥4% (n=2,388)	1.00 (0.90-1.10) P=0.93	0.92 (0.81-1.04), P=0.18

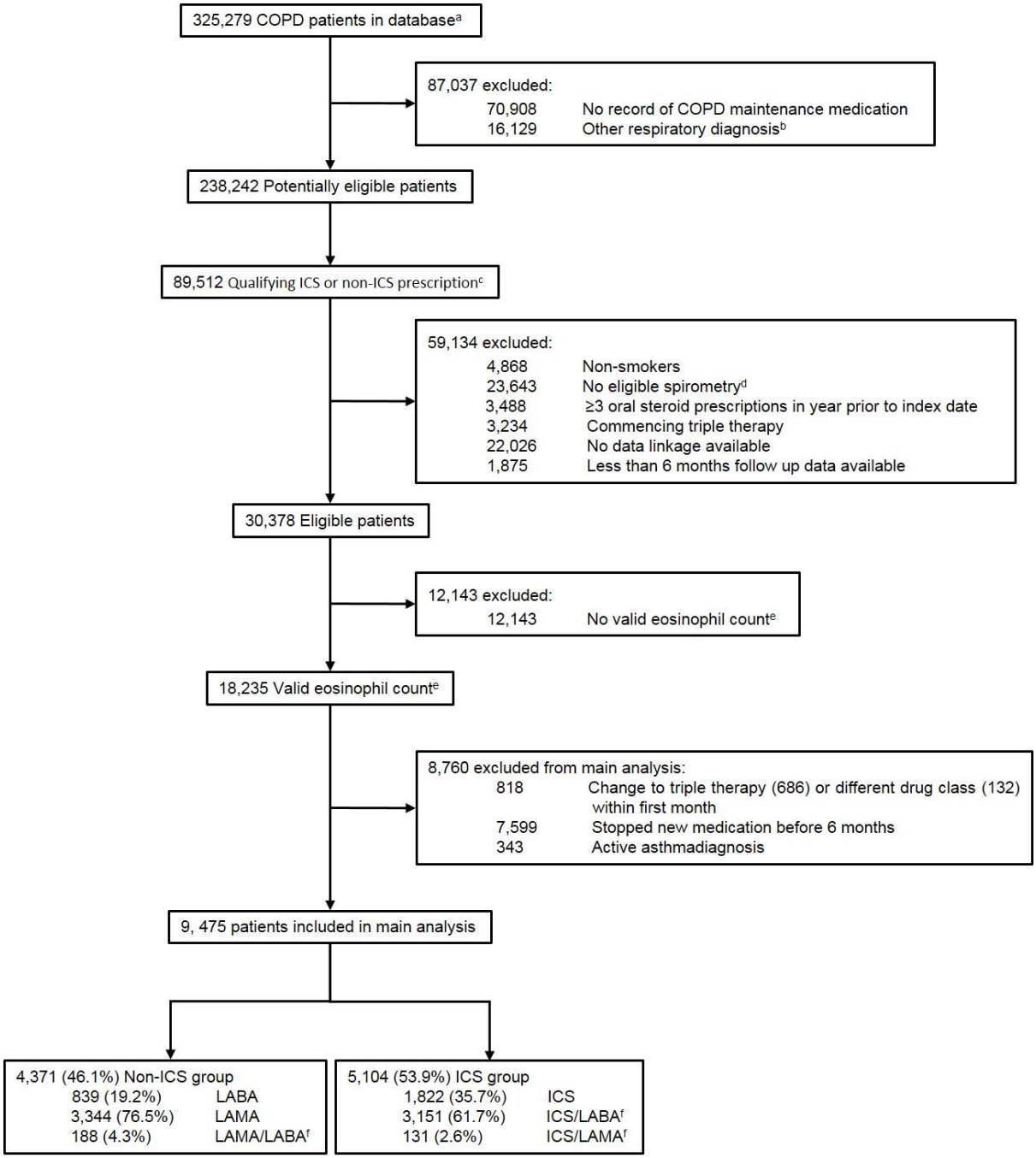
* gives reference group for hazard ratios. † Eosinophil percentages are as percentage of total leucocytes; leucocytes missing for n=13. Proportional hazards assumption was valid for all eosinophil-related variables. Adjusted Cox regression model including interaction term as detailed in Figure 1 legend. Hazard ratios are for low eosinophil group for sensitivity analyses except for continuous eosinophils where this is set at 100 cells/μL; hazard ratio in the high eosinophil group can be calculated by multiplying the hazard ratio in the low group by the interaction term.

Supplementary Table 5: Secondary outcomes

Number experiencing outcome/total§	**150 cells/μL eosinophil threshold**		**340 cells/μL eosinophil threshold**		**Continuous eosinophils***
	Hazard ratio†	Interaction‡	Hazard ratio†	Interaction‡	Interaction‡
Pneumonia episodes					
n=4,210/9,192	1.10 (0.99-1.24) P=0.09	0.95 (0.83-1.08) P=0.44	1.06 (0.99-1.14) P=0.10	1.01 (0.87-1.19) P=0.86	0.99 (0.89-1.09) P=0.77
Hospitalisation due to any cause					
n=6,392/9,007	1.04 (0.95-1.14) P=0.42	0.95 (0.85-1.06) P=0.35	1.01 (0.95-1.07) P=0.78	0.97 (0.86-1.10) P=0.67	0.96 (0.89-1.04) P=0.32
Hospitalisation due to pneumonia					
n=1,533/9,449	1.26 (1.05-1.50) P=0.01	0.80 (0.64-0.99) P=0.04	1.13 (1.00-1.27) P=0.05	0.79 (0.61-1.03) P=0.08	0.88 (0.75-1.04) P=0.13
Hospitalisation due to COPD					
n=2,621/9,384	1.17 (1.02-1.35) P=0.03	0.85 (0.72-1.01) P=0.07	1.05 (0.96-1.15) P=0.29	1.02 (0.83-1.25) P=0.85	0.92 (0.81-1.04) P=0.18
Death due to any cause					
n=2,071/9,475	1.01 (0.87-1.19) P=0.86	0.93 (0.77-1.12) P=0.45	0.97 (0.87-1.07) P=0.52	0.99 (0.79-1.25) P=0.96	1.00 (0.87-1.15) P=0.96
Death due to pneumonia					
n=61‖ /9,475	1.19 (0.50-2.84) P=0.70	0.44 (0.15-1.31) P=0.14	0.64 (0.35-1.17) P=0.15	1.74 (0.46-6.55) P=0.41	0.87 (0.38-1.99) P=0.75
Death due to COPD					
n=568/9,475	1.07 (0.80-1.43) P=0.66	0.97 (0.68-1.39) P=0.87	1.04 (0.86-1.26) P=0.68	1.03 (0.66-1.62) P=0.90	1.06 (0.81-1.40) P=0.66

* Continuous eosinophils were logarithmically transformed for analyses. † Hazard ratios are for time-to-first event comparing ICS with non-ICS treatment groups (hazard ratio >1 favours non-ICS treatment), in the low eosinophil group. Model is including the interaction term and adjusted for covariates as listed in Figure 1 legend. ‡ Interaction is the hazard ratio for the interaction of baseline blood eosinophils with treatment group, describing magnitude of difference (hazard ratio <1 describes reduced overall hazard ratio in ICS group, with higher eosinophils). Hazard ratio in the high eosinophil group can be calculated by multiplying the hazard ratio in the low group by the interaction term. 95% confidence intervals and P Values are given. § As for exacerbations in main analysis, those experiencing the event of interest in the first month after initiating treatment were excluded. ‖ Low number of deaths due to pneumonia likely to be because of changes in coding of primary cause of death by the Office for National Statistics away from acute causes to chronic underlying causes (CPRD ONS Death Registration Data Data Specification V1.5 (15 August 2016).

Supplementary Figure 1: Study flow chart for inclusion of patients



LAMA, long-acting muscarinic antagonist. LABA, long-acting β_2-agonist. ICS, inhaled corticosteroid

[a] CPRD August 2016 release.

[b] Other respiratory diagnoses excluded were bronchiectasis, cystic fibrosis and pulmonary fibrosis.

[c] Qualifying prescription required patients be ICS-naïve (no previous ICS in the preceding 12 months), have at least 2 years of data, 1st January 2005 or later, and be aged 40 or older on the date of the prescription, which was the first prescription for that drug in at least 12 months.

[d] Eligible spirometry was spirometry diagnostic for COPD (FEV_1/FVC ratio <0.7) at any time point.

[e] Valid eosinophil counts were those within the 2 years prior to the index date, with extreme values (zero or ≥1500 cells/μL) and those within 2 weeks of an acute event (exacerbation or pneumonia episode or C-reactive protein >100mg/L) excluded.

[f] Combination classes were either a single combined inhaler or separate inhalers with prescription issued on the same date.

Supplementary References

1. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *International journal of epidemiology* 2015: 44(3): 827-836.
2. Quint JK, Mullerova H, DiSantostefano RL, Forbes H, Eaton S, Hurst JR, Davis K, Smeeth L. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). *BMJ open* 2014: 4(7): e005540.
3. Rothnie KJ, Mullerova H, Hurst JR, Smeeth L, Davis K, Thomas SL, Quint JK. Validation of the Recording of Acute Exacerbations of COPD in UK Primary Care Electronic Healthcare Records. *PloS one* 2016: 11(3): e0151357.
4. Oshagbemi OA, Burden AM, Braeken DCW, Henskens Y, Wouters EFM, Driessen JHM, Maitland-van der Zee AH, de Vries F, Franssen FME. 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. *American journal of respiratory and critical care medicine* 2017: 195(10): 1402-1404.
5. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. *American journal of respiratory and critical care medicine* 2016: 193(9): 965-974.
6. Bafadhel M, Peterson S, De Blas MA, Calverley PM, Rennard SI, Richter K, Fageras M. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *The Lancet Respiratory medicine* 2018: 6(2): 117-126.
7. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993: 16: 5-40.
8. Bhaskaran K, Smeeth L. What is the difference between missing completely at random and missing at random? *International journal of epidemiology* 2014: 43(4): 1336-1339.
9. Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC family practice* 2010: 11: 1.