

Supplementary appendix

Supplementary material

Operational definitions of moderate-to-severe exacerbations and severe exacerbations of COPD The primary outcome of interest was acute exacerbations of COPD, as recorded by validated read codes (H312200, H3y1.00) from clinical and referral files [16]. We defined this as moderate-to-severe exacerbations of COPD. The secondary outcomes were COPD-related hospitalisations/A&E visit evaluated using Read codes (8H2R.00, 66Yi.00) from both clinical and/or referral file in addition to validated Read codes (H312200, H3y1.00) for acute exacerbations of COPD from the referral file. This was defined as severe exacerbations of COPD. We also evaluate the risk of all-cause mortality. The clinical file contains all the medical history data entered on the GP system, including symptoms, signs and diagnoses. This can be used to identify any clinical diagnoses, and deaths. The data is coded using Read codes, which allow linkage of codes to the medical terms provided while the referral file contain information involving patient referrals to external care centres (normally to secondary care locations such as hospitals for inpatient or outpatient care) [17].

Table S1. Read codes and descriptions

Read code	Medical code	Clinical event	Read term
H312200	1446	172705	Acute exacerbation of chronic obstructive airways disease
H3y1.00	7884	58765	Chron Obstruct Pulmonary dis with exacerbation, unspec
8H2R.00	11019	13645	Admit COPD emergency
66Yi.00	46036	956	Multiple COPD emergency hospital admissions

Table S2 Risk of moderate-to-severe exacerbations with ICS use stratified by absolute and relative eosinophil counts among COPD patients.				
	Moderate-to-severe exacerbations (n=6,767) [¶]	IR (/1000PY)	Age and gender adjusted HR (95% CI)	Adjusted HR (95% CI) ^a
Absolute eosinophil's counts				
Withdrawal of ICS				
<0.40 x 10 ⁹ cells/L	1,677	49.4	0.55(0.51-0.60) ^c	0.72(0.66-0.79) ^c
≥0.40 x 10 ⁹ cells/L	314	48.8	0.56(0.49-0.63)	0.70(0.62-0.80)
Continuous ICS user				
<0.40 x 10 ⁹ cells/L	3,970	85.4	0.96(0.89-1.03)	0.98(0.91-1.05)
≥0.40 x 10 ⁹ cells/L	806	87.9	Reference	Reference
Relative eosinophil counts				
Withdrawal of ICS				
<6.0%	1,817	49.3	0.54(0.49-0.60) ^c	0.67(0.60-0.74) ^c
≥6.0%	174	48.6	0.54(0.46-0.65)	0.68(0.57-0.81)
Continuous ICS user				
<6.0%	4,333	85.4	0.94(0.85-1.03)	0.91(0.82-1.00)
≥6.0%	443	89.6	Reference	Reference
Abbreviations: ICS, Inhaled corticosteroids; IR, incidence rate; HR, hazard ratio; CI, confidence interval; PY, person-years. a) Adjusted for age, gender, smoking status, body mass index, alcohol use, history of heart failure, chronic liver disease, ischemic heart disease, 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 to the start of an interval. b) Wald's statistics: Withdrawal of ICS with low eosinophil counts statistically significantly different (P<0.05) from withdrawal of ICS with high eosinophil count. c) Wald's statistics: Withdrawal of ICS with low eosinophil counts statistically significantly different (P<0.05) from continuous ICS use with low eosinophil count. [¶] numbers of never ICS user with moderate-to-severe exacerbations not included.				

Table S3. Risk of severe exacerbations with ICS use stratified by absolute and relative eosinophil counts among COPD patients.				
	Severe exacerbations (n=1,177) [¶]	IR (/1000PY)	Age and gender adjusted HR (95% CI)	Adjusted HR (95% CI) ^a
Absolute eosinophil's counts				
Withdrawal of ICS				
<0.40 x 10 ⁹ cells/L	268	6.9	0.57(0.47-0.71) ^c	0.79(0.64-0.98) ^c
≥0.40 x 10 ⁹ cells/L	58	7.8	0.65(0.48-0.89)	0.87(0.64-1.19)
Continuous ICS user				
<0.40 x 10 ⁹ cells/L	713	12.4	1.03(0.86-1.24)	1.05(0.88-1.26)
≥0.40 x 10 ⁹ cells/L	138	11.9	Reference	Reference
Relative eosinophil counts				
Withdrawal of ICS				
<6.0%	298	7.0	0.59(0.46-0.76) ^c	0.78(0.60-1.01) ^c
≥6.0%	28	6.8	0.58(0.37-0.89)	0.77(0.50-1.20)
Continuous ICS user				
<6.0%	776	12.3	1.04(0.82-1.32)	1.01(0.79-1.28)
≥6.0%	75	11.9	Reference	Reference
Abbreviations: ICS, Inhaled corticosteroids; IR, incidence rate; HR, hazard ratio; CI, confidence interval; PY, person-years; AE, accident & emergency. a) Adjusted for age, gender, smoking status, body mass index, alcohol use, history of heart failure, chronic liver disease, diabetes mellitus, ischemic heart disease, osteoporosis, 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 corticosteroid 6 months prior to the start of an interval. b) Wald's statistics: Withdrawal of ICS with low eosinophil counts statistically significantly different (P<0.05) from withdrawal of ICS with high eosinophil count. c) Wald's statistics: Withdrawal of ICS with low eosinophil counts statistically significantly different (P<0.05) from continuous ICS use with low eosinophil count. [¶] numbers of never ICS user with severe exacerbations not included.				

Table S4. Risk of all-cause mortality with ICS use stratified by absolute and relative eosinophil counts among COPD patients.				
	All-cause mortality (n=6,008) [¶]	IR (/1000PY)	Age and gender adjusted HR (95% CI)	Adjusted HR (95% CI) ^a
Absolute eosinophil's counts				
Withdrawal of ICS				
<0.40 x 10 ⁹ cells/L	1,805	45.3	0.94(0.86-1.03) ^c	1.15(1.05 -1.26) ^c
≥0.40 x 10 ⁹ cells/L	373	49.0	0.96(0.85-1.10)	1.13(0.99-1.28)
Continuous ICS user				
<0. 40 x 10 ⁹ cells/L	3,220	54.3	1.13(1.04-1.24)	1.15(1.05-1.25)
≥0.40 x 10 ⁹ cells/L	610	51.1	Reference	Reference
Relative eosinophil counts				
Withdrawal of ICS				
<6.0%	1,982	45.8	1.04 (0.93-1.17) ^c	1.27(1.12-1.43)
≥6.0%	196	46.6	0.93(0.78-1.11)	1.11(0.93-1.33)
Continuous ICS user				
<6.0%	3,506	54.1	1.24(1.11-1.39)	1.25(1.12-1.40)
≥6.0%	324	49.8	Reference	Reference
<p>Abbreviations: ICS, Inhaled corticosteroids; IR, incidence rate; HR, hazard ratio; CI, confidence interval; PY, person-years.</p> <p>a) Adjusted for age, gender, smoking status, body mass index, alcohol use, history of heart failure, chronic liver disease, ischemic heart disease, atopic dermatitis, diabetes mellitus, cancer, 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 6 months prior to the start of an interval.</p> <p>b) Wald's statistics: Withdrawal of ICS low eosinophil counts statistically significantly different (P<0.05) from withdrawal of ICS with high eosinophil count.</p> <p>c) Wald's statistics: Withdrawal of ICS with low eosinophil counts statistically significantly different (P<0.05) from continuous ICS use with low eosinophil count.</p> <p>[¶] numbers of never ICS user who died not included.</p>				

Table S5. Risk of moderate-to-severe exacerbations with ICS use stratified by absolute and relative eosinophil counts among COPD patients.				
	Moderate-to-severe exacerbations (n=6,767) [¶]	IR (/1000PY)	Age and gender adjusted HR (95% CI)	Adjusted HR (95% CI) ^a
Absolute eosinophil counts				
Withdrawal of ICS				
<0.15 x 10 ⁹ cells/L	640	47.9	0.56(0.51-0.61) ^c	0.71(0.65-0.78) ^c
≥0.15 x 10 ⁹ cells/L	1,351	50.0	0.59(0.55-0.63)	0.74(0.69-0.79)
Continuous ICS user				
<0.15 x 10 ⁹ cells/L	1,617	87.0	1.02(0.96-1.08)	1.00 (0.94-1.06)
≥0.15 x 10 ⁹ cells/L	3,159	85.2	Reference	Reference
Relative eosinophil counts				
Withdrawal of ICS				
<2.0%	701	49.8	0.59(0.54-0.64) ^c	0.72(0.67-0.79) ^c
≥2.0%	1,290	49.0	0.59(0.55-0.63)	0.74(0.69-0.79)
Continuous ICS user				
<2.0%	1,799	89.8	1.07(1.01-1.13)	1.02(0.96-1.08)
≥2.0%	2,977	83.6	Reference	Reference
Abbreviations: ICS, Inhaled corticosteroids; IR, incidence rate; HR, hazard ratio; CI, confidence interval; PY, person-years.				
a) Adjusted for age, gender, smoking status, body mass index, alcohol use, history of heart failure, chronic liver disease, ischemic heart disease, 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 to the start of an interval.				
b) Wald's statistics: Withdrawal of ICS with low eosinophil counts statistically significantly different (P<0.05) from withdrawal of ICS with high eosinophil count.				
c) Wald's statistics: Withdrawal of ICS with low eosinophil counts statistically significantly different (P<0.05) from continuous ICS use with low eosinophil count.				
[¶] numbers of never ICS user with moderate-to-severe exacerbations not included.				

Table S6. Risk of severe exacerbations with ICS use stratified by absolute and relative eosinophil counts among COPD patients.				
	Severe exacerbations (n=1,177) [¶]	IR (/1000PY)	Age and gender adjusted HR (95% CI)	Adjusted HR (95% CI) ^a
Absolute eosinophil counts				
Withdrawal of ICS				
<0.15 x 10 ⁹ cells/L	115	7.5	0.65(0.53-0.80) ^c	0.88(0.71-1.08) ^c
≥0.15 x 10 ⁹ cells/L	211	6.8	0.59(0.50-0.69)	0.79(0.67-0.93)
Continuous ICS user				
<0.15 x 10 ⁹ cells/L	317	13.8	1.19(1.04-1.37)	1.17(1.02-1.35)
≥0.15 x 10 ⁹ cells/L	534	11.6	Reference	Reference
Relative eosinophil counts				
Withdrawal of ICS				
<2.0%	125	7.7	0.69(0.57-0.85) ^c	0.89(0.73-1.09) ^c
≥2.0%	201	6.6	0.59(0.50-0.70)	0.80(0.67-0.95)
Continuous ICS user				
<2.0%	355	14.3	1.28(1.11-1.46)	1.20(1.05-1.38)
≥2.0%	496	11.2	Reference	Reference
<p>Abbreviations: ICS, Inhaled corticosteroids; IR, incidence rate; HR, hazard ratio; CI, confidence interval; PY, person-years; AE, accident & emergency.</p> <p>a) Adjusted for age, gender, smoking status, body mass index, alcohol use, history of heart failure, chronic liver disease, diabetes mellitus, ischemic heart disease, osteoporosis, 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 corticosteroid 6 months prior to the start of an interval.</p> <p>b) Wald's statistics: Withdrawal of ICS with low eosinophil counts statistically significantly different (P<0.05) from withdrawal of ICS with high eosinophil count.</p> <p>c) Wald's statistics: Withdrawal of ICS with low eosinophil counts statistically significantly different (P<0.05) from continuous ICS use with low eosinophil count.</p> <p>[¶] numbers of never ICS user with severe exacerbations not included.</p>				

Table S7. Risk of all-cause mortality with ICS use stratified by absolute and relative eosinophil counts among COPD patients.				
	All-cause mortality (n=6,008) [¶]	IR (/1000PY)	Age and gender adjusted HR (95% CI)	Adjusted HR (95% CI) ^a
Absolute eosinophil counts				
Withdrawal of ICS				
<0.15 x 10 ⁹ cells/L	825	52.8	1.06(0.97-1.14) ^{b, c}	1.23(1.13-1.33)
≥0.15 x 10 ⁹ cells/L	1,353	42.5	0.88(0.82-0.94)	1.05(0.98-1.13)
Continuous ICS user				
<0.15 x 10 ⁹ cells/L	1,526	64.4	1.31(1.23-1.40)	1.27(1.19-1.35)
≥0.15 x 10 ⁹ cells/L	2,304	48.4	Reference	Reference
Relative eosinophil counts				
Withdrawal of ICS				
<2.0%	892	54.0	1.16(1.07-1.25) ^{b, c}	1.30(1.20-1.41) ^b
≥2.0%	1,286	41.6	0.89(0.83-0.95)	1.06(0.99-1.14)
Continuous ICS user				
<2.0%	1,692	65.8	1.44(1.35-1.53)	1.34(1.26-1.43)
≥2.0%	2,138	46.9	Reference	Reference
<p>Abbreviations: ICS, Inhaled corticosteroids; IR, incidence rate; HR, hazard ratio; CI, confidence interval; PY, person-years.</p> <p>a) Adjusted for age, gender, smoking status, body mass index, alcohol use, history of heart failure, chronic liver disease, ischemic heart disease, atopic dermatitis, diabetes mellitus, cancer, 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 6 months prior to the start of an interval.</p> <p>b) Wald's statistics: Withdrawal of ICS with low eosinophil counts statistically significantly different (P<0.05) from withdrawal of ICS with high eosinophil count.</p> <p>c) Wald's statistics: Withdrawal of ICS with low eosinophil counts statistically significantly different (P<0.05) from continuous ICS use with low eosinophil count.</p> <p>[¶] numbers of never ICS user who died not included.</p>				