

GSK Medicine: Beclomethasone, Fluticasone propionate, salmeterol
Study No: WWE113659/WEUK716/EPI40287
Title: Pharmacoepidemiologic Analysis of the Impact of Regular Inhaled Corticosteroid (Ics) Use on Outcomes in Patients with Chronic Obstructive Pulmonary Disease (COPD)
Rationale: Inhaled corticosteroids (ICS) are often used in the management of patients with COPD, although their long-term efficacy in terms of preventing or reducing adverse health outcomes is uncertain.
Objectives: The objective of the study was to use electronic medical record data from a large health maintenance organization in the northwestern United States to further address the question of whether regular ICS use, either alone or in combination with long-acting beta agonist (LABA) inhalers, leads to fewer acute exacerbations and/or death.
Indication: COPD
Study Investigators/Centers: GSK Conducted Study
Research Methods:
Study Design: The study design was a retrospective cohort.
Data Source: We used administrative and clinical databases of the Northwest Region of Kaiser Permanente (KPNW) to gather information about age, health plan membership, and COPD utilization and diagnoses. Epic Care (EPIC) is KPNW's automated clinical information system. This computerized medical record database includes information on all clinic-based outpatient contacts occurring within KP. The Membership Information Processing System (MIPS) contains basic demographic information (date of birth, sex, name) and dates of KPNW membership. We used these data to determine who met the age criterion for this study and to calculate the number of months of health plan eligibility in each study year for all study participants.
Study Population: The study cohort was initially restricted to health plan members who were aged > 50 years as of January 1, 2000 and were continuously enrolled in the health plan for the two-year period from January 1998 through December 1999. From among individuals meeting these criteria, we further restricted attention to those who, during the period 1998-1999, met our criteria for having COPD and for receiving current pharmacotherapy for COPD as of the start of the follow-up period.
Study Exposures, Outcomes: Our primary outcome was the occurrence of either (a) an emergency department visit or overnight hospitalization for COPD or (b) death from any cause. Inpatient visits were considered COPD-related if either 491, 492, or 496 was listed as a primary or secondary diagnosis. Mortality data was gathered from KPNW hospital discharge records and from the state Health Departments of Oregon and Washington. For both ICS and LABA, regular medication use at any time t was defined as one or more dispensing events during each of the three preceding two-month intervals and was meant to reflect regular use over the preceding six months. Regular use of oral steroids at the start of follow-up was defined as above.
Data Analysis Methods: The primary analysis used the Cox proportional hazards regression model to examine the influence of ICS and/or LABA use on COPD exacerbations and all cause mortality, while adjusting for the other (fixed) factors. Sensitivity analyses were also used to examine the impact of adopting alternative definitions of "regular use". The analyses for the two primary study aims were repeated with and without co-morbid asthma. Finally, an intent-to-treat analysis was conducted that defined medication use as of the end of 1999 as a fixed covariate.
Limitations: The primary limitation of the proposed study was the relatively small sample size compared to other studies of large, administrative databases.

Study Results:

A total of 2905 individuals met the eligibility criteria. At the start of follow-up, 863 participants (30%) were regular users of ICS, another 996 (34%) used ICS on an irregular basis, and 1043 (36%) had no ICS dispensings during the last six months of 1999. The mean age was 69 years (SD=10 years), 57% were women and 71% were ever smokers. Forty three percent had co-morbid asthma, 20% had been treated by a pulmonologist during the two-year baseline period, and 30% had been hospitalized for COPD during the baseline period. Smoking status, the presence of co-morbid asthma, and pulmonologist care all differed noticeably across the medication groups.

Time-Dependent Cox Regression Analyses: Among those with co-morbid asthma, regular use of ICS was consistently associated with reduced risk of the composite outcome (emergency department care/hospitalization for COPD or all-cause mortality). These associations were highly statistically significant for never smokers and ex-smokers, and borderline significant ($p=0.086$) for current smokers. Borderline significant beneficial effects from ICS use were observed in never smokers without co-morbid asthma (RR=0.59, 95%CI = 0.34, 1.00, $p=0.052$). No evidence of any beneficial effect from ICS use was seen among ever smokers without co-morbid asthma. Essentially equivalent results were seen when we looked at the effect of irregular (instead of regular) ICS use.

Compared to non-ICS users who regularly used some combination of breathing medications, regular use of ICS and LABA appeared to be beneficial only among those with co-morbid asthma. For this subgroup, relative risk estimates were comparable to those all regular ICS users combined (RRs ranging from 0.50 to 0.78). Among those without co-morbid asthma, including the never smokers, regular use of both ICS and LABA was associated with worse outcomes than regular use of breathing medications other than ICS, with relative risks ranging from 1.48 to 2.30.

All-cause Mortality Outcome: A pattern of apparent benefit associated with both regular and irregular ICS use in those with co-morbid asthma was observed with all cause mortality. Results were statistically significant for regular ICS use in never and ex smokers and for irregular ICS use in ex smokers. Among those without co-morbid asthma, we again saw no significant effect in smokers and, at least for regular ICS use, a suggestion of a positive (though not significant) benefit.

Subgroup Analyses: Among those with co-morbid asthma, regular use of ICS was associated with significantly reduced risk in never smokers (RR=0.39, 95%CI = 0.19, 0.82) and ex smokers (RR=0.64, 95%CI = 0.44, 0.94). Unlike the combined runs, however, we found no suggestion of a beneficial effect in current smokers (RR=1.16, 95%CI = 0.57, 2.36). Results for the effects of irregular ICS use were similar. Among those without co-morbid asthma, we again saw a (non-significant) suggestion of a beneficial effect among never smokers who regularly use ICS (RR=0.64, 95%CI = 0.31, 1.35).

Sensitivity Analysis: Our basic results were very stable across these alternative definitions; ICS use improves outcomes in all individuals with co-morbid asthma and among never smokers without co-morbid asthma, while having no effect among current and ex smokers without co-morbid asthma.

Characteristics of sample at start of follow-up according to medication use categories

	Medication use at start of follow-up					Total
	Regular LABA use	No regular LABA use		Regular use of breathing meds	No regular medication use	
(n)	88	775	996	610	433	2,902
Age, years ¹	68.0±10.2	69.0±9.8	67.5±10.5	69.7±10.4	69.4±10.6	68.7±10.3
Female	51%	57%	61%	51%	57%	57%
Current smoker	10%	15%	17%	32%	28%	21%
Ex smoker	59%	56%	51%	45%	45%	50%
Co-existing asthma	69%	48%	55%	20%	30%	43%
Comorbidity index ^{1,2}	1.00±0.63	0.96±0.69	0.99±0.75	1.00±0.76	1.08±0.81	1.00±0.74
ICS use propensity score ^{1,3}	0.35±0.06	0.32±0.06	0.32±0.07	0.28±0.07	0.28±0.07	0.31±0.07
Home oxygen ⁴	5%	4%	4%	7%	3%	4%
Pulmonologist care ⁴	33%	24%	19%	21%	15%	20%

ED care for COPD ⁴	31%	18%	17%	20%	14%	18%
Hospitalization for COPD ⁴	33%	3%	27%	35%	31%	30%
Regular oral steroid use	8%	5%	3%	6%	3%	5%

¹ Continuous data expressed as mean \pm standard deviation

² Ratio of individual predicted cost of care to average predicted cost for total sample (see methods)

³ Probability of regular ICS use at start of follow-up

⁴ Any use during two-year baseline period

Cox-regression results¹ – effect of ICS use ignoring LABA use (composite outcome)

Variable	Relative Risk	95% Confidence Interval		p-value	Comment
<i>Regular ICS use</i>					Compared to regular users of non-ICS meds
Never smokers, no asthma	0.59	0.34	1.00	0.0520	
Never smokers, with asthma	0.38	0.22	0.65	0.0003	
Ex-smokers, no asthma	1.02	0.83	1.25	0.8853	
Ex-smokers, with asthma	0.66	0.48	0.90	0.0092	
Current smokers, no asthma	1.09	0.79	1.49	0.6070	
Current smokers, with asthma	0.70	0.47	1.05	0.0864	
<i>Irregular ICS use</i>					Compared to regular users of non-ICS meds
Never smokers, no asthma	0.62	0.39	0.99	0.0458	
Never smokers, with asthma	0.43	0.27	0.68	0.0003	
Ex-smokers, no asthma	0.90	0.74	1.10	0.2912	
Ex-smokers, with asthma	0.62	0.46	0.83	0.0016	
Current smokers, no asthma	1.04	0.79	1.38	0.7568	
Current smokers, with asthma	0.72	0.50	1.04	0.0794	

¹ Regular use of oral steroids at baseline included as a stratifying variable. data for unknown smoking status and main effect terms for smoking and co- morbid asthma not shown

² Ratio of individual predicted cost of care to average predicted cost for total sample (see Methods for description of groupings)

³ Probability of regular ICS use at start of follow-up

⁴ Any use during two-year baseline period

Cox-regression results¹ – regular ICS with and without regular use of LABA medications (composite outcome)

Variable	Relative Risk	95% Confidence Interval		p-value	Comment
<i>Regular ICS and LABA use</i>					Compared to regular users of non-ICS meds

Never smokers, no asthma	1.59	0.60	4.22	0.3564	
Never smokers, with asthma	0.53	0.21	1.33	0.1777	
Ex-smokers, no asthma	1.48	0.97	2.25	0.0683	
Ex-smokers, with asthma	0.50	0.29	0.86	0.0124	
Current smokers, no asthma	2.30	0.95	5.59	0.0646	
Current smokers, with asthma	0.78	0.32	1.90	0.5789	
Relative risks derived from Cox proportional hazards regression models adjusting for age, gender, comorbidity index, propensity to use ICS index, home oxygen use, pulmonologist care, and baseline COPD-related HCU; regular use of oral steroids at baseline was included as a stratifying variable in the Cox models					
Cox-regression results¹ – effect of ICS use ignoring LABA use (all-cause mortality)					
Variable	Relative Risk	95% Confidence Interval		p-value	Comment
<i>Regular ICS use</i>					Compared to regular users of non-ICS meds
Never smokers, no asthma	0.47	0.19	1.16	0.1010	
Never smokers, with asthma	0.29	0.12	0.71	0.0065	
Ex-smokers, no asthma	0.76	0.56	1.02	0.0702	
Ex-smokers, with asthma	0.46	0.28	0.75	0.0020	
Current smokers, no asthma	1.09	0.65	1.83	0.7434	
Current smokers, with asthma	0.66	0.34	1.30	0.2308	
<i>Irregular ICS use</i>					Compared to regular users of non-ICS meds
Never smokers, no asthma	1.07	0.56	2.06	0.8387	
Never smokers, with asthma	0.66	0.34	1.29	0.2206	
Ex-smokers, no asthma	0.87	0.67	1.12	0.2764	
Ex-smokers, with asthma	0.53	0.35	0.81	0.0034	
Current smokers, no asthma	1.18	0.76	1.83	0.4695	
Current smokers, with asthma	0.72	0.41	1.29	0.2720	
¹ Regular use of oral steroids at baseline included as a stratifying variable. data for unknown smoking status and main effect terms for smoking and co- morbid asthma not shown ² Ratio of individual predicted cost of care to average predicted cost for total sample (see Methods for description of groupings) ³ Probability of regular ICS use at start of follow-up ⁴ Any use during two-year baseline period					
Subgroup Analyses – effect of ICS use ignoring LABA use (composite outcome), separated by asthma status					

Variable	Relative Risk	95% Confidence Interval		p-value	Comment
<i>With co-morbid asthma</i>					
<i>Regular ICS use</i>					Compared to regular users of non-ICS meds
Never smokers	0.39	0.19	0.82	0.0125	
Ex smokers	0.64	0.44	0.94	0.0232	
Current smokers	1.16	0.57	2.36	0.6774	
<i>Irregular ICS use</i>					Compared to regular users of non-ICS meds
Never smokers	0.41	0.21	0.81	0.0096	
Ex smokers	0.60	0.42	0.87	0.0065	
Current smokers	1.44	0.77	2.68	0.2493	
<i>Without co-morbid asthma</i>					
<i>Regular ICS use</i>					Compared to regular users of non-ICS meds
Never smokers	0.64	0.31	1.35	0.2443	
Ex smokers	1.01	0.81	1.26	0.9317	
Current smokers	1.02	0.72	1.45	0.9063	
<i>Irregular ICS use</i>					Compared to regular users of non-ICS meds
Never smokers	0.82	0.45	1.48	0.5087	
Ex smokers	0.90	0.73	1.12	0.3414	
Current smokers	0.84	0.61	1.16	0.2880	
Relative risks derived from Cox proportional hazards regression models run separately for those with and without co-morbid asthma and adjusting for age, gender, comorbidity index, propensity to use ICS index, home oxygen use, pulmonologist care, and baseline COPD-related HCU; regular use of oral steroids at baseline was included as a stratifying variable in the Cox models					
Conclusion: See publication below					
Publications: Vollmer WM, Peters D, Crane B, Kelleher C, Buist AS. Impact of regular inhaled corticosteroid use on chronic obstructive pulmonary disease outcomes. <i>COPD: J of Chronic Obstructive Pulmonary Disease</i> 2007;4:145-142.					

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