

GSK Medicine: Fluticasone propionate/salmeterol,fluticasone,salmeterol,beclomethasone,fluticasone propionate/salmeterol/norflurane
Study No: WWE113656/WEUK199/EPI40288
Title: Survival Among COPD Patients Using Fluticasone Priopionate/Salmeterol in Combination versus Other Inhaled Steroids and Bronchdilators Alone
Rationale: Recent retrospective studies have suggested that use of inhaled corticosteroids (ICS) may improve survival in COPD, particularly when combined with a long-acting beta agonist (LABA). However, the methods used to conduct these studies have been questioned, and none have examined what effect the newer combination ICS/LABA inhalers may have on survival.
Objectives: The goal of this project was to further examine the relationship between ICS treatment, with or without LABA, and survival in COPD.
Indication: COPD
Study Investigators/Centers: GSK Conducted Study
Research Methods:
<u>Data Source:</u> Research centers affiliated with the four regional managed care organizations participated in this project. The Lovelace Health Plan had approximately 240,000 members in 2001, which includes participants in their Medicare, Medicaid, and over 700 different employer sponsored programs. The Lovelace Health Plan is the insurance component of the Lovelace Health System, which includes four hospital facilities and 20 outpatient centers. The three collaborating centers included the Health Partners Research Foundation, the Center for Health Services Research, and the Channing Laboratory. Health Partners has approximately 650,000 members in its staff and network model managed care programs. The Henry Ford's Health Alliance Plan is a primarily staff-model managed care system serving over 600,000 members in the metropolitan Detroit area. The Channing Laboratory is affiliated with Harvard Pilgrim Health Care, which is the oldest non-profit managed care organization in New England and serves approximately 750,000 members. The Institutional Review Boards at all four centers reviewed and approved this project.
<u>Study Design:</u> The overall study design was a retrospective follow-up or historical cohort study. A second analysis approach employed a nested case-control design where up to four controls were matched to each case.
<u>Study Population:</u> COPD patients were identified from the administrative databases of four different managed care programs. All patients who were diagnosed with COPD between September 1, 2000 and August 31, 2001 and who had at least 3 months treatment with fluticasone propionate and salmeterol used together in a single inhaler (FSC,N=866), any ICS used with a LABA (ICS/LABA, N=525), ICS alone (N=742), LABA alone (N=531), or a short-acting bronchodilator alone (SABD, N=1832), were included. Patients with other chronic lung diseases not typically included in the classification of COPD, such as coal workers pneumoconiosis or idiopathic pulmonary fibrosis, were excluded.
<u>Study Exposures, Outcomes:</u> COPD patients were identified using the ICD-9 diagnosis codes included in the administrative data. Patients were required to be continuously enrolled in their health plan from September 1, 2000 until August 31, 2001, which is known as the study's baseline year. All study subjects were required to have 1 inpatient visit or 2 outpatient visits on separate days for COPD (ICD-9 codes 491.x [chronic bronchitis], 492.x [emphysema], or 496 [chronic airway obstruction]) during the baseline year. Five different exposure cohorts were considered: 1) users of the fluticasone propionate/salmeterol inhaler (FSC); 2) any ICS and LABA used concurrently in separate inhalers (ICS/LABA); 3) ICS alone; 4) LABA alone; and 5) short-acting bronchodilators (SABD) alone. The NDC codes for all drugs that fell within each of these classes were abstracted from our managed care databases. A minimal exposure criterion of 3-months cumulative treatment within the five categories of medications was required. Prescriptions filled prior to meeting the inclusion criteria for a COPD diagnosis were included in the cumulative exposure. Clinical factors shown to affect survival in previous COPD studies were captured in the baseline year including age, gender, asthma diagnosis, Charlson/Deyo co-morbidity score, COPD hospitalizations, other respiratory related hospitalizations, the number of emergency department visits for COPD, the number of outpatient encounters for COPD, and oral corticosteroid use. Survival status of patients in the Lovelace, Health Partners, and Harvard Pilgrim systems was confirmed through matching with local state vital statistics registries.
<u>Data Analysis Methods:</u> The initial survival analysis was based on a traditional Cox proportional hazards model.

Four separate models were generated each using the SABD alone group as the reference cohort: 1) FSC vs. SABD, 2) ICS/LABA vs. SABD, 3) ICS alone vs. SABD, and 4) LABA alone vs. SABD. All available demographic and comorbid conditions expected to affect survival, such as age and Charlson/Deyo score, were included in each model. The follow-up period was initiated when the patient had met the exposure criteria for the treatment cohort and ended at either the time of death or censoring from the cohort.

The second analysis approach used the propensity score matched cohort method. According to this method, patients were matched in the treatment group to selected individuals in the reference group in order to minimize the selection bias that is inherent to observational studies.

The third analysis approach employed a nested case-control design. Cases were defined as patients who died, and controls were limited to those survivors who had an equivalent amount of follow-up time. In addition to follow-up duration, we also matched cases and controls on gender, age (within one year), and the date survival follow-up began (within 30 days of when the treatment criteria were met). Up to four controls were matched to each case.

Limitations: These results represent observational data and are subject to the limitations inherent to non-randomized assignment of treatment. 1) the traditional Cox proportional hazards model can adjust for some of the imbalances between the treated and reference groups, but it may still be susceptible to bias by indication and other effects introduced by the study design 2) variables that are not part of the multivariate model may remain unbalanced between cohorts with the possibility of residual confounding 3) observational studies reflect medication utilization in the real world, so compliance is highly variable and patients may switch from treatment to treatment or elect to discontinue treatment 4) the major limitation of the nested case-control approach is that the inclusion and exclusion criteria were so narrow that the study cohort ended up being only a small sample of the total population, thus leading to uncertainty about the generalizability of the results.

Study Results:

A total of 4,496 COPD patients met the study inclusion criteria. The majority of the patients in the LABA group came from Harvard Pilgrim; otherwise, none of the other treatment groups were dominated by any one health plan. The total time required to accumulate the 3-months minimum exposure in each of the respective categories was relatively similar. Yet, patients in the SABD group took longer to accumulate a full 3-months exposure to treatment (median 132 days) than seen in any of the treatment cohorts (90 days in each), so any immortal time bias would work against seeing a treatment benefit.

The mean ages across all the cohorts was 3.3 years with slightly more women than men in each of the five study cohorts and four health plans. Patients in the FSC and ICS/LABA groups were more likely to have an asthma diagnosis or be treated with oral steroids in the baseline year. The ICS/LABA group also tended to have a high number of outpatient encounters for COPD and hospitalizations for COPD and other respiratory ailments, suggesting that this group tended to have more severe disease.

In the basic Cox proportional hazards models, use of FSC, ICS/LABA, and ICS alone had significant survival benefits compared to SABD alone, after adjustment for differences in age, gender, comorbidities, asthma status, and disease severity (HRs 0.638, 0.603, and 0.784, respectively, $p < 0.05$). A Cox model with propensity score matching to reduce the baseline clinical differences between the treatment groups found very similar results. The hazard ratios for each of the treatments were slightly lower than in the basic models with the exception of the ICS/LABA group, suggesting some confounding was likely removed with the propensity score matching. A matched, nested case-control study also showed a highly significant survival benefit for FSC, while ICS and ICS/LABA had favorable risk reductions that did not reach statistical significance.

Baseline Characteristics of Cohort Subjects According to Treatment Group Status

Cohort characteristic (Unmatched N=4496)	FSC N = 866	ICS/LAB A N = 525	ICS alone N = 742	LABA alone N = 531	SABD alone N=1832	Chi-Square p value
Mean age, yr [SD] (95% CI)	64.5 [10.1] (63.8, 65.1)	67.6 [9.7] (66.8, 68.5)	68.8 [10.6] (68.0, 69.5)	66.5 [9.8] (65.7, 67.3)	68.6 [10.2] (68.2, 69.1)	NA
Age group, %						
40-56	23.3	12.8	14.3	15.4	13.1	

57-65	28.2	25.9	20.8	28.3	21.1	
66-72	24.1	28.8	25.3	26.2	26.0	
73+	24.4	32.5	39.6	30.1	39.8	*<.001
Male, %	46.4	43.2	42.3	45.8	47.5	0.124
Asthma diagnosis in baseline year, %	31.8	31.4	22.9	19.2	17.9	*<.001
Oral corticosteroid use in baseline year, %	54.0	56.0	43.4	46.1	39.9	*<.001
HMO member, %						
Henry Ford (N = 1468)	30.4	45.1	35.3	23.3	31.8	
Health Partners (N = 552)	10.4	17.5	21.7	3.6	10.4	
Lovelace (N = 691)	17.8	20.8	22.0	8.9	11.9	
Harvard Pilgrim (N = 1785)	41.4	16.6	21.0	64.2	45.9	*<.001
Days to 3-month Exposure (median)	90	90	90	90	132	‡0.01
COPD outpatient visits in baseline year, %						
0-2	24.7	17.7	28.7	23.7	27.6	
3-4	25.7	23.8	25.3	23.0	23.9	
4-12	27.8	28.8	24.3	33.0	28.5	
13+	21.8	29.7	21.7	20.3	20.0	*<.001
At least one COPD ED visit in baseline year, %	11.4	12.8	11.6	15.4	14.4	0.074
At least one COPD Inpatient visit in baseline year, %	16.1	23.2	16.7	16.2	17.4	*0.007
At least one respiratory-related inpatient visit in baseline year, %	12.1	17.5	15.9	10.4	17.8	*<.001
Charlson-Deyo Outpatient Index >= 1 in baseline year, %	33.4	36.2	39.1	41.4	40.8	*0.002

‡ Kruskal-Wallis test p-value * p-value significant at the .05 level

Cox Proportional Hazard Models for the Unmatched Treatment Groups Versus SABD

Variable	FSC N = 2698			ICS/LABA N = 2357			ICS Alone N = 2574			LABA Alone N = 2363		
	Hazard Ratio	95% Confidence Limits		Hazard Ratio	95% Confidence Limits		Hazard Ratio	95% Confidence Limits		Hazard Ratio	95% Confidence Limits	
Treatment versus SABD	*0.638	0.459	0.888	*0.603	0.454	0.801	*0.784	0.616	0.999	0.809	0.603	1.086
57-65 years old	1.191	0.675	2.102	1.114	0.637	1.947	1.361	0.762	2.429	1.595	0.888	2.864

66-72 years old	*1.94 4	1.15 5	3.27 4	*1.68 6	1.00 8	2.81 9	*1.95 3	1.14 0	3.34 8	*1.942	1.109	3.398
73+ years old	*3.03 2	1.84 6	4.98 0	*2.62 6	1.60 8	4.28 8	*3.16 6	1.89 1	5.30 0	*3.077	1.802	5.253
Male	1.103	0.88 4	1.37 7	1.155	0.93 1	1.43 3	1.040	0.84 6	1.27 8	1.173	0.943	1.460
3-4 COPD outpatient encounters	0.945	0.64 8	1.37 8	0.973	0.67 0	1.41 4	0.727	0.50 4	1.04 7	0.835	0.571	1.221
5-12 COPD outpatient encounters	1.053	0.75 0	1.47 9	1.009	0.71 6	1.42 2	1.002	0.73 4	1.36 7	0.913	0.652	1.279
13+ COPD outpatient encounters	*1.54 4	1.09 1	2.18 5	*1.70 8	1.21 4	2.40 4	*1.44 8	1.05 5	1.98 8	*1.536	1.094	2.156
≥ 1 COPD emergency dept. encounter	*0.71 0	0.51 2	0.98 4	*0.72 5	0.53 1	0.98 9	0.807	0.60 3	1.07 9	0.839	0.619	1.138
≥ 1 COPD hospitalization	*1.67 5	1.26 5	2.21 9	*1.49 8	1.14 3	1.96 2	*1.72 7	1.33 7	2.23 1	*1.706	1.301	2.238
≥ 1 respiratory hospitalization	*1.77 8	1.35 0	2.34 0	*1.94 7	1.49 6	2.53 3	*1.77 4	1.37 6	2.28 8	*1.910	1.466	2.489
Asthma diagnosis	0.855	0.63 5	1.15 1	0.777	0.57 7	1.04 6	*0.71 3	0.53 1	0.95 9	0.794	0.583	1.082
Oral Steroid Rx	0.905	0.70 7	1.15 8	0.844	0.66 3	1.07 4	0.959	0.76 5	1.20 2	0.897	0.704	1.143
Charlson score ≥ 1 based on outpatient encounters	*1.44 2	1.14 2	1.82 0	*1.50 3	1.20 0	1.88 3	*1.41 9	1.14 4	1.75 9	*1.364	1.082	1.718

* Significant at the 0.05 level

Cox Proportional Hazards Model: Propensity Score Matched Treatment Groups versus SABD

Variable	FSC N = 2698			ICS/LABA N = 2357			ICS Alone N = 2574			LABA Alone N = 2363		
	Hazard Ratio	95% Confidence Limits		Hazard Ratio	95% Confidence Limits		Hazard Ratio	95% Confidence Limits		Hazard Ratio	95% Confidence Limits	
Treatment versus SABD	*0.607	0.420	0.878	*0.650	0.458	0.923	*0.753	0.572	0.992	0.700	0.490	1.001
57-65 years old	1.153	0.583	2.281	0.672	0.261	1.730	1.246	0.606	2.560	1.647	0.664	4.088
66-72 years old	1.706	0.892	3.263	1.623	0.719	3.662	1.519	0.778	2.967	1.898	0.772	4.664
73+ years old	*2.877	1.552	5.333	*2.491	1.117	5.554	*2.458	1.301	4.644	*3.563	1.519	8.355
Male	1.138	0.817	1.584	1.268	0.892	1.801	0.858	0.648	1.136	0.986	0.697	1.395

3-4 COPD outpatient encounters	0.875	0.495	1.546	1.335	0.613	2.904	0.618	0.376	1.018	1.274	0.730	2.222
5-12 COPD outpatient encounters	1.029	0.594	1.780	1.109	0.509	2.414	0.914	0.595	1.406	0.808	0.446	1.463
13+ COPD outpatient encounters	1.511	0.895	2.551	*2.361	1.122	4.970	1.374	0.897	2.106	0.691	0.405	1.180
≥ 1 COPD emergency dept. encounter	*0.543	0.304	0.970	0.612	0.359	1.041	0.812	0.551	1.195	1.000	0.617	1.621
≥ 1 COPD hospitalization	1.357	0.898	2.051	1.309	0.845	2.028	*1.636	1.158	2.311	*1.854	1.193	2.881
≥ 1 respiratory hospitalization	*2.354	1.528	3.625	*1.881	1.214	2.916	*1.752	1.241	2.474	*1.628	1.043	2.540
Asthma diagnosis	0.942	0.644	1.379	0.789	0.500	1.245	*0.539	0.364	0.799	*0.556	0.336	0.920
Oral Steroid Rx	0.880	0.614	1.262	0.791	0.528	1.184	1.142	0.844	1.545	1.085	0.740	1.592
Charlson score ≥ 1 based on outpatient encounters	*1.474	1.051	2.068	*1.795	1.248	2.581	*1.340	1.008	1.780	1.098	0.763	1.580

* Significant at the 0.05 level

Conclusion: See publication below.

Publications:

Mapel DW, Nelson LS, Lydick E, Soriano JB, Yood MU, Davis KJ. Survival among COPD patients using fluticasone/salmeterol in combination versus other inhaled steroids and bronchodilators alone. *COPD: J of Chronic Obstructive Pulmonary Disease* 2007;4:127-134.

Date updated: 10-Apr-2008