

Economic Assessment of Initial Maintenance Therapy for Chronic Obstructive Pulmonary Disease

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Objective: To compare the effects of initial maintenance therapy with fluticasone 250 µg plus salmeterol 50 µg in a single inhaler versus other inhaled medications on exacerbation risks and treatment costs among chronic obstructive pulmonary disease (COPD) patients.

Study Design: A retrospective observational analysis was conducted by using medical/pharmacy claims from a large managed care database between January 2000 and February 2004. Patients age 40 years or older with a primary diagnosis of COPD (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 490, 491, 492, or 496), at least 18 months of continuous eligibility, and an index prescription for fluticasone/salmeterol combination, salmeterol alone, inhaled corticosteroid alone, ipratropium/albuterol combination, or ipratropium alone (reference) were identified.

Methods: Time to first COPD-related hospitalization or emergency department (ED) visit was estimated by using Cox proportional hazard models. All-cause and COPD-related treatment costs were estimated by using generalized linear models with a gamma distribution and log link. Multivariable regressions were used, controlling for age, sex, comorbidities, COPD subtype, preindex medications, and hospitalizations and ED visits.

Results: Initial maintenance therapy with fluticasone/salmeterol combination was associated with a 31% to 56% lower risk of hospitalization or ED visit compared with ipratropium alone, adjusting for baseline characteristics and preindex resource utilization. Fluticasone/salmeterol combination therapy was related to lower medical costs, higher pharmacy costs, and almost similar total costs in all populations studied.

Conclusion: Fluticasone/salmeterol combination therapy was considered to be cost-effective compared with ipratropium alone because it achieved better clinical outcomes with similar or lower treatment costs.

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For author information and disclosures, see end of text.

According to the Global Initiative for Chronic Obstructive Pulmonary Disease (COPD) guidelines, prevention of exacerbations is an important goal of COPD management.¹ However, data from the third National Health and Nutrition Examination Survey suggest that the burden of COPD still is substantial.² The surveys reveal high rates of COPD-related hospitalizations and emergency department (ED) visits, outcomes that serve as proxies of exacerbations in the real-world setting. In 2000, COPD accounted for 1.5 million ED visits and 726,000 hospitalizations in the United States.² Hospitalizations for COPD have increased across all age groups since 1990.

Acute exacerbations of COPD have a negative impact on quality of life.^{3,4} Additionally, exacerbations generate a high demand for healthcare services. Studies have consistently shown that hospitalizations account for the largest portion of healthcare expenditures for COPD.⁵⁻¹⁰ For example, the Confronting COPD survey, a large-scale international patient survey of disease burden, demonstrated that inpatient hospitalizations accounted for approximately 70% of the total direct costs of COPD in the United States.⁶ Thus, identification of therapeutic agents that prevent or reduce the risk of hospitalization and ED visits is an important strategy for reducing the overall burden of the disease.

Because airway obstruction is a common feature of COPD, bronchodilators are commonly provided for symptomatic relief. Anticholinergics (eg, ipratropium), short-acting β_2 agonists (eg, albuterol), long-acting β_2 agonists (eg, salmeterol), or a combination of these drug classes appear to increase lung function (forced expiratory volume in the first second of expiration), decrease frequency of exacerbations, and improve quality of life.¹¹ Inhaled corticosteroid (ie, fluticasone) is used to augment regular bronchodilator treatment for attenuating airway hyperresponsiveness and inflammation. Results of several prospective clinical studies showed a reduction in the rate and/or severity of exacerbations of COPD with the use of inhaled corticosteroid alone or in combination with long-acting β_2 agonists.¹²⁻¹⁶

Moreover, a recent randomized clinical trial, the Towards a Revolution in COPD Health survival study, reported the combination therapy with fluticasone and salmeterol significantly reduced exacerbations by 25% and hospitalizations by 17% compared with placebo among 6000 patients over 3 years.¹⁷ However, information about economic benefits of selecting appropriate initial main-

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tenance therapy for COPD remains limited, especially in the real-world setting.

Therefore, the present study was conducted to investigate the effect of various COPD medication regimens on (1) the risk of all-cause and COPD-related hospitalization and ED visits (risk analysis) and (2) all-cause and COPD-related treatment costs (cost analysis) using claims from a large managed care database. Of note, this was the first observational study to investigate the effect of fluticasone/salmeterol combination therapy in a single inhaler on utilization and costs in a managed care population.

METHODS

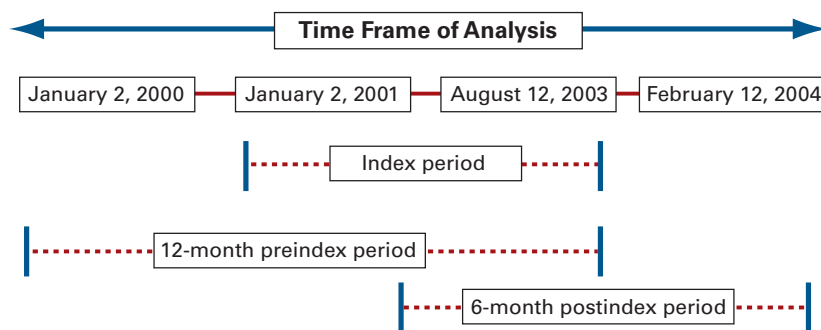
Study Design and Sample

This was a retrospective, observational cohort study using medical and pharmacy claims from a large managed care database encompassing more than 30 different managed care plans and 33 million patients across the United States. This study was exempt from institutional review board oversight because no human subjects were involved and all data were HIPAA (Health Insurance Portability and Accountability Act) compliant, with all health plan and personal information identifiers removed to ensure confidentiality.

The study population consisted of patients ≥ 40 years of age with a diagnosis of COPD less than 1 year prior to initial treatment with fluticasone 250 μg and salmeterol 50 μg in a single inhaler, salmeterol alone, inhaled corticosteroid alone, ipratropium and albuterol in a single inhaler, and ipratropium alone (index medications). COPD was identified by *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 490.xx, 491.xx, 492.xx, or 496.xx*. Patient data were included in the study if the first pharmacy claim for the index medications occurred between January 2, 2001, and August 12, 2003 (index date). The time frame of the analysis is summarized in **Figure 1**. For the risk analysis, patients were required to have 18 months of continuous eligibility (12-month preindex period and 6-month postindex period). The cost analysis included a subpopulation who had a 12-month postindex period in order to calculate annual costs.

Patients were not permitted to receive any COPD treatment other than oral corticosteroids, short-acting β_2 agonists, or theophylline during the 12-month preindex period, and patients could not initiate treatment with any other COPD

Figure 1. Time Frame of Analysis^a



^aPatients were required to have a postindex period of at least 6 months to analyze time-to-exacerbation events (for risk analysis). The subgroup of patients who had a 12-month postindex period were selected to calculate annual costs (for cost analysis).

medications within 60 days of the index date. Additionally, patients without a pharmacy benefit through their health plan were excluded.

Outcomes

The risk analysis assessed the time to first all-cause hospitalization, ED visit, or a combined end point of either of them, and time to first COPD-related hospitalization, ED visit, or a combined end point of either of them as defined by the primary diagnosis. Patients without a hospitalization or ED visit were censored when they lost eligibility or changed health insurance plans. Additionally, patients who remained eligible at completion of the database in February 2004 also were censored.

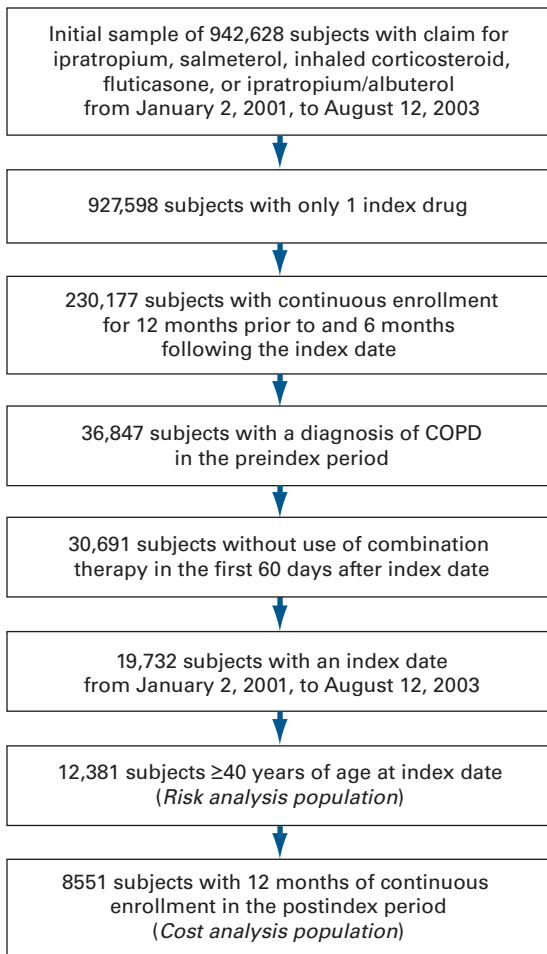
The cost analysis evaluated all-cause and COPD-related medical, pharmacy, and total costs during the 12-month postindex period. All cost outcomes were expressed as annual costs per patient. Costs of COPD-related care were identified by the primary diagnosis codes of COPD (*ICD-9-CM code 490.xx, 491.xx, 492.xx, or 496.xx*), COPD-related medical procedures (ie, spirometry test, oxygen therapy, pulmonary rehabilitation), and COPD-related medications (index medications plus oral corticosteroids, short-acting β_2 agonists, theophylline, and oral antibiotics).

Statistical Analyses

Differences in demographic and utilization characteristics measured during the preindex period were assessed by using Wilcoxon's rank sum tests for continuous variables and χ^2 tests for categorical variables. Because of the large number of comparison tests ($n = 56$), the alpha level was adjusted by using a Bonferroni correction procedure (ie, $0.05/56 = .001$).

For the risk analysis, Cox proportional hazard analyses on the time to the first all-cause/COPD-related hospitalization and/or ED visit were performed comparing the fluticasone/

■ **Figure 2.** Sample Selection



COPD indicates chronic obstructive pulmonary disease.

salmeterol combination, salmeterol, inhaled corticosteroid, and ipratropium/albuterol combination cohorts with the ipratropium cohort.¹⁸ The model was adjusted for underlying differences in age (continuous), sex (female as reference), comorbidities (asthma [ICD-9 code 493.xx], congestive heart failure [CHF; ICD-9 code 428.xx], upper respiratory tract infection [ICD-9 code 460.xx, 462.xx, 464.xx, 466.xx, or 487.xx], and lower respiratory tract infection [ICD-9 code 480.xx, 481.xx, 482.xx, or 483.xx]), COPD subtype (chronic bronchitis [ICD-9 code 491.xx] or emphysema [ICD-9 code 492.xx]), number of preindex prescriptions for respiratory medications (oral corticosteroids, short-acting β_2 agonists, theophylline), number of preindex prescriptions for all medications, and number of preindex all-cause hospitalizations and ED visits. The hazard ratio (HR) and 95% confidence interval (CI) were calculated for each variable of interest. The proportional hazards assumptions were confirmed through a graphical approach (Kaplan-Meier survival curve) and Cox significance

test. The final model was selected after examining interaction terms with age, asthma, and CHF diagnosis.

For the cost analysis, annual all-cause and COPD-related costs were compared across study groups. Unadjusted costs were summarized using means, SDs, and 95% CIs. Then, multivariate generalized linear models with a log link and gamma distribution were used to estimate treatment costs, controlling for differences in demographic and utilization characteristics during the preindex period.¹⁹ Adjusted costs were reported with 95% CI of cost differences (vs ipratropium), which were obtained by the bootstrap method with 1000 replications.²⁰

Stratified analyses for patients with and without an asthma diagnosis were conducted to examine whether observed treatment effects were modified by this diagnosis. All statistical analyses were conducted with SAS version 8.2 (SAS Institute Inc., Cary, NC) or STATA version 9.2 (StataCorp LP, College Station, TX).

RESULTS

Risk Analysis

A total of 12,381 patients met the established inclusion and exclusion criteria for the risk analysis (Figure 2), including 1832 patients in the fluticasone/salmeterol combination cohort, 1099 patients in the salmeterol cohort, 3940 patients in the inhaled-corticosteroid cohort, 3388 patients in the ipratropium/albuterol combination cohort, and 2122 patients in the ipratropium cohort. Demographic and utilization characteristics during the preindex period for the 5 cohorts are shown in Table 1. Several statistically significant differences were observed between treatment groups. For example, patients in the ipratropium cohort were significantly older (mean age = 63.3 years), had a higher frequency of comorbid CHF (21.4%), and had a higher mean [SD] number of preindex ED visits (2.3 [6.3]) and hospitalizations (0.8 [1.4]) compared with the other cohorts. A comorbid diagnosis of asthma was significantly more common in the fluticasone/salmeterol combination (40.5%), salmeterol (29.7%), and inhaled-corticosteroid (39.6%) groups compared with the group receiving ipratropium alone (20.8%). A diagnosis of chronic bronchitis was more common than emphysema across all cohorts. The mean number of preindex prescriptions for oral corticosteroids ranged from 0.2 to 0.4 across cohorts. Compared with the ipratropium cohort, preindex utilization of short-acting β_2 agonists was significantly higher in the fluticasone/salmeterol combination, salmeterol, and inhaled-corticosteroid cohorts and was significantly lower in the ipratropium/albuterol combination cohort.

All-cause Hospitalization/Emergency Department Visits. Table 2 shows the adjusted risk of all-cause hospitalization,

Table 1. Demographic and Utilization Characteristics Observed During the Preindex Period Among the Risk Analysis Population

Characteristic	Fluticasone/ Salmeterol Combination (n = 1832)	Salmeterol Alone (n = 1099)	Inhaled Corticosteroid Alone (n = 3940)	Ipratropium/ Albuterol Combination (n = 3388)	Ipratropium Alone (n = 2122)
Male, %	43.6	43.5	37.2 ^a	51.0 ^a	45.8
Mean (SD) age, y	56.9 (10.4) ^a	58.5 (10.9) ^a	55.7 (10.4) ^a	61.2 (10.6) ^a	63.3 (11.5)
Comorbid diagnosis, %					
Asthma	40.5 ^a	29.7 ^a	39.6 ^a	17.5 ^a	20.8
Congestive heart failure	7.7 ^a	8.6 ^a	5.7 ^a	15.3 ^a	21.4
Upper respiratory tract infection	35.9 ^a	29.6	33.7 ^a	29.5	30.6
Lower respiratory tract infection	2.8 ^a	3.4 ^a	2.5 ^a	5.5	6.7
COPD subtype, %					
Emphysema	7.6 ^a	10.3	4.3 ^a	11.6	12.0
Chronic bronchitis	31.1	24.1 ^a	25.6 ^a	28.4 ^a	31.7
Mean (SD) preindex utilization					
ED visits	1.1 (3.2) ^a	1.4 (3.6) ^a	1.5 (6.1) ^a	1.7 (4.9) ^a	2.3 (6.3)
Hospitalizations	0.3 (0.7) ^a	0.3 (0.8) ^a	0.3 (0.7) ^a	0.6 (1.1) ^a	0.8 (1.4)
Oral steroid Rx	0.4 (1.1) ^a	0.3 (1.0)	0.3 (1.0)	0.2 (1.0) ^a	0.4 (1.5)
Short-acting β_2 -agonist Rx	1.0 (2.5) ^a	0.9 (2.2) ^a	1.0 (2.3) ^a	0.4 (1.5) ^a	0.7 (2.3)
Theophylline Rx	0.1 (0.9) ^a	0.2 (1.2)	0.1 (0.8) ^a	0.1 (0.9) ^a	0.2 (1.1)
Any medication Rx	28.3 (27.4) ^a	28.2 (27.8) ^a	26.7 (26.7) ^a	28.3 (28.7) ^a	31.4 (30.5)
COPD indicates chronic obstructive pulmonary disease; ED, emergency department; Rx, prescription. ^a P < .05 vs ipratropium alone with a Bonferroni correction.					

ED visit, and a combined hospitalization/ED visit end point in the total sample, as well as stratified by asthma diagnosis as determined by the Cox proportional hazard analyses. After adjusting for differences in baseline characteristics, use of fluticasone/salmeterol combination therapy was associated with a 32% reduction in the risk of all-cause hospitalization or ED visit compared with ipratropium alone (adjusted HR = 0.685; 95% CI = 0.620, 0.757). Similarly, use of salmeterol alone was associated with a 21% reduction (adjusted HR = 0.790; 95% CI = 0.709, 0.879), and the use of inhaled corticosteroid alone was associated with a 23% reduction (adjusted HR = 0.772; 95% CI = 0.713, 0.835) in the risk of all-cause hospitalization or ED visit. In contrast, the risk of all-cause hospitalization or ED visit was not significantly different between the ipratropium/albuterol combination cohort and the cohort receiving ipratropium alone (adjusted HR = 0.948; 95% CI = 0.879, 1.021).

Findings were similar when stratified by comorbid asthma diagnosis. In COPD patients with asthma, the use of fluticasone/salmeterol combination therapy was associ-

ated with a 36% reduction in the risk of all-cause hospitalization or ED visit compared with ipratropium alone (adjusted HR = 0.642; 95% CI = 0.537, 0.766). In COPD patients without asthma, the use of fluticasone/salmeterol combination therapy was associated with a 28% reduction in the risk of all-cause hospitalization or ED visit compared with ipratropium alone (adjusted HR = 0.719; 95% CI = 0.636, 0.813).

Variables indicative of an increased risk of all-cause hospitalization or ED visit included increasing age; a comorbid diagnosis of chronic bronchitis, CHF, or lower respiratory tract infection; the number of preindex ED visits and hospitalizations; and the number of preindex prescriptions for oral steroids and any medication.

COPD-related Hospitalization/Emergency Department Visit. Use of combination fluticasone/salmeterol, salmeterol, or inhaled corticosteroid was associated with a significantly reduced risk of COPD-related hospitalization or ED visit compared with ipratropium alone (Table 2). Use of fluticasone/salmeterol combination therapy was associated with a 56% lower

■ **Table 2.** Adjusted Risks of All-cause and COPD-r-related Hospitalization/Emergency Department Visit^a

Study Population/Index Medications	Hazard Ratio (95% CI) ^b		
	All-cause Events		
	Hospitalization	ED Visit	Hospitalization or ED Visit
All COPD patients for risk analysis			
Fluticasone/salmeterol combination	0.717 (0.629, 0.817)	0.685 (0.615, 0.763)	0.685 (0.620, 0.757)
Salmeterol alone	0.782 (0.681, 0.899)	0.795 (0.708, 0.892)	0.790 (0.709, 0.879)
Inhaled corticosteroid alone	0.717 (0.647, 0.796)	0.792 (0.728, 0.863)	0.772 (0.713, 0.835)
Ipratropium/albuterol combination	0.970 (0.885, 1.063)	0.959 (0.885, 1.040)	0.948 (0.879, 1.021)
COPD patients with asthma diagnosis			
Fluticasone/salmeterol combination	0.637 (0.505, 0.803)	0.649 (0.536, 0.786)	0.642 (0.537, 0.766)
Salmeterol alone	0.744 (0.568, 0.975)	0.755 (0.604, 0.944)	0.769 (0.625, 0.946)
Inhaled corticosteroid alone	0.665 (0.548, 0.808)	0.822 (0.700, 0.965)	0.769 (0.662, 0.893)
Ipratropium/albuterol combination	0.925 (0.753, 1.136)	1.015 (0.850, 1.211)	0.991 (0.840, 1.168)
COPD patients without asthma diagnosis			
Fluticasone/salmeterol combination	0.760 (0.647, 0.891)	0.720 (0.630, 0.823)	0.719 (0.636, 0.813)
Salmeterol alone	0.796 (0.677, 0.937)	0.821 (0.716, 0.940)	0.801 (0.706, 0.909)
Inhaled corticosteroid alone	0.743 (0.656, 0.841)	0.784 (0.708, 0.868)	0.778 (0.708, 0.855)
Ipratropium/albuterol combination	0.980 (0.884, 1.086)	0.947 (0.865, 1.037)	0.938 (0.862, 1.021)

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; ED, emergency department; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*.

^aCox proportional hazards regression models were used to estimate time to first hospitalization/ED visit, controlling for age (continuous), sex (female as reference), comorbidities (asthma [*ICD-9-CM* code 493.xx], congestive heart failure [*ICD-9-CM* code 428.xx], upper respiratory tract infection [*ICD-9-CM* code 460.xx, 462.xx, 464.xx, 466.xx, or 487.xx], and lower respiratory tract infection [*ICD-9-CM* code 480.xx, 481.xx, 482.xx, or 483.xx]), COPD subtype (chronic bronchitis [*ICD-9-CM* code 491.xx] or emphysema [*ICD-9-CM* code 492.xx]), number of preindex prescriptions (oral corticosteroids, short-acting β_2 agonists, theophylline, and any medications), and number of preindex all-cause hospitalizations and ED visits.

^bCompared with ipratropium alone (reference medication). Statistically significant results ($P < .05$) are highlighted in bold.

risk of COPD-related hospitalization or ED visit (adjusted HR = 0.442; 95% CI = 0.341, 0.573). The risk of COPD-related hospitalization or ED visit also was reduced by 34% with salmeterol alone (adjusted HR = 0.656; 95% CI = 0.514, 0.836) and by 37% with inhaled corticosteroid alone (adjusted HR = 0.631; 95% CI = 0.530, 0.752). The use of ipratropium/albuter-

ol combination therapy did not significantly change the risk of COPD-related hospitalization or ED visit compared with ipratropium alone (adjusted HR = 0.960; 95% CI = 0.829, 1.113).

Like the findings on the risk of all-cause hospitalization or ED visit, findings on COPD-related hospitalization or ED visit were similar to those obtained for the total sample when strat-

Hazard Ratio (95% CI) ^b		
COPD-related Events		
Hospitalization	ED Visit	Hospitalization or ED Visit
0.433 (0.279, 0.672)	0.422 (0.320, 0.557)	0.442 (0.341, 0.573)
0.517 (0.333, 0.804)	0.631 (0.487, 0.817)	0.656 (0.514, 0.836)
0.568 (0.423, 0.765)	0.597 (0.496, 0.720)	0.631 (0.530, 0.752)
0.887 (0.696, 1.130)	0.972 (0.832, 1.135)	0.960 (0.829, 1.113)
0.260 (0.120, 0.563)	0.235 (0.138, 0.402)	0.271 (0.168, 0.437)
0.410 (0.181, 0.929)	0.368 (0.209, 0.647)	0.417 (0.251, 0.692)
0.403 (0.242, 0.669)	0.519 (0.373, 0.723)	0.520 (0.381, 0.710)
0.772 (0.480, 1.240)	0.894 (0.644, 1.243)	0.863 (0.632, 1.179)
0.576 (0.340, 0.978)	0.552 (0.399, 0.762)	0.558 (0.410, 0.758)
0.581 (0.345, 0.981)	0.761 (0.569, 1.018)	0.771 (0.584, 1.016)
0.696 (0.485, 0.998)	0.628 (0.500, 0.788)	0.687 (0.556, 0.849)
0.960 (0.721, 1.277)	1.008 (0.844, 1.204)	1.007 (0.850, 1.192)

ified by comorbid asthma diagnosis. In COPD patients with asthma, use of fluticasone/salmeterol combination therapy was associated with a 73% reduction in the risk of COPD-related hospitalization or ED visit compared with ipratropium alone (adjusted HR = 0.271; 95% CI = 0.168, 0.437). In COPD patients without asthma, use of fluticasone/salmeterol

combination therapy was associated with a 44% reduction in the risk of COPD-related hospitalization or ED visit compared with ipratropium alone (adjusted HR = 0.558; 95% CI = 0.410, 0.758).

The following variables also were associated with an increased risk of COPD-related hospitalization or ED visit: increasing age; a comorbid diagnosis of chronic bronchitis, emphysema, or CHF; number of preindex ED visits or hospitalizations; and number of preindex prescriptions for oral steroids, short-acting β₂ agonists, and theophylline. A comorbid diagnosis of asthma was not associated with an increased risk of COPD-related hospitalization or ED visit.

Cost Analysis

A total of 8551 patients had at least 12 months of continuous enrollment after the index date and were included in the cost analysis (Figure 2). The cost analysis population included 1062 patients in the fluticasone/salmeterol combination cohort, 842 patients in the salmeterol cohort, 2903 patients in the inhaled-corticosteroid cohort, 2258 patients in the ipratropium/albuterol combination cohort, and 1486 patients in the ipratropium cohort. Demographic and utilization characteristics during the preindex period for the 5 cohorts in the cost analysis were similar to those for the cohorts in the risk analysis (data not shown). As illustrated in Table 3, large variations in unadjusted annual costs during the postindex period were observed. Especially with respect to medical costs, only a few patients accounted for a large portion of the costs associated with inpatient admissions and ED visits. By comparing mean values, the ipratropium/albuterol combination and ipratropium cohorts were more likely to have higher all-cause and COPD-related medical costs than the other cohorts.

Mean refill counts during the 12-month follow-up period were highest in the fluticasone/salmeterol combination cohort.

All-cause Costs

The fluticasone/salmeterol combination and inhaled-corticosteroid cohorts had statistically significant lower annual

medical costs compared with the ipratropium cohort (Table 4). Annual pharmacy costs were higher but not statistically significant in the fluticasone/salmeterol combination group compared with the group receiving ipratropium alone. As for total costs (medical plus pharmacy costs), statistically significant reductions were observed in the fluticasone/salmeterol combination cohort (mean: \$5317; 95% CI = \$2556, \$7967) and in the inhaled-corticosteroid cohort (mean: \$4766; 95% CI = \$2377, \$7344). Similar trends were observed regardless of asthma diagnosis.

COPD-related Costs

Compared with the ipratropium cohort, the fluticasone/salmeterol combination, salmeterol, and inhaled-corticosteroid cohorts had statistically significant lower annual COPD-related medical costs (Table 4). Annual pharmacy costs were significantly higher in the fluticasone/salmeterol combination cohort, but significantly lower in the ipratropium/albuterol combination group, compared with the ipratropium cohort. Overall, annual total costs were significantly decreased in the salmeterol, inhaled-corticosteroid, and ipratropium/albuterol combination cohorts, with annual reductions of \$536 (95% CI = \$128, \$961), \$541 (95% CI = \$202, \$944), and \$456 (95% CI = \$98, \$842), respectively, compared with the ipratropium group. In contrast, there was no significant difference in annual total costs between the fluticasone/salmeterol combination and ipratropium cohorts. Similar trends were observed among patients with an asthma diagnosis. However, among patients without an asthma diagnosis, no significant treatment effects on annual costs were observed except higher pharmacy costs in the fluticasone/salmeterol combination cohort.

DISCUSSION

The findings from our analysis suggested that COPD-related illnesses, particularly acute exacerbations, were associated with significant morbidity and economic costs. The risk analysis investigated the risk of hospitalization or ED visit among persons with COPD receiving initial treatment for COPD in the managed care setting. After adjustment for differences in demographics, comorbidities, and utilization during the preindex period, the risk of all-cause hospitalization or ED visit was reduced by 32% with the fluticasone/salmeterol combination, 21% with salmeterol alone, and 23% with inhaled corticosteroid alone compared with ipratropium alone. Similarly, the risk of COPD-related hospitalization or ED visit was reduced 56% with the fluticasone/salmeterol combination, 37% with inhaled corticosteroid alone, and 34% with salmeterol alone compared with ipratropium alone. In contrast, the ipratropium/albuterol combination co-

hort and the ipratropium-only cohort had similar risks of all-cause and COPD-related hospitalization or ED visit. When the analysis was stratified by asthma diagnosis, findings still favored use of the fluticasone/salmeterol combination with a 36% (asthma) and 28% (no asthma) risk reduction of all-cause hospitalization or ED visit and a 73% (asthma) and 44% (no asthma) risk reduction of COPD-related hospitalization or ED visit compared with ipratropium alone.

These findings are consistent with the results of a similarly designed study that compared the risks of hospitalization in Medicaid patients with COPD who were treated with various medication regimens.²¹ Medicaid patients treated with the combination of salmeterol plus inhaled corticosteroid had a 27% lower risk of COPD-related hospitalization compared with those treated with ipratropium alone. The risk of hospitalization was not significantly altered with salmeterol alone or inhaled corticosteroid alone. Thus, these 2 analyses yielded consistent results despite notable differences between the Medicaid and commercially insured populations. In the Medicaid study, patients ≥ 65 years of age were excluded from the analysis because the Medicaid database does not completely cover dual Medicare/Medicaid eligibility. Consequently, our population was generally older than the one in the Medicaid study. Moreover, patients in the current study had higher rates of preindex hospitalizations and ED visits, whereas patients in the Medicaid study had higher rates of preindex short-acting β_2 agonist and theophylline use.

Other observational studies using medical claims databases also have demonstrated a reduced risk of hospitalization with the use of inhaled corticosteroid alone or in combination with salmeterol in patients with COPD.²²⁻²⁴ Additionally, several prospective, controlled clinical trials have documented a reduction in the rate and/or severity of COPD exacerbations with inhaled corticosteroid alone or in combination with long-acting β_2 agonists.¹¹⁻¹⁷ In a 12-month, double-blind, placebo-controlled study, the rate of exacerbations decreased by 25% with fluticasone/salmeterol combination ($P < .0001$), 19% with fluticasone propionate alone ($P = .0033$), and 20% with salmeterol alone ($P = .0027$) compared with placebo.¹³ In another 12-month, double-blind, placebo-controlled study, the combination of budesonide plus formoterol in a single device reduced the rate of severe exacerbations by 24% ($P = .035$) compared with placebo.¹⁶ Although these controlled studies did not specifically evaluate the effect of treatment on resource utilization, a reduction in the rate and severity of exacerbations would likely translate into a decrease in hospitalizations and ED visits, as demonstrated in the observational studies.

Our risk analysis suggests that combination therapy with fluticasone and salmeterol may result in improved outcomes

Table 3. Unadjusted Annual per Patient Costs and Therapy Adherence for the Cost Analysis Population

Cost/Adherence	Mean (SD) [95% CI]					
	Fluticasone/ Salmeterol Combination (n = 1062)	Salmeterol Alone (n = 842)	Inhaled Corticosteroid Alone (n = 2903)	Ipratropium/ Albuterol Combination (n = 2258)	Ipratropium Alone (n = 1486)	Total (N = 8551)
All cause, \$						
Medical costs	7166 (16,965) [132, 35,602]	9942 (25,196) [141, 92,785]	7611 (18,562) [146, 49,646]	11,887 (25,363) [153, 87,570]	15,785 (32,865) [198, 100,578]	10,335 (24,127) [156, 73,606]
Hospitalizations	2492 (12,556) [0, 22,774]	3666 (15,661) [0, 37,498]	2801 (11,134) [0, 29,724]	5330 (16,138) [0, 56,264]	7812 (24,845) [0, 62,298]	4386 (16,289) [0, 43,083]
ED visits	105 (292) [0, 877]	144 (382) [0, 1191]	131 (451) [0, 1032]	185 (588) [0, 1391]	231 (738) [0, 1923]	161 (531) [0, 1265]
Pharmacy costs	2579 (3845) [210, 10,448]	2230 (3029) [132, 9837]	2009 (2797) [109, 8389]	2222 (3096) [93, 8997]	2495 (3778) [101, 9694]	2242 (3232) [109, 8950]
Total	9745 (17,949) [625, 43,477]	12,171 (26,249) [425, 97,614]	9621 (19,510) [409, 56,305]	14,109 (26,210) [468, 90,597]	18,281 (33,643) [653, 105,969]	12,578 (25,002) [469, 80,084]
COPD related, \$^a						
Medical costs	1198 (2248) [24, 6823]	1468 (3372) [11, 12,650]	1107 (3797) [0, 9065]	2114 (5686) [19, 14,499]	3288 (9894) [16, 21,147]	1799 (5728) [11, 13,956]
Hospitalizations	112 (1127) [0, 0]	124 (1210) [0, 0]	192 (2389) [0, 0]	309 (2964) [0, 3990]	673 (5965) [0, 6106]	290 (3282) [0, 0]
ED visits	15 (77) [0, 238]	26 (117) [0, 291]	23 (121) [0, 271]	49 (232) [0, 516]	56 (217) [0, 670]	35 (172) [0, 391]
Pharmacy costs	630 (539) [123, 1948]	356 (352) [73, 1451]	337 (395) [58, 1406]	305 (354) [48, 1280]	393 (501) [41, 1980]	376 (433) [47, 1580]
Total	1828 (2408) [222, 8146]	1824 (3466) [126, 13,871]	1444 (3884) [108, 9729]	2419 (5771) [116, 15,345]	3681 (10,059) [104, 2149]	2175 (5831) [117, 14,646]
Therapy adherence^b						
Refill counts	3.21 (2.98)	2.31 (2.32)	1.94 (1.88)	2.56 (2.96)	2.57 (2.96)	—

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; ED, emergency department.
^aCOPD-related costs were identified by using primary diagnosis codes (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 490.xx, 491.xx, 492.xx, 496.xx) as well as COPD-related procedures (ie, spirometry test, oxygen therapy, pulmonary rehabilitation) and medications (index medications plus oral corticosteroids, short-acting β_2 agonists, theophylline, and oral antibiotics). Medical costs included all institutional and professional service costs (including costs associated with inpatient admissions and ED visits).
^bTherapy adherence is expressed by the number of refill counts of the index medications over the 12-month period after the index date.

compared with the anticholinergic therapy when used as initial therapy in patients with COPD. These findings agree with results from short-term controlled clinical trials. In two 8-week, randomized, double-blind, double-dummy, parallel-group studies, use of fluticasone/salmeterol combination therapy (250 µg/50 µg twice daily) resulted in better control of lung function and symptoms than use of ipratropium/albuterol combination therapy (36 µg/206 µg 4 times daily).^{25, 26} The incidence of exacerbations was similar with both treatments; however, the short duration of treatment did not allow for an adequate assessment of the impact of treatment on exacerbations.

A retrospective review of data from the National Hospital Discharge Survey, 1979 to 2001, found that patients with COPD have an increased risk of hospitalization for other comorbidities, including pneumonia, hypertension, CHF, ischemic heart disease, pulmonary vascular disease, thoracic malignancies, and ventilatory failure.²⁷ These findings suggest that a decrease in the risk of all-cause hospitalization or ED visit with salmeterol and inhaled corticosteroid, as observed in our study, may translate into a reduction in the overall burden of COPD. However, additional studies are needed to fully evaluate the impact of COPD medications on the risk of hospitalization for common comorbidities.

■ **Table 4.** Adjusted Differences in All-cause and COPD-related Annual per Patient Costs^a

Study Population/ Index Medications	Cost Differences (95% CI) ^b					
	All-cause Costs, \$			COPD-related Costs, \$		
	Medical	Pharmacy	Total	Medical	Pharmacy	Total
All COPD patients for cost analysis (n = 8551)						
Fluticasone/salmeterol combination	-5679 (-8398, -2982)	+362 (-42, +763)	-5317 (-7967, -2556)	-578 (-984, -165)	+417 (+356, +479)	+64 (-344, +432)
Salmeterol alone	-2880 (-6300, +582)	-417 (-757, -85)	-3241 (-6743, +51)	-641 (-1059, -200)	+22 (-26, +68)	-536 (-961, -128)
Inhaled corticosteroid alone	-4237 (-6980, -1792)	-559 (-882, -238)	-4766 (-7344, -2377)	-642 (-1069, -237)	+14 (-30, +54)	-541 (-944, -202)
Ipratropium/albuterol combination	-2213 (-4866, +238)	-115 (-542, +262)	-2279 (-4823, +336)	-358 (-760, +35)	-58 (-97, -20)	-456 (-842, -98)
COPD patients with asthma diagnosis (n = 2570)						
Fluticasone/salmeterol combination	-4462 (-8221, -853)	+532 (-132, +1236)	-4278 (-8470, -26)	-1080 (-1887, -346)	+488 (+376, +897)	-180 (-751, +345)
Salmeterol alone	-1280 (-6092, +4664)	+28 (-625, +758)	-1511 (-6851, +5339)	-1253 (-2060, -537)	+18 (-82, +121)	-997 (-1545, -502)
Inhaled corticosteroid alone	-4544 (-7604, -1825)	-414 (-1009, +86)	-5175 (-8609, -1852)	-1099 (-1922, -372)	+58 (-25, +141)	-747 (-1296, -224)
Ipratropium/albuterol combination	-2917 (-6308, +467)	-195 (-912, +523)	-3370 (-7031, +625)	-601 (-1456, +113)	-129 (-224, -44)	-609 (-1221, -50)
COPD patients without asthma diagnosis (n = 5981)						
Fluticasone/salmeterol combination	-6420 (-9765, -3119)	+310 (-152, +900)	-6025 (-9305, -2813)	-340 (-882, +151)	+388 (+315, +458)	+167 (-313, +620)
Salmeterol alone	-3882 (-7761, +463)	-554 (-979, -171)	-4341 (-8189, +357)	-369 (-928, +154)	+23 (-25, +77)	-331 (-843, +150)
Inhaled corticosteroid alone	-3728 (-6972, -462)	-538 (-925, -154)	-4238 (-7979, -802)	-434 (-943, +4)	-4 (-50, +42)	-470 (-941, -16)
Ipratropium/albuterol combination	-2038 (-5184, +832)	-144 (-572, +284)	-2001 (-5319, +1266)	-256 (-743, +189)	-47 (-87, -6)	-398 (-851, +40)

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*.

^aGeneralized linear models were used to estimate differences in all-cause and COPD-related annual costs, controlling for age (continuous), sex (female as reference), comorbidities (asthma [*ICD-9-CM* code 493.xx], congestive heart failure [*ICD-9-CM* code 428.xx], upper respiratory tract infection [*ICD-9-CM* code 460.xx, 462.xx, 464.xx, 466.xx, or 487.xx], and lower respiratory tract infection [*ICD-9-CM* code 480.xx, 481.xx, 482.xx, or 483.xx]), COPD subtype (chronic bronchitis [*ICD-9-CM* code 491.xx] or emphysema [*ICD-9-CM* code 492.xx]), number of preindex prescriptions (oral corticosteroids, short-acting β_2 agonists, theophylline, and any medications), number of preindex all-cause hospitalizations and emergency department visits, and log of preindex medical and pharmacy costs.

^bCompared with ipratropium alone (reference medication). Statistically significant results ($P < .05$) are highlighted in bold.

The current study was not designed to compare the effects of fluticasone/salmeterol combination, salmeterol alone, and inhaled corticosteroid alone. However, fluticasone/salmeterol combination therapy was associated with numerically greater reductions in the risk of all-cause and COPD-related hospitalization and ED visit compared with salmeterol alone or inhaled corticosteroid alone. These results are not surprising

because combination therapy with inhaled corticosteroid and long-acting β_2 agonists has been shown to be more effective than individual agents in several controlled clinical studies.^{13,16,17,28-30} For example, one of these studies demonstrated superior improvements in lung function with fluticasone/salmeterol combination therapy (250 μ g/50 μ g) compared with fluticasone propionate 250 μ g or salmeterol 50 μ g alone.³⁰

Our cost analysis demonstrated that use of fluticasone/salmeterol combination and inhaled corticosteroid alone were associated with significant reductions in all-cause and COPD-related treatment costs compared with ipratropium alone. Similar treatment effects on all-cause costs were observed regardless of an asthma diagnosis; however, for COPD-related medical costs, treatment benefits of fluticasone/salmeterol combination and inhaled corticosteroid were observed only in patients with COPD and asthma. These findings likely reflect the observed differences in the risk of hospitalization and ED visit with these therapies compared with ipratropium alone. Although fluticasone/salmeterol combination therapy was associated with significantly higher COPD-related pharmacy costs, there was no significant difference in COPD-related total costs between the fluticasone/salmeterol combination and ipratropium cohorts. Collectively, these data suggest that fluticasone/salmeterol combination therapy is a cost-effective alternative to ipratropium alone because it achieves better COPD-related outcomes at similar COPD-related costs.

Misclassification of exposure can be problematic in observational studies.³¹ In the current study, exposed status was defined at the cohort entry because we were interested in investigating the effect of initial treatment choice. We used an intent-to-treat approach in which patients were allowed to change the medication after 2 months of follow-up. We assumed that patients' medication use was stable if they used the same medication for 2 months. This approach may have caused misclassification of person-time because we considered all follow-up time as the exposed person-time even though some patients may not have been fully exposed. Because patients with ineffective medications are more likely to switch to or add more effective medications, this misclassification of exposure may have resulted in underestimation of the treatment effects.

Our study has a number of limitations that are inherent in administrative claims studies. Although baseline differences in demographic and utilization characteristics were adjusted by multivariate models, potential confounders (eg, disease severity, smoking behavior) could not have been fully controlled because extensive measures of such information are not generally collected in claims databases. Moreover, without clinical information, we had to rely on diagnosis codes and resource utilization patterns to identify COPD patients and to estimate the burden of this disease; however, the impact of potential misclassification was not predictable. We included ICD-9-CM code 490.xx, bronchitis not specified as chronic or acute, as

Take-away Points

Medical/pharmacy claims from a large managed care database were used to compare fluticasone 250 µg plus salmeterol 50 µg in a single inhaler with other inhaled medications for initial maintenance therapy in patients with chronic obstructive pulmonary disease.

- Fluticasone/salmeterol combination therapy was associated with a 31%-56% lower risk of hospitalization or emergency department visit compared with ipratropium alone.
- Fluticasone/salmeterol combination therapy was considered to be cost-effective compared with ipratropium alone because it achieved better clinical outcomes with similar or lower total treatment costs.

a measure of COPD. Use of this code might have introduced misclassification bias, as patients with acute bronchitis may have been included in the analysis; however, because of the other inclusion criteria specified in the Methods section, specifically the age restriction and index medication, we expected this measure to increase the validity of the study by capturing patients with chronic bronchitis whose condition was coded incorrectly. For the cost analysis, we included pharmacy costs of index medications; therefore, the relationship between initial treatment choice and outcomes is one of association rather than causation. Also, we could not consider end-of-life costs because of a lack of mortality information.

There also was a high prevalence of CHF comorbidity in the ipratropium and ipratropium/albuterol combination groups. Individuals with both COPD and CHF are more likely to have poorer outcomes, which is why we included CHF as a covariate in the multivariate analysis. However, because the diseases have similar clinical features, resulting in some CHF patients not being identified, there is a potential for misclassification. Also, it is possible that the combined effects of CHF and COPD may result in poorer outcomes than those observed with either condition independently, or they may have a multiplicative effect. Finally, because our study was conducted using data from a managed care organization, the results may not be generalizable to all patients with COPD. Managed care populations tend to be younger and healthier than the overall population of patients with COPD. Indeed, only 28.1% of patients in our study were ≥65 years of age. National surveys estimate that approximately 30% to 50% of patients with COPD are age ≥65 years²; therefore, elderly patients may have been underrepresented in our study. Nevertheless, our sample was more representative of the general COPD population than the observational study in Medicaid patients, in which patients older than age 65 years were excluded.²¹

CONCLUSION

Our study demonstrated that the use of fluticasone and salmeterol, particularly when used in combination in a single in-

haler, was significantly associated with a reduction in the risk of all-cause and COPD-related hospitalization or ED visit compared with ipratropium therapy. These benefits were achieved at similar or lower COPD-related treatment costs compared with ipratropium therapy. Our findings support the existing literature regarding the effectiveness of inhaled corticosteroid alone or in combination with long-acting β_2 agonists in patients with COPD.

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REFERENCES

1. **Global Initiative for Chronic Obstructive Lung Disease.** *Global Strategy for the Diagnosis, Management, and Prevention of COPD.* 2007. <http://www.goldcopd.com>. Accessed March 31, 2008.
2. **Mannino DM, Homa DM, Akinbami LJ, et al.** Chronic obstructive pulmonary disease surveillance—United States, 1971-2000. *MMWR Surveill Summ.* 2002;51(6):1-16.
3. **Miravittles M, Ferrer M, Pont A, et al; for the IMPAC Study Group.** Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. *Thorax.* 2004;59(5):387-395.
4. **Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA.** Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1998;157(5, pt 1):1418-1422.
5. **Grasso ME, Weller WE, Shaffer TJ, Diette GB, Anderson GF.** Capitation, managed care, and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1998;158(1):133-138.
6. **Halpern MT, Stanford RH, Borker R.** The burden of COPD in the USA: results from the Confronting COPD survey. *Respir Med.* 2003;97(suppl C):S81-S89.
7. **Hilleman DE, Dewan N, Malesker M, Friedman M.** Pharmacoeconomic evaluation of COPD. *Chest.* 2000;118(5):1278-1285.
8. **Mapel DW, Hurley JS, Frost FJ, Peterson HV, Picchi MA, Coultas DB.** Health care utilization in chronic obstructive pulmonary disease. A case-control study in a health maintenance organization. *Arch Intern Med.* 2000;160(17):2653-2658.
9. **Strassels SA, Smith DH, Sullivan SD, Mahajan PS.** The costs of treating COPD in the United States. *Chest.* 2001;119(2):344-352.
10. **Stanford RH, Shen Y, McLaughlin T.** Cost of chronic obstructive pulmonary disease in the emergency department and hospital: an analysis of administrative data from 218 US hospitals. *Treat Respir Med.* 2006;5(5):343-349.

11. **Sin DD, McAlister FA, Man SF, Anthonisen NR.** Contemporary management of chronic obstructive pulmonary disease: scientific review. *JAMA.* 2003;290(17):2301-2312.
12. **Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK.** Randomized, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ.* 2000;320(7245):1297-1303.
13. **Calverley P, Pauwels R, Vestbo J, et al; for the TRIAL of Inhaled Steroids ANd long-acting beta2 agonists study group.** Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomized controlled trial [Correction published in: *Lancet.* 2003;361(9369):1660]. *Lancet.* 2003;361(9356):449-456.
14. **Jones PW, Willits LR, Burge PS, Calverley PM; for the Inhaled Steroids in Obstructive Lung Disease in Europe study investigators.** Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations. *Eur Respir J.* 2003;21(1):68-73.
15. **Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingsworth K, Efthimiou J.** Multicenter randomized placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. [Correction published in: *Lancet.* 1998 Jun 27;351(9130):1968]. *Lancet.* 1998;351(9105):773-780.
16. **Szafranski W, Cukier A, Ramirez A, et al.** Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. [Correction published in: *Eur Respir J.* 2003 May;21(s):912]. *Eur Respir J.* 2003;21(1):74-81.
17. **Calverley DM, Anderson JA, Celli B, et al; TORCH investigators.** Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med.* 2007;356(8):775-789.
18. **Allison PD.** *Survival Analysis Using SAS: A Practical Guide.* Cary, NC: SAS Institute; 1995.
19. **Manning WG, Mullahy J.** Estimating log models: to transform or not to transform? *J Health Econ.* 2001;20(4):461-494.
20. **Efron B, Tibshirani R.** *An Introduction to the Bootstrap.* New York: Chapman & Hall; 1993.
21. **Rascati KL, Akazawa M, Johnsrud M, Stanford RH, Blanchette CM.** Comparison of hospitalizations, emergency department visits, and costs in a historical cohort of Texas Medicaid patients with chronic obstructive pulmonary disease, by initial medication regimen. *Clin Ther.* 2007;29(6):1203-1213.
22. **Kiri VA, Bettoncelli G, Testi R, Viegi G.** Inhaled corticosteroids are more effective in COPD patients when used with LABA than with SABA. *Respir Med.* 2005;99(9):1115-1124.
23. **Sin DD, Tu JV.** Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2001;164(4):580-584.
24. **Soriano JB, Kiri VA, Pride NB, Vestbo J.** Inhaled corticosteroids with/without long-acting β -agonists reduce the risk of rehospitalization and death in COPD patients. *Am J Respir Med.* 2003;21(1):67-74.
25. **Donahue JF, Kalberg C, Emmett A, Merchant K, Knobil K.** A short-term comparison of fluticasone propionate/salmeterol with ipratropium bromide/albuterol for the treatment of COPD. *Treat Respir Med.* 2004;3(3):173-181.
26. **Make B, Hanania NA, ZuWallack R, et al.** The efficacy and safety of inhaled fluticasone propionate/salmeterol and ipratropium/albuterol for the treatment of chronic obstructive pulmonary disease: an eight-week, multicenter, randomized, double-blind, double-dummy, parallel-group study. *Clin Ther.* 2005;27(5):531-542.
27. **Holguin F, Folch E, Redd SC, Mannino DM.** Comorbidity and mortality in COPD-related hospitalizations in the United States. *Chest.* 2005;128(4):2005-2011.
28. **Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H.** Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J.* 2003;22(6):912-919.
29. **Mahler DA, Wire P, Horstman D, et al.** Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2002;166(8):1084-1091.
30. **Hanania NA, Darken P, Hortsman D, et al.** The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. *Chest.* 2003;124(3):834-843.
31. **Rothman KJ, Greenland S.** *Modern Epidemiology.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1998. ■