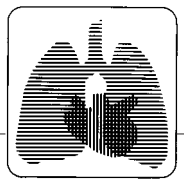

clinical investigations

Two-Year Retrospective Economic Evaluation of Three Dual-Controller Therapies Used in the Treatment of Asthma*

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Objective: **To compare asthma-related health-care utilization and expenditures for patients prescribed one of three dual-controller therapies: fluticasone plus salmeterol, inhaled corticosteroids (ICS) [excluding fluticasone] plus salmeterol, and ICS plus a leukotriene modifier (LTM).**
Materials and methods: **Asthma-related medical claims from two major health plans were obtained for the 12 months before and after the initiation of dual therapy. A total of 1,325 patients ≥ 12 years old with no claims for COPD or respiratory tract cancer were selected from the approximately 3.5 million lives covered. Multivariable regression was used to assess differences in asthma-related expenditures. To compensate for positive skew, all cost variables were log-transformed.**
Results: **Risk-adjusted total asthma-related costs for the fluticasone-plus-salmeterol cohort (n = 121), the ICS-plus-salmeterol cohort (n = 844), and the ICS-plus-LTM cohort (n = 30) were $975, $1,089, and $1,268, respectively. Risk-adjusted pharmacy costs were $813, $841, and $996, respectively. Generalized linear modeling, controlling for baseline covariates, indicated that compared to ICS-plus-LTM therapy, fluticasone-plus-salmeterol therapy was associated with a significant reduction in asthma-related total ($p = 0.0014$) and pharmacy ($p = 0.001$) costs. Similar results were found when the ICS-plus-salmeterol group and the ICS-plus-LTM group were compared ($p = 0.0001$). The number of inpatient, outpatient, and emergency department visits and their corresponding costs were lower for the fluticasone-plus-salmeterol cohort, but were not statistically significant ($p > 0.05$).**
Conclusion: **Results from managed-care practice suggest that treatment with fluticasone plus salmeterol, and more broadly ICS plus salmeterol, yield important cost savings when compared to treatment with ICS plus LTM.** ***(CHEST 2002; 121:1028–1035)***

Key words: asthma; dual-controller therapy; fluticasone; inhaled corticosteroids; leukotriene modifiers; pharmacoeconomic evaluation; salmeterol

Abbreviations: ED = emergency department; ICS = inhaled corticosteroids; LTM = leukotriene modifier; PHS = Physician Health Services; SABA = short-acting β_2-agonist

Asthma is a common chronic disease affecting approximately 17 million people in the United States in 1998.[1] Asthma-related symptoms account for 10 million missed school days, > 1.5 million emergency department (ED) visits, approximately 500,000 hospitalizations, and > 5,000 deaths annually.[1–4] In 1998, the estimated direct and indirect expenditures for the treatment of asthma in the United States were approximately $11.3 billion.[4]

The high cost and increasing morbidity and mortality associated with asthma make effective pharmaceutical management of the disease a priority to most

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health-care organizations. Recently, the National Asthma Education and Prevention Program Expert Panel of the National Heart, Lung, and Blood Institute, recognizing the dual characteristics of asthma of chronic inflammation and bronchoconstriction, recommended the combined use of inhaled corticosteroids (ICS) and an inhaled long-acting β_2-agonist for patients with moderate-to severe persistent asthma.[2] Support for this recommendation can be found in several randomized controlled trials,[5,6] which have shown that in symptomatic patients, adding long-acting bronchodilators to ICS therapy is more effective than doubling the dose of ICS. Jenkins et al[5] showed that patients receiving a salmeterol/fluticasone (50 μg/250 μg bid) combination therapy had significantly better symptom control and mean morning peak expiratory flow than patients receiving budesonide, 800 μg bid. In another study, Pearlman et al[6] showed that asthmatics initiating maintenance therapy with salmeterol and fluticasone propionate had larger improvements in pulmonary function and better control of symptoms than patients started on maintenance fluticasone propionate alone. In addition, Lundback et al[7] demonstrated that dual-controller therapies were more cost-effective than a single ICS therapy. Their study showed that use of salmeterol plus fluticasone resulted in lower costs per symptom-free and episode-free day than budesonide alone.

Among dual-controller therapies, ICS plus salmeterol was found to be more effective than ICS plus leukotriene modifiers (LTMs) in the treatment of patients with persistent asthma.[8,9] Results of the randomized clinical trials conducted by Fish et al[9] and Busse et al[8] showed that the addition of salmeterol to ICS produced significantly greater improvements in lung function, as measured by morning peak expiratory flow, than dual-controller therapy of ICS plus LTMs, with comparable adverse-event profiles.

Although the results of these randomized clinical trials provide very compelling evidence in support of the management of moderate-to-severe persistent asthma with the dual-controller therapy of ICS plus salmeterol, the question remains whether these results can be replicated in the clinical practice beyond the confines of tightly controlled clinical trials in which patients are carefully screened and compliance is closely monitored. An effective way to resolve these issues surrounding the effectiveness of dual-controller therapy is to use managed-care administrative claims databases. These databases record the medical costs incurred by asthmatics and provide insights into actual costs and benefits of competing drug regimens in the actual health-care delivery system. There is a wealth of literature examining the effective use of claims databases, with many of these studies specifically focusing on medical utilization and cost issues.[10–13] The objective of this study was to use a large claims database to compare asthma-related health-care costs incurred by asthma patients using three commonly prescribed dual-controller regimens. It was hypothesized that the improved lung function observed in clinical trials among patients receiving ICS (and fluticasone) plus salmeterol relative to patients receiving ICS plus LTMs would translate into observable savings in asthma-related costs and utilization in actual clinical practice.

Materials and Methods

Design and Sample

This study was designed to compare health-care resource utilization and costs among three common dual-controller therapies. It employed a 2-year preretrospective/postretrospective cohort design in which patients were observed retrospectively for 1 year prior to their initiation of dual-controller therapy and then 1 year after initiation. Pharmacy and medical claims, including outpatient, hospitalization, and ED visits, were obtained from two major health plans—Health Net and Physician Health Services (PHS)—for the period starting January 1, 1996, and ending December 31, 1999. Health Net is a major health maintenance organization in California with $>$ 2.2 million members. It consists of both independent and network-type physician associations. PHS is structured similarly to the Health Net health maintenance organization model but is based in the Connecticut, New York, and Pennsylvania tri-state area, and has a membership of approximately 1.3 million. The initial sample consisted of patients who had a primary or secondary diagnosis of asthma during the study period (*International Classification of Diseases, Ninth Revision, Clinical Modification*[14] code of 493.xx, excluding 493.2). The final sample included patients who had switched from ICS monotherapy to dual therapy (with either salmeterol or LTMs added to their therapy) between January 1, 1997 and December 31, 1998 (index period).

This research design intentionally mirrored the stepwise approach to the pharmacologic management of asthma recommended by the National Asthma Education and Prevention Program Expert Panel.[2] All study participants had at least one refill for ICS in the 12-month preindex period and were then "stepped-up" to dual-controller therapy through the addition of salmeterol or an LTM to their existing steroid regimen. To ensure combination therapy, patients were required to have filled their ICS prescription within 30 days of filling their index prescription (*ie*, salmeterol or LTM). Patients were excluded if they were $<$ 12 years old or had a diagnosis of COPD (*International Classification of Diseases, Ninth Revision, Clinical Modification*[14] codes of 491.0, 491.1, 491.20, 491.21, 491.8, 491.9 492.0, 492.8, 494, 496) or respiratory tract cancer (codes 160.xx to 164.xx, 231.xx). Patients receiving treatment in a skilled nursing or intermediate-care facility during the study period also were excluded. To eliminate potential contamination effects in the design, patients were also excluded if they had received either of the index drugs in the preindex period; thus, study participants were naïve to salmeterol and LTM in the preindex period.

This design yielded three dual-controller cohorts for comparison: (1) fluticasone plus salmeterol, (2) ICS (excluding fluticasone) plus salmeterol, and (3) ICS plus LTM. This research involved the collection of existing data, recorded in such a manner that participants could not be identified to any personnel outside the participating plans, and therefore was exempt from institution review board review.

Outcomes

Total asthma-related health-care costs per patient per year was the major outcome variable. Total health-care cost was divided into four components: pharmacy, outpatient, hospital, and ED costs. Pharmacy cost was calculated as a sum of average wholesale price of the prescription and any applicable co-pays. To avoid double counting, ED visits resulting in a hospitalization were counted as a hospitalization. Since Health Net follows a predominantly capitated reimbursement structure, participating providers have less incentive to consistently report expenditures related to outpatient visits. Therefore, the outpatient cost structure for PHS was used to estimate costs related to specific outpatient visits reported by Health Net providers.

Statistical Analysis

To ensure the accuracy of the data, medical and pharmacy claims were reviewed for internal consistency with respect to fixed and time-varying patient characteristics such as birth date and age. Univariate descriptive statistics were then used to assess the distributional properties of the study variables, such as skewness and normality. Analyses included univariate summary statistics, histograms, and frequency tables.

The comparison of outcomes among treatment groups was conducted using multivariable linear regression. This technique is widely used in observational research to control for baseline differences among treatment groups arising from adverse selection. In effect, unlike the clinical trial, which uses randomization to assign patients to treatment groups, patients in observational studies self-select or are selected by the physician into treatment groups. Consequently, potential confounds such as age are differentially assigned by treatment group based on prescribing decisions. When their assumptions are met, regression techniques provide unbiased comparisons of outcomes by controlling for these systematic differences.

Regression modeling, controlling for age, gender, plan of enrollment, continuous insurance eligibility, preindex short-acting β_2-agonist (SABA) use, and preindex pharmacy, inpatient, outpatient, or ED costs, was used to evaluate the association between postindex asthma-related expenditures and type of dual-controller therapy used. Preindex cost and utilization covariates acted as markers or proxies for asthma severity, a variable that is not routinely collected in administrative claims databases. Multivariable models were developed for four dependent variables: postindex total cost, postindex pharmacy cost, postindex ED cost, and postindex hospital cost.

To account for positive skew, which is characteristic of cost distributions, cost variables were log-transformed prior to multivariable modeling. After this transformation, the cost variables were approximately normally distributed, facilitating the use of linear regression techniques. Risk-adjusted mean asthma expenditures for each treatment group were calculated using both logged and untransformed cost variables. To facilitate interpretation, we present the risk-adjusted means yielded by the analysis of the untransformed data, in real dollar units. However all p values are derived, appropriately, from the logged models.

Residuals from the multivariable regressions were assessed for violations of the assumptions of normality, linearity, and homoscedasticity.[15–17] Selection of variables included in the models was facilitated by the use of Student's t and/or F tests of the null hypothesis that the introduced variable(s) did not add significantly to the model. Potential interactions between independent variables were similarly investigated.

Outliers were identified using partial regression plots and studentized residuals.[18] Four patients in the fluticasone-plus-salmeterol group, 19 patients in the ICS-plus-salmeterol group, and 10 patients in the ICS-plus-LTM group were identified as outliers in the total cost model, and a similar number were detected in the other models. Reanalyzing the regression models after the exclusion of outliers did not alter the direction or statistical significance of findings, so these outliers were retained in all analyses.

The sample size comprises the total universe of patients from the participating plans who met the study criteria. *Post hoc* power calculations indicate that given the available sample size, the study had a power of > 0.90 to detect differences in total cost of the magnitude observed. However, in outcomes such as ED costs, which had greater variation, the power was in the range of 0.60 to 0.80. Therefore, our analysis of ED and hospital costs should be viewed with caution because the probability of type II error was high, *ie*, not detecting a significant difference among treatment groups when indeed one exists.

Results

Demographics

A total of 1,325 patients met all the study criteria: 121 patients in the fluticasone-plus-salmeterol cohort, 844 patients in the ICS-plus-salmeterol cohort, and 360 patients in the ICS-plus-LTM cohort. Demographic characteristics for the three groups are presented in Table 1. Most of the patients in the three groups were women (64 to 67%). The mean ages of patients in the fluticasone-plus-salmeterol cohort, the ICS-plus-salmeterol cohort, and the ICS-plus-LTM cohort were 41.0 years, 45.4 years, and 47.2 years, respectively. The fluticasone-plus-salmeterol cohort had a significantly lower mean age compared to the ICS-plus-salmeterol cohort ($p = 0.0026$) and the ICS-plus-LTM cohort ($p = 0.0001$). Approximately 80% of the patients in the ICS-plus-salmeterol cohort were enrolled in Health Net, while the percentages enrolled in Health Net for the fluticasone-plus-salmeterol cohort and the ICS-plus-LTM cohort were 50% and 68%, respectively. The ICS used by patients were a mix comprised primarily of beclomethasone, budesonide, triamcinolone, and fluticasone. The LTM used by the ICS-plus-LTM patients was primarily montelukast. The two participating plans had no special asthma management protocols in place during the study period, though they both had global policies in place to encourage the use of National Institutes of Health asthma guidelines. Lower use of ICS plus salmeterol in the PHS plan was a result of restrictive formulary positioning for fluticasone during the start of the study period, not of an asthma management program.

Table 1—*Demographics and Preindex Health-Services Utilization and Cost by Dual-Controller Groups

Variables	Fluticasone Plus Salmeterol	ICS Plus Salmeterol	ICS Plus LTM
Patients, No.	121	844	360
Demographics			
Mean age, yr	41.0 (14.4)‡§	45.4 (15.3)†‡	47.2 (14.3)†§
Gender, % female	66.9	64.7	66.9
Plan type, % in Health Net	50.4‡§	80.3†‡	68.3†§
Continuously eligible, %	57.0‡§	71.1†	68.6†
Utilization, No.			
Prescriptions	10.0‡	10.4‡	13.5
SABA	5.7 (6.0)‡	5.5 (5.5)‡	6.7 (6.1)
ED visits	0.18 (0.61)‡§	0.07 (0.4)†	0.05 (0.23)†
Patients with at least one ED visit	15 (12.4%)‡§	45 (5.3%)†	17 (4.7%)†
Hospitalizations	0.03 (0.18)	0.02 (0.16)	0.03 (0.22)
Patients with at least one hospitalization	4 (3.3%)	15 (1.8%)	10 (2.8%)
Cost, $			
Pharmacy	363 (368)‡	369 (368)‡	551 (520)†§
Hospital	174 (1,208)	49 (494)	142 (1,078)
ED	50 (144)‡§	24 (119)†	17 (89)†
Outpatient	315 (546)‡§	175 (211)†‡	234 (300)†§
Total	902 (1,417)§	617 (716)†‡	943 (1,325)§

*Data are presented as mean (± SD) unless otherwise indicated.
†$p \leq 0.05$ compared to fluticasone plus salmeterol.
‡$p \leq 0.05$ compared to ICS plus LTM.
§$p \leq 0.05$ compared to ICS plus salmeterol.

Preindex Utilization and Cost

Utilization and cost data for the preindex period are also presented in Table 1. The three treatment groups were significantly different with respect to all preindex utilization and cost parameters except for hospital use and cost. While preindex drug use and costs were lowest in the fluticasone-plus-salmeterol group, the number of ED visits and its cost was highest in the fluticasone-plus-salmeterol group. Compared to the ICS-plus-LTM group, SABA use was significantly lower in the fluticasone-plus-salmeterol group and the ICS-plus-salmeterol group. Though number of hospitalizations and corresponding costs were highest in the fluticasone-plus-salmeterol group, the differences were not statistically significant. The percentage of patients with at least one ED or hospital visit was also highest in the fluticasone-plus-salmeterol group.

Preindex to Postindex Change

In general and as expected, prescription use increased while ED visits and hospitalizations decreased from the preindex period to the postindex period. SABA use increased modestly in the ICS-plus-LTM cohort but decreased in other cohorts. In all three cohorts, ED visits and hospitalizations reduced modestly from the preindex period to the postindex period, with the exception of a marked decrease in mean ED visits from 0.20 in the preindex period to 0.06 in the postindex period in the fluticasone-plus-salmeterol cohort. For all three cohorts, the percentage of patients with at least one hospitalization or ED visit decreased substantially from the preindex period to the postindex period. The fluticasone-plus-salmeterol cohort had both the highest preindex percentage (3.3%) of patients with at least one hospitalization, and the lowest postindex percentage (0.0%) across the study groups.

Preindex to postindex cost comparisons are provided in Figure 1. Compared to the utilization data, the cost data provided a clearer picture of the change in care patterns from the preindex period to the postindex period. In all three dual-controller therapy groups, similar to the utilization results, prescription cost increased while ED, hospital, and outpatient cost decreased from the preindex period to the postindex period. In the preindex period, ED, and hospitalization costs were substantially higher in the fluticasone plus salmeterol group compared to the ICS plus salmeterol group. This group also witnessed the smallest increase in pharmacy and total asthma costs and the largest reduction in ED, and hospitalization costs from the preindex period to the postindex period.

The addition of a new pharmaceutical to the treatment regimen served to increase total asthma costs. However, total costs increased on average $22 in the fluticasone-plus-salmeterol group, $333 in the ICS-plus-salmeterol group, and $378 in the ICS-

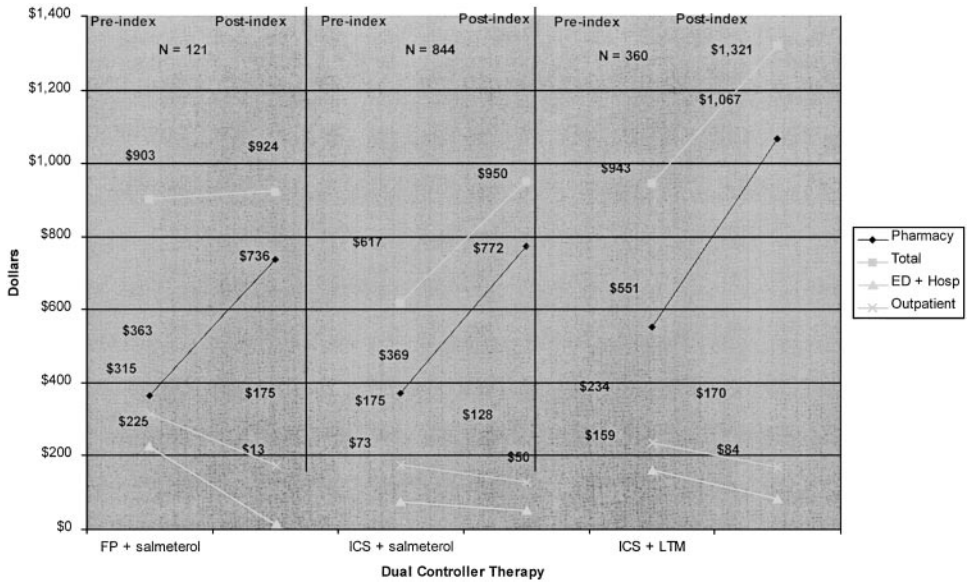

FIGURE 1. Change in preindex and postindex costs among dual-controller therapy groups. FP = fluticasone; Hosp = hospital.

plus-montelukast group. A cost shift is evident because ED and hospital costs declined while pharmacy costs increased, but the fluticasone-plus-salmeterol group came very close to providing a complete offset of the additional cost of the new pharmaceutical.

Risk-Adjusted Models

Table 2 provides the regression estimates for the total, pharmacy, hospital, and ED cost models. Controlling for differences in age, gender, plan type, continuous eligibility, and preindex utilization and costs, compared to the ICS-plus-LTM group, the fluticasone-plus-salmeterol group was associated with a statistically significant savings in asthma-related total costs (p = 0 0.0014). Risk-adjusted total costs for the fluticasone-plus-salmeterol group were the lowest at $975, followed by the ICS-plus-salmeterol group ($1,089), and the ICS-plus-LTM cohort ($1,268; Fig 2). Risk-adjusted pharmacy costs for the fluticasone-plus-salmeterol group ($814) were also significantly lower than for the ICS-plus-LTM group ($996). Although both risk-adjusted total costs and pharmacy costs were lower for the fluticasone-plus-salmeterol group than the ICS-plus-salmeterol group, these differences were not statistically significant at the conventional p = 0.05 level.

Table 2—*Regression Estimates From the Total, Pharmacy, ED, and Hospital Costs Models**

Independent Variables	Total Cost	Pharmacy Cost	ED Cost	Hospital Cost
Age	0.01‖	0.01‖	− 0.004‡	− 0.001
Male gender	0.003	0.04	0.01	− 0.03
Plan	0.14‖	0.08‡	0.11	0.06
Continuous eligibility	0.10§	0.09‡	− 0.02	− 0.01
Preindex ED visits	0.09	0.03	0.88‖	0.09
Preindex cost variable†	0.29‖	0.34‖		− 0.02
Preindex outpatient cost	0.03‖			
Preindex No. of SABAs	0.003	− 0.00	0.01‡	0.003
ICS plus salmeterol	0.04	0.03	0.05	0.10
ICS plus LTM	0.20§	0.20‖	0.02	0.19‡
F statistic	$46.15_{(10,1314)}$‖	$65.68_{(9,1315)}$‖	$11.00_{(8,1316)}$‖	$0.98_{(9,1315)}$
R^2/adjusted R^2	0.26/0.25	0.31/0.305	0.063/0.06	0.007/0.00

*All dependent variables were logarithmically transformed.
†This variable type varied with the type of dependent variable.
‡p ≤ 0.05.
§p ≤ 0.01.
‖p ≤ 0.001.

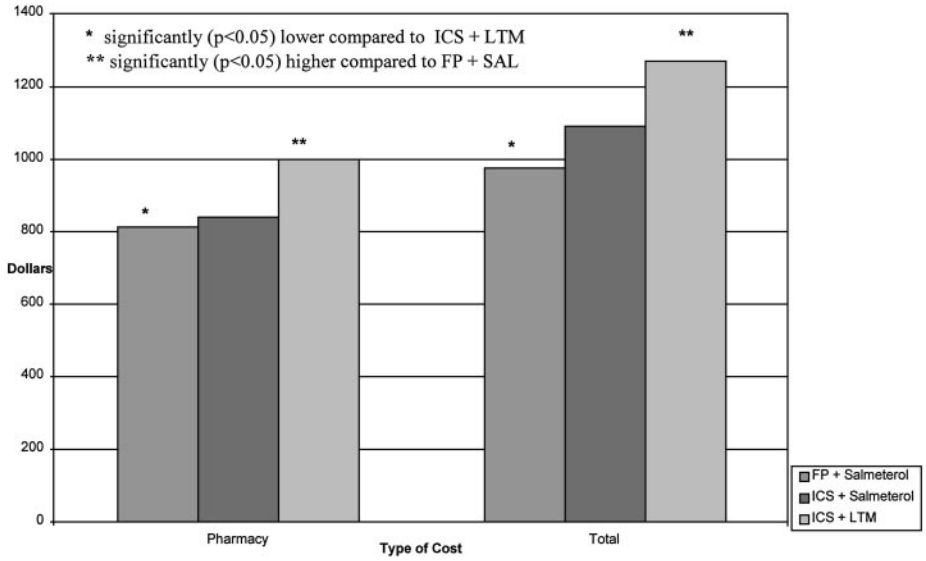

FIGURE 2. Risk-adjusted asthma-related pharmacy and total costs by dual-controller groups. SAL = salmeterol; see Figure 1 for expansion of other abbreviation.

Patients receiving fluticasone plus salmeterol had lower hospitalization and ED costs compared to the ICS-plus-salmeterol and ICS-plus-LTM groups, but these results were not statistically significant since very few subjects incurred these costs, and variability in the cost data were high (Fig 3). Risk-adjusted hospital costs were actually negative in the fluticasone-plus-salmeterol group, primarily because the actual postindex hospital cost was $0. Because hospital and ED cost data were highly skewed, we also performed a logistic regression assessing whether or not the probability of experiencing hospitalization or an ED visit was associated with the dual-controller group. Consistent with the cost data, the results indicated that odds of experiencing a hospitalization or ED visit was lower for fluticasone-plus-salmeterol group compared to the ICS-plus-LTM group, but these results did not achieve statistical significance.

DISCUSSION

In this study, we compared the annual asthma-related utilization and costs associated with three

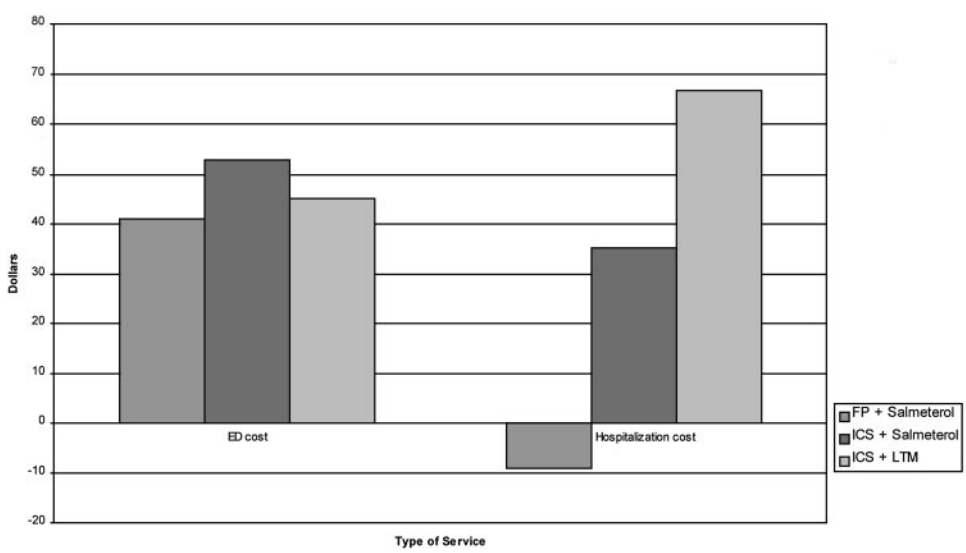

FIGURE 3. Risk-adjusted asthma-related ED and hospitalization costs by dual-controller groups. See Figure 1 for expansion of abbreviation.

dual-controller therapies: fluticasone plus salmeterol; ICS (excluding fluticasone) plus salmeterol; and ICS plus LTM. These combination regimens were chosen because of their inclusion in previous clinical trials and their wide use in asthma management today. The results indicate that the fluticasone-plus-salmeterol group had significantly lower pharmacy and total asthma costs compared to the ICS-plus-LTM group. Moreover, the mean differences observed in nearly all utilization and cost parameters favored the fluticasone-plus-salmeterol group. Although total asthma costs for the fluticasone-plus-salmeterol group were lower than the ICS-plus-salmeterol group, these results did not achieve significance at conventional levels. These findings are drawn from actual treatment experience across two large and diverse health plans of Foundation Health Systems, one of the largest managed-care organizations in the nation.

In the economic evaluation of asthma, it is useful to divide costs into investment costs vs treatment-failure costs. The former are comprised largely of the unavoidable costs of pharmaceutical management; the latter are comprised of the avoidable costs of emergent and short-term care needed to treat asthma exacerbations. Viewed from this perspective, the results of this study indicate that the use of fluticasone plus salmeterol required lower investment costs, while providing a larger decrease in emergent/short-term costs. By contrast, the use of ICS plus LTM was associated with much higher investment costs, yet yielded little appreciable savings in emergent/short-term costs.

The findings in this study support the existing body of knowledge regarding the effectiveness of dual-controller therapies. A retrospective claims analysis of a large New England insurer showed that patients in the ICS-plus-salmeterol group had significantly lower pharmacy and total costs compared to patients in the ICS-plus-LTM group.[19] In a study of UnitedHealthcare patients, the fluticasone-plus-salmeterol group had significantly lower pharmacy and total costs compared to the ICS-plus-LTM group. At the same time, the fluticasone-plus-salmeterol group had the lowest probability of ED visits and hospitalizations compared to the ICS-plus-LTM group.[20]

Our results show that addition of salmeterol to the fluticasone and ICS monotherapy produced different effects in these two groups. In the fluticasone-plus-salmeterol group, the cost increase due to the pharmacy component was significantly offset by reductions in inpatient, outpatient, and ED costs. In contrast, when salmeterol was added to the ICS group, the postindex inpatient, outpatient, and ED cost reductions were significantly smaller but with an absolute and proportionally similar increase in pharmacy costs from the baseline. Our findings imply that the use of fluticasone vs ICS (excluding fluticasone) is associated with different utilization and cost patterns.

The goal of pharmacoeconomic studies such as this one is to assist clinicians in the choice of alternative therapeutic regimens. The decisions made by an individual practitioner in the office or examination room have both clinical and economic consequences when considered collectively. Overall, these results help inform clinical practice about the appropriate add-on therapy for patients experiencing breakthrough symptoms on ICS alone. Physicians are often confronted with patients who have persistent asthma and are still symptomatic on single-controller therapy with ICS. The data in this study show that salmeterol may be a better choice than an LTM for add-on therapy, and that the combination of salmeterol with fluticasone represents a more effective and efficient choice than salmeterol with other ICS, as evidenced by the difference in utilization patterns. This latter observation—that fluticasone plus salmeterol may be more efficient and effective than other ICS plus salmeterol—is a chief contribution of this study.

These results should be interpreted with some caution due to potential limitations inherent in retrospective claims studies. In general, adequately controlling for confounding effects is a challenge in claims studies. In this study, though variations in demographics, plan type and prior utilization were controlled statistically, confounding from disease severity may not have been fully accounted for. However, since preindex asthma-related ED visits and hospitalizations were substantially higher in the fluticasone-plus-salmeterol group, inadequate control of severity may have biased the results in favor of the ICS-plus-salmeterol group and the ICS-plus-LTM group. Second, since costs in this study were measured from the payer perspective, they do not include indirect costs (loss of productivity and absenteeism). Hence, from a societal perspective, these costs reported here are grossly underestimated, as indirect costs constitute a significant portion of total asthma-related health-care expenditures.[4] We speculate, however, that the savings in direct costs observed in the fluticasone-plus-salmeterol group suggest commensurate savings in indirect personal and societal costs. As a significant portion of the outpatient cost data for Health Net patients was incomplete, we used the PHS outpatient cost structure as proxy to estimate outpatient expenditures for Health Net patients. Though this extrapolation method may have overestimated outpatient costs for Health Net patients, it could not have adversely affected the

overall study results, as outpatient costs constituted a very small portion of the total costs. Finally, the majority of the study patients were commercially insured, and indigent or Medicaid populations were underrepresented.

Conclusion

In the era of rising health-care costs, the choice of an appropriate dual-controller therapy for the treatment of moderate-to-severe persistent asthma should be governed not only by the safety and clinical efficacy of the dual controllers but also by its effectiveness and efficiency in actual clinical practice. Although several randomized clinical trials have consistently demonstrated superior improvements in clinical outcomes with ICS plus salmeterol compared to ICS plus LTM, questions of effectiveness in actual clinical practice remain unanswered. Our study demonstrates clearly that fluticasone plus salmeterol provides superior clinical benefit as evidenced by lower ED utilization and hospitalization as well as less reliance on rescue medication. These data are all the more remarkable since the results were obtained at substantially lower cost compared to the ICS-plus-LTM regimen. In addition, our study illustrates the value of using claims cohort analyses to supplement and confirm findings from randomized controlled trials. Future observational research should seek to address the comparative clinical and economic impact of single-controller vs dual-controller therapies.

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