

Cost impact of monitoring exhaled nitric oxide in asthma management

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ABSTRACT

Background: Asthma guidelines recommend periodic assessment of impairment and risk factors to prevent exacerbations, which can lead to hospitalization and increased health care utilization and cost. According to recent meta-analysis data, fractional exhaled nitric oxide (FeNO) monitoring is associated with a 40–50% reduction in the risk of exacerbations.

Objective: Cost modeling of these data indicates the potential for significant cost savings with FeNO use. Therefore, we attempted to verify this potential for cost savings within a real-world data base of Medicare beneficiaries.

Methods: This retrospective observational study investigated asthma-related claims from a Medicare data base. Beneficiaries were included who had 2 years of records after an asthma-related inpatient hospitalization (IP) or emergency department (ED) claim. A case-crossover analysis was completed of asthma-related IP or ED events before and after FeNO use during the 2-year study period.

Results: Of the 5911 asthma beneficiaries who met the inclusion criteria within the data base, 101 had an FeNO test during the 2-year study period. During the period before FeNO use, 98 of 101 (97%) beneficiaries had an asthma-related IP or ED event compared with 46 of 101 (46%) during the FeNO period. Asthma-related IP or ED claims and charges per beneficiary per day during the period before FeNO were 0.004 and \$16.21 compared with 0.002 and \$6.46 during the FeNO period ($p = 0.0433$ and $p = 0.0133$, respectively).

Conclusion: FeNO monitoring in beneficiaries with a history of exacerbations was associated with a substantial reduction in asthma-related IP and ED claims and charges. These data supported cost modeling estimates and demonstrated that FeNO use in asthma management was associated with significant cost savings.

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Although, today, a minority of patients with asthma experience disease-related emergency department (ED) visits and hospitalizations, these events continue to result in significantly disproportionate use of health care resources and expenses.¹ Fractional exhaled nitric oxide (FeNO) testing assists in the management of asthma by providing clinicians with an objective assessment of underlying type 2 helper cells and/or type 2–driven airway inflammation and corresponding corticosteroid sensitivity. In addition, FeNO is one of several risk factors that has been shown to predict the likelihood of a future asthma exacerbation.^{2,3} Val-

idation of the impact of incorporating FeNO into asthma management has been documented in recent Cochrane meta-analyses, which demonstrated a 40–50% reduction in exacerbations in both children and adults. The investigators of these meta-analyses concluded that the number of needed-to-treat patients to benefit was 9 in children and 12 in adults.^{4,5}

Analysis of considerable evidence indicates that FeNO can offer therapeutic value for appropriate monitoring populations in the United States and internationally.^{2,3} In addition, the benefits of FeNO use can be investigated by examining the health economic impact of FeNO testing for directing asthma management; if asthma exacerbations and associated treatment costs decline with FeNO use, then adding FeNO to management algorithms has implicit clinical utility. To date, however, most well-designed health economic studies of FeNO use have relied on data from European patient populations, which limit their applicability to the U.S. health care system.^{6–8}

This study evaluated the association of FeNO measurements with asthma exacerbation, health care resource utilization, and costs of care among U.S. beneficiaries with asthma by using real-world Medicare data. It was hypothesized that monitoring FeNO measurements would decrease asthma exacerbations by optimizing use of anti-inflammatory treatments, thereby lowering

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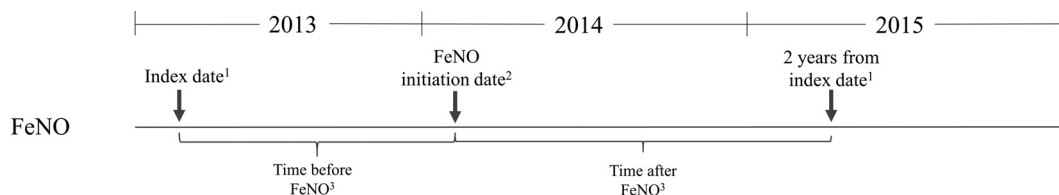


Figure 1. Study design. 1. Index date was defined as the first inpatient admission or emergency department visit for asthma; the index date varied for each patient but must have been within the year 2013. 2. Fractional exhaled nitric oxide (FeNO) initiation date was defined as the start date for use of NIOX (Circassia Pharmaceuticals, Inc., Morrisville, NC) VERO; the FeNO initiation date varied for each patient but must have been within 2 years of the index date. 3. Analysis periods are listed as “Time before FeNO” and “Time after FeNO.” All identified patients were required to have full Medicare Part A and Part B benefits throughout the study period.

health care resource utilization and costs. This expected reduction in health care costs was hypothesized to be greatest in beneficiaries with a history of moderate-to-severe exacerbations.^{6–14} The primary objectives of this study were to (1) examine demographics, clinical characteristics, and treatment patterns of beneficiaries who received FeNO monitoring, and (2) compare the change in asthma exacerbation rates, health care resource utilization, and costs of care in those who received FeNO monitoring by comparing the time periods before and after measuring FeNO when using a case-crossover study design.

METHODS

Study Design and Cohort Identification

This retrospective observational study used claims data from the Medicare 5% Standard Analytic Files from January 1, 2012 through December 31, 2015. The Centers for Medicare and Medicaid Services’ 5% Standard Analytic Files contain every fully adjudicated Medicare claim filed for 5% of the Medicare fee-for-service population. Medicare beneficiaries are randomly selected by their beneficiary identification, which is usually a form of the social security number. Although the beneficiary identification is encrypted, it is consistent among all claims in a year and across years, which allows for longitudinal analysis. A denominator file provides demographic and coverage data about the beneficiaries in the dataset. These data include ~5 million claims annually, of which a large majority are Carrier Part B claims for physician services.

We chose those patients who had a history of exacerbation so as to best study the potential impact of the FeNO intervention because frequency of future exacerbation is best determined by the history of exacerbation.² The moderate-to-severe exacerbator cohort was identified by using the guidelines from the American Thoracic Society, which address asthma clinical research, and included beneficiaries who had at least one inpatient (IP) hospitalization or ED visit with a primary diagnosis of asthma (The *International Classification of Diseases, Ninth Revision, Clinical Modification*

[ICD-9-CM] Dx 493.xx) in 2013.^{15,16} The date of the first identified asthma IP or ED visit was the index date. Beneficiaries with 24 months of continuous Medicare Part A and Part B enrollment from the index date were included.

The study period was 2 years to the day from the patient’s index date (Fig. 1). Data were collected before FeNO use and after FeNO use.

Outcomes Measures

All-cause and asthma-related health care resource utilization and costs were assessed at baseline and during follow-up periods. All-cause health care resource utilization and costs included all medical encounters; asthma-related health care resource utilization and costs were limited to medical encounters with a primary diagnosis of asthma. Costs were calculated as the sum of the amount paid by the health plan, the beneficiary, and any third-party payer. Costs were also reported as per patient per day. Index events claims and costs were excluded from all pre-FeNO analyses. All the costs were adjusted to 2016 U.S. dollars by using the annual figure for the Medical Care Component of the Consumer Price Index.

Analysis

Outcomes were compared among patients being monitored with FeNO, from before FeNO use to outcomes after FeNO use, in a case-crossover analysis. Patient characteristics, changes in asthma exacerbation rates, time to exacerbation, health care resource utilization, and costs of care were compared by using the paired *t*-test or Wilcoxon signed rank test for continuous variables, and the McNemar or χ^2 test for categorical variables. The Kaplan-Meier method was used to describe and compare time to exacerbation and to compare the risk of developing an exacerbation after using FeNO monitoring. A conventional alpha of 0.05 and two-tailed level of significance were used. The time between the index date and the first asthma-related ED or IP service was compared with the time between the FeNO initiation date and the next asthma-related ED or IP service by using the Kaplan-Meier method. The

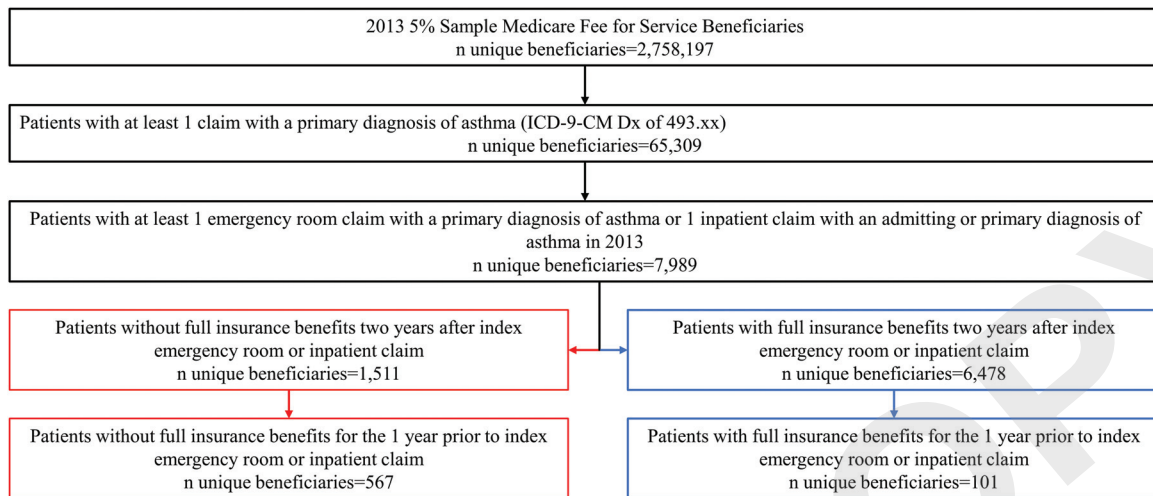


Figure 2. Consort diagram of patient inclusion and exclusion criteria.

log-rank test was used for significance testing on the time between the next event before FeNO monitoring versus after FeNO monitoring.

RESULTS

There were 5911 unique beneficiaries with full insurance benefits for the year preceding the index ED or IP claim, including 101 beneficiaries with FeNO monitoring (Fig. 2). Fifty-four percent of the patients were included in the study due to an ED visit; the remainder had an IP stay (index event). We evaluated “all claims” and a subset of just the ED or IP claims. We completed an additional analysis on “only asthma-related claims,” *i.e.*, those claims with a primary diagnosis of asthma (ICD-9-CM 493.xx).

All Beneficiaries

The demographics of the patients in the FeNO group within the entire cohort are shown in Table 1. Even though Medicare beneficiaries are generally people ≥ 65 years old, in the current study, almost half of the population (49%) were ages <65 years; this indicated that they likely had coexisting disabilities. In fact, the mean $\pm$ standard deviation comorbidity score was 3.2 ± 1.69 (within a defined range of 1 to 8). Documented comorbid diagnoses included chronic obstructive pulmonary disease (COPD) (all patients), diabetes without complications (51.5%), congestive heart failure (32.7%), and peripheral vascular disease (20.8%). This case-crossover analysis (by using the patient as his or her own control, a pre/post study design) consistently demonstrated that asthma-related claims, as well as asthma-related ED or IP claims and charges per patient per day, were statistically significantly lower after FeNO use (Table 2). This was not the case with all-cause claims, in which the opposite occurred, that is,

Table 1 Demographics of the patients who had FeNO use during the study period

Demographics	FeNO Group (N = 101)
Age, mean $\pm$ SD (range), y	60.8 $\pm$ 15.3 (30–88)
Age group, no. (%)	
<65 y	49 (48.5)
65–69 y	12 (11.9)
70–74 y	22 (21.8)
75–79 y	9 (8.9)
≥ 80 y	9 (8.9)
Gender, no. (%)	
Women	85 (84.2)
Men	16 (15.8)
Race, no. (%)	
White	63 (62.4)
Black	30 (29.7)
Hispanic	7 (6.9)
Asian	0 (0)
North American Native	0 (0)
Other	1 (1.0)
Unknown	0 (0)
Charlson Comorbidity Index score, mean $\pm$ SD	3.2 $\pm$ 1.69

FeNO = Fractional exhaled nitric oxide; SD = standard deviation.

that these figures were higher after FeNO than before FeNO use.

The post-FeNO follow-up period was longer, on average, than the pre-FeNO follow-up period. In addition, fewer beneficiaries had asthma-related claims in the post-FeNO group. As such, analysis of the data indicated that the beneficiaries in the post-FeNO time period experienced fewer asthma-related

Table 2 Health care utilization of pre-FeNO and post-FeNO analyses*

Variables	Pre-FeNO Analysis (N = 101)	Post-FeNO Analysis (N = 101)	p
All-cause claims with index claims excluded			
All claims per patient per day	0.25	0.21	0.1077
Allowed charges per patient per day	\$81.72	\$81.07	0.9709
ED or IP claims per patient per day	0.01	0.01	0.4938
Allowed charges per patient per day	\$41.01	\$40.35	0.9635
Asthma-related claims with index claims excluded			
Asthma-related claims per patient per day	0.05	0.03	0.0018#
Asthma-related allowed charges per patient per day	\$25.40	\$18.81	0.3566
Asthma-related ED or IP claims per patient per day	0.004	0.002	0.0433#
Asthma-related ED or IP allowed charges per patient per day	\$16.21	\$6.46	0.0133#
All-cause claims			
Follow-up days			
Mean $\pm$ SD	244.2 $\pm$ 214.3	485.8 $\pm$ 214.3	<0.0001
Median	173	557	<0.0001
Range	0–717	13–730	
Beneficiaries with no claims, no. (%)	1 (0.99)	0	
All-cause ED or IP claims			
Follow-up days			
Mean $\pm$ SD	244.2 $\pm$ 214.3	429.3 $\pm$ 262.5	<0.0001
Median	173	526	<0.0001
Range	0–717	0–730	
Beneficiaries with no claims, no. (%)	1 (0.99)	18 (17.82)	

FeNO = Fractional exhaled nitric oxide; ED = emergency department; IP = inpatient; SD = standard deviation.

* The paired *t*-test was used for the pre-FeNO and post-FeNO comparison, with a significance level of 0.05.

Statistically significant at $\alpha = 0.05$.

exacerbations, which occurred at longer intervals compared with the pre-FeNO time period (Table 2). The Kaplan-Meier survival curve (Fig. 3) demonstrated a trend (although not statistically significant) for a reduced exacerbation rate (pre-FeNO time period, 59.4%; post-FeNO time period, 57.6%) and increased time to exacerbation (mean days to ED or IP service: pre-FeNO time period, 327.7 days; post-FeNO time period, 439.9 days) ($p = 0.097$).

DISCUSSION

Available Centers for Disease Control and Prevention data indicate that the direct economic impact of asthma exceeds \$38 billion annually nationwide and that having asthma is associated with 78% higher incremental medical costs per patient per year.⁹ Asthma guidelines recommend periodic assessment of impairment and risk factors to prevent exacerbations, which are the primary cause of increased hospitalizations, health care utilization, and expenditures.^{17,18} According to recent Cochrane meta-analysis data, FeNO monitoring is associated with a 40–50% reduction in the risk of exacerbations;^{4,5} accordingly, cost modeling of

these data indicated the potential for significant cost savings with FeNO use.¹⁹ In the current study, when using a case-crossover design, we verified this potential cost savings within a real-world data base of Medicare recipients, which demonstrated that both asthma-related claims and asthma-related charges per patient per day were statistically significantly lower after FeNO use than before FeNO use.

The current study also found a large percentage of patients with asthma who were ages <65 years in this Medicare population, which indicated that asthma was associated with other chronic illnesses that increase disability among working-age adults. The mean Charlson Comorbidity Index (CCI) score of 3.2 was relatively higher than the documented CCI of 0.9 among asthma patients under age 65,²⁰ and 1.47 for Medicare Advantage participants with severe asthma,²¹ but close to a CCI score of 2.6 in a COPD combined with asthma Medicare population,²² which indicates that these patients had substantial comorbidities in addition to asthma, all of which generated a large economic burden.

Emerging research continues to confirm the value of FeNO monitoring as an optimal approach to managing

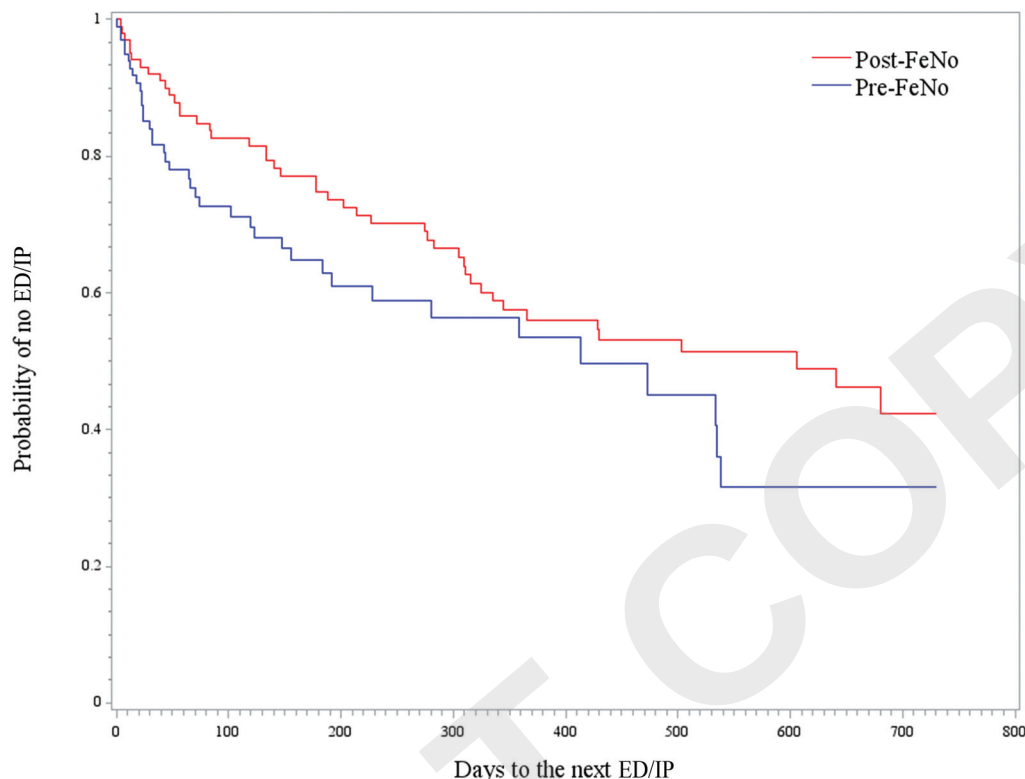


Figure 3. Kaplan-Meier curves comparison between pre-FeNO and post-FeNO time periods. FeNO = Fractional exhaled nitric oxide.

patients with chronic asthma. Although alternative diagnostic methodologies exist, a substantial base of clinical literature finds that the health economic value of FeNO monitoring is complemented by clinical benefit.^{3,6,10} In addition, these individual study results are supplemented by endorsements from the American Thoracic Society and the British Thoracic Society and recent favorable evidence reviews from the Agency for Health Care Research and Quality and the National Institute for Health and Care Excellence (United Kingdom), which recommend FeNO integration into standard treatment and management algorithms.^{11–14}

The study design was of the utmost importance when determining how best to assess any influence of an intervention such as FeNO on asthma exacerbations. We considered using a case-cohort analysis but were concerned that there may be associated confounding and/or unmeasurable factors that would result in biases that would undermine the integrity of the study. Because of the matched nature of a case-cross-over study design, all time-invariant confounders were automatically corrected for without having to measure the confounders.²³ Case-control analyses are especially relevant in cases such as the current study in which there is an acute “exposure” (FeNO) and an outcome defined by an acute event (asthma exacerbation).²⁴

When using a similar methodology, Sadatsafavi et al found an increased 30-day risk of asthma-related hospital readmission after an episode of asthma-related

hospitalization. Interestingly, similar to our study, in which non-asthma-related events (“all claims”) were less likely to be as highly statistically significant as asthma-related events, there was no correlation of readmission after an episode of hospitalization not related to asthma.²⁴ In addition, the ED and IP claims analyses (when using the ED or hospital as the place of service), in general, were more favorable to FeNO than were the “all claims” analyses, which included office visits (less-sick beneficiaries). This made sense if one considers that they are the more difficult asthma cases (in terms of place of treatment), regardless of comorbidities or other reasons why beneficiaries would be hospitalized, that account for FeNO use resulting in positive outcomes, hence, our concentration on beneficiaries with frequent moderate-to-severe exacerbations in the study.

As mentioned in the results, the post-FeNO group’s follow-up period was longer, on average, than the pre-FeNO group’s follow-up period. In addition, fewer beneficiaries had asthma-related claims in the post-FeNO group. Analysis of the data indicated that this group experienced fewer asthma-related exacerbations, which occurred at longer intervals, in the post-FeNO time period than during the pre-FeNO time period.

There were a few limitations to the study. All retrospective analyses have biases, such as those related to misclassification (identifying subjects as being exposed

when they are not or vice versa), nonrandomization, and so forth.^{25–28} However, eligibility was controlled for and multiple sensitivity analyses were conducted to examine exposure time frames and cost drivers. Nonetheless, the current analyses seemed robust, and the use of FeNO seemed to reduce resource utilization and costs in beneficiaries with asthma and Medicare insurance. In addition, in recent years, patients with an ICD-9-CM code of 493.2 (asthmatic bronchitis) have been noted to have characteristics more similar to patients with COPD than those with only asthma.^{29,30}

Because 39% of the patients in the current study had an ICD-9-CM diagnosis code of 493.2 at their index date and FeNO is less predictive of responsiveness in patients with COPD,^{10,31,32} this would bias the study against FeNO. Also, it was unfortunate that more patients could not be identified who were monitored with FeNO. This relatively small number of patients did not allow us to stratify patients according to type of asthma care providers (primary care versus specialist), which could have had an impact on how FeNO was used. Nonetheless, although small patient numbers may have prevented some of the differences from being statistically significant, asthma-related claims and charges were shown to be lower after FeNO use than before FeNO use in this cohort of Medicare beneficiaries, concordant with other published analyses.⁷ Because this was an observational study, only an association can be identified, rather than a causal relationship, between FeNO use and lower asthma expenses.

CONCLUSION

Among a Medicare cohort of beneficiaries with asthma who had a history of exacerbations, monitoring FeNO was associated with a significant reduction in health care costs. This finding coincided with several recent independent studies, which supported the role of FeNO as a cost-effective diagnostic tool with clinical utility for managing asthma exacerbations.

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