Rapid Lung Function Decline in Smokers Is a Risk Factor for COPD and Is Attenuated by Angiotensin-Converting Enzyme Inhibitor Use

Hans Petersen, MS; Akshay Sood, MD, MPH, FCCP; Paula M. Meek, PhD, RN; Xian Shen, MS; Yan Cheng, MS; Steven A. Belinsky, PhD; Caroline A. Owen, MD, PhD; George Washko, MD; Victor Pinto-Plata, MD, FCCP; Emer Kelly, MD; Bartolome Celli, MD, FCCP; and Yohannes Tesfayigzi, PhD

Objective: Cigarette smoking is the most important risk factor for COPD in the United States. Host factors that influence the rapid rate of FEV₁ decline in smokers and how decline rate influences risk for developing COPD are unknown. The aim of this study was to characterize the rate of FEV₁ decline in ever smokers, compare the risk of incident COPD between those with rapid decline and others, and determine the effect of selected drugs on rapid decline.

Methods: A total of 1,170 eligible ever smokers from the longitudinal Lovelace Smokers Cohort with repeat spirometry tests over a minimum follow-up period of 3 years (mean follow-up, 5.9 years) were examined, including 809 ever smokers without a spirometric abnormality at baseline. Longitudinal absolute decline in postbronchodilator FEV₁ from the slope of the spirometric values over all examinations was annualized and classified as rapid (≥ 30 mL/y), normal (0-29.9 mL/y), or no (> 0 mL/y) decline. Logistic regression and Kaplan-Meier survival curves were used for the analysis.

Results: Approximately 32% of ever smokers exhibited rapid decline. Among ever smokers without a baseline spirometric abnormality, rapid decline was associated with an increased risk for incident COPD (OR, 1.88; $P = .003$). The use of angiotensin-converting enzyme (ACE) inhibitors at baseline examination was protective against rapid decline, particularly among those with comorbid cardiovascular disease, hypertension, or diabetes (ORs 0.48, 0.48, and 0.12, respectively; $P \leq .02$ for all analyses).

Conclusions: Ever smokers with a rapid decline in FEV₁ are at higher risk for COPD. Use of ACE inhibitors by smokers may protect against this rapid decline and the progression to COPD.

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Abbreviations: ACE = angiotensin-converting enzyme; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LSC = Lovelace Smokers Cohort

COPD is characterized by poorly reversible airflow obstruction secondary to an abnormal host response to noxious environmental stimuli. Cigarette smoking is the most important risk factor for COPD in the United States, and COPD is currently an important cause of mortality in the United States and the world.¹ Population studies have reported a low value of FEV₁ to be an independent predictor for all-cause mortality²⁻⁴ and mortality from respiratory and cardiovascular causes and from several malignancies.⁵⁻⁹ A low FEV₁ value is also central to the diagnosis, severity rating, and prognosis of COPD.¹⁰

From the seminal work by Fletcher and Peto,¹¹ it was assumed that rapid decline in lung function resulted in the development of COPD. Furthermore, the rate of decline was assumed to be uniformly progressive

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and was analyzed as such in most studies addressing lung function change in COPD. Several more studies, however, have challenged this notion.¹²⁻¹⁶ In these studies, lung function in most subjects followed for

3 to 10 years showed little decline or actually improved over time, with rapid decline occurring in a minority.¹³⁻¹⁶ The reasons for this variation are not fully understood, but these studies suggested that a higher baseline FEV₁, a lower BMI, and a greater degree of emphysema on CT scan are related to rapid decline; no medications were related to lung function change. These studies established the presence of three distinct phenotypic populations among patients with COPD: rapid decliners, normal decliners, and nondecliners. Whether the same patterns are seen in ever smokers at risk for COPD has not been studied.

Although one in four individuals aged 80 years is likely to receive a diagnosis of and medical attention for COPD during his or her lifetime,¹⁷ the relative risk for developing COPD among ever smokers with different FEV₁ decline patterns has not been reported. Of note, host factors that modulate the rate of FEV₁ decline in ever smokers are not known.

With use of the New Mexico-based longitudinal Lovelace Smokers Cohort (LSC), the present study examined three hypotheses. First, ever smokers demonstrate similar heterogeneity in FEV₁ change as patients with COPD. Second, the incidence rate of COPD in ever smokers is higher in rapid decliners than in normal or nondecliners. Third, select factors (including medications) affect FEV₁ decline over time. This knowledge is important because it would help with determining the incidence rate of COPD in at-risk smokers and establishing a novel approach to identify at-risk smokers on the basis of their pre-morbid FEV₁ rate of decline. In addition, given the limited treatment options once the disease is established, novel therapeutic approaches aimed at high-risk smokers before COPD becomes established may alter the natural history of this disease.

Study Population

The LSC is a well-characterized cohort of current and former smokers in New Mexico. Recruitment, inclusion, and exclusion criteria have been described previously.^{18,19} Regular follow-up examination visits occur at 18-month intervals for anthropometrics, spirometry, self-reported prescription drug use, detailed smoking and environmental exposure history, and induced sputum.^{20,21} More than 95% of all spirometry tests met standard criteria as described in e-Appendix 1. The LSC disproportionately enrolled female ever smokers because the disease prevalence from 1998 onward is significantly higher among women than among men²² and because women are underrepresented in most US COPD studies.²³ This study was approved by the Western Institutional Review Board (Olympia, Washington; #20031684), and all subjects signed informed consent for their participation.

Inclusion and Exclusion Criteria

LSC participants who performed multiple spirometry tests with a minimum interval observation period of 36 months between the baseline and the final examinations were included. This minimum period was considered necessary to obtain stable FEV₁ decline rates.^{14,24,25} Excluded from the primary analyses were individuals with prevalent COPD GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage I or greater (defined as post-bronchodilator FEV₁/FVC < 70) at the baseline examination. We performed sensitivity analyses in the subset of subjects without a self-reported history of asthma. Among the 2,273 participants enrolled in LSC between 2001 and 2011, 809 and 1,170 eligible subjects met the inclusion criteria for the primary and secondary analyses, respectively (Figs 1A, 1B).

Study Measures

Outcome and predictor measures were obtained in all participants at all visits. Information on demographics, cigarette smoking, prescription drug use, respiratory diseases, BMI, and quality of life was obtained by self-report from all participants as described.^{26,27}

Predictor and Outcome Variables

The primary predictor (also the secondary outcome) variable was rapid decline in absolute postbronchodilator FEV₁ from spirometry data as described in detail^{28,29} (e-Appendix 1). Independent auditing revealed that > 95% of all tests met American Thoracic Society criteria.

Decline Categories

Change in postbronchodilator FEV₁ decline was based on the slope defined by the first and last data points over all examination visits. Annualized FEV₁ decline was classified into three categories, as previously reported.^{14,24} Thus, rapid decline was defined by an annualized average FEV₁ loss of ≥ 30 mL/y, normal decline by an annualized average FEV₁ loss of 0 to 29.9 mL/y, and no decline by an annualized average improvement in FEV₁ (Table 1).

In a sensitivity analysis, two alternate ternary classifications of FEV₁ decline were also used. The first classification was based on tertiles of annualized percent decline (> 1.51% loss, 1.51% loss to 0.11% improvement, and > 0.11% improvement). The second was based on a more extreme definition of rapid decline (annualized absolute loss of FEV₁ of > 40 mL/y, 20-40 mL/y, and < 20 mL/y) (e-Tables 1, 2).

The primary outcome variable, tested in 809 ever smokers without prevalent COPD at baseline, was incident COPD as defined

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Affiliations: From the COPD and Lung Cancer Programs (Mr Petersen and Drs Belinsky and Tesfaigzi), Lovelace Respiratory Research Institute, Albuquerque, NM; Department of Medicine (Dr Sood and Mss Shen and Cheng), University of New Mexico, Albuquerque, NM; University of Colorado-Denver (Dr Meek), Denver, CO; and Pulmonary Division (Drs Owen, Washko, Pinto-Plata, Kelly, and Celli), Brigham and Women's Hospital, Boston, MA.

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Correspondence to: Hans Petersen, MS, Lovelace Respiratory Research Institute, 2425 Ridgecrest Dr SE, Albuquerque, NM 87108; e-mail: hpeterse@lrri.org

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FIGURE 1. A, Study profile. B, An overview of the analytic approach.

by the GOLD criteria.³⁰ The secondary predictor variables were demographics and non-COPD drugs used to treat hypertension, cardiovascular disease, and diabetes mellitus comorbidities at baseline, including statins, β -blockers, calcium channel blockers, angiotensin II receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, oral hypoglycemic agents, and insulin. Information on prescription and nonprescription drug use was obtained from self-report.

Covariates

Covariates considered in the adjusted models were sex, age, pack-years of smoking, current smoking, Hispanic ethnicity, BMI, baseline COPD, hypertension, diabetes, and cardiovascular disease. COPD was defined spirometrically on the basis of GOLD criteria.³⁰

Statistical Analysis

Summary statistics, including mean $\pm$ SD, median, and interquartile range for continuous variables and proportion for categorical variables, were obtained. Jonckheere-Terpstra tests for ordered alternatives and general linear models with multivariate analysis of variance tests were used to compare frequencies and means, respectively, across the ordered categories. Logistic regression models were used for both primary and secondary analyses. In addition, univariate primary analysis used Kaplan-Meier survival curves. All analyses were conducted with SAS, version 9.2

(SAS Institute, Inc) statistical software. A two-sided $P < .05$ was considered statistically significant.

RESULTS

From the total cohort of 1,170 eligible subjects, 379 (32%) were categorized as rapid decliners, 397 (34%) were normal decliners, and 394 (34%) were nondecliners (Table 1). Thus, the three categories of longitudinal FEV₁ decline patterns were evenly distributed among smokers. No significant differences were observed for chronic bronchitis or the scores based on the St. George's Respiratory Questionnaire among the three decline categories.

Primary Analysis

The adjusted multivariable analyses showed that rapid decline status was a significant predictor for incident COPD among ever smokers without prevalent obstructive and nonobstructive lung disease at baseline examination (OR, 1.88; 95% CI, 1.24-2.83; $P = .003$) (Table 2). Rapid decline in lung function as $> 1.5\%$ or > 40 mL/y showed similar results (e-Tables 1, 2). In addition, similar results were seen by Kaplan-Meier survival analysis comparing subjects in the rapid decline category with those in other categories and with a failure event defined as incident COPD (Fig 2).

Secondary Analysis

A univariate cross-sectional analysis demonstrated that older age and higher baseline FEV₁ percent were associated with the rapid FEV₁ decline category compared with other FEV₁ decline categories ($P = .045$ and $< .001$, respectively) (Table 1). On the other hand, Hispanic ethnicity, BMI, and diabetes mellitus were inversely associated with the rapid FEV₁ decline category ($P \leq .01$ for all analyses). Neither current smoking nor pack-years of smoking at baseline were significantly associated. Additionally, sex and the presence of COPD, hypertension, or cardiovascular disease at baseline were not associated. Similar results were noted when the analysis was limited to the 809 subjects eligible for the primary analysis.

ACE Inhibitor Protection

Of all the medications evaluated, only ACE inhibitor use at baseline was inversely associated with rapid FEV₁ decline category ($P = .04$) (Table 3). The potential protective effect of ACE inhibitor use on rapid decline was further investigated in multivariable logistic regression analyses, with normal decliners and nondecliners combined as the reference group. Results from these multivariable models confirmed that ACE

Table 1—Univariate Analysis of the Cross-sectional Associations Between Subject Characteristics and Categories of FEV₁ Decline Among Smokers (N = 1,170)

Characteristic	All Subjects (N = 1,170)	Rapid Decliners (n = 379)	Normal Decliners (n = 397)	Nondecliners (n = 394)	P Value ^a
Follow-up period, y	5.9 ± 2.0	5.5 ± 2.0	6.6 ± 1.9	5.6 ± 1.9	.62
Male sex	19.7	23.0	14.6	21.6	.67
Age, y	56.3 ± 9.4	57.0 ± 9.4	56.5 ± 9.3	55.6 ± 9.4	.045
Hispanic ethnicity	16.4	14.2	14.1	20.8	.013
BMI, kg/m ²	28.2 ± 6.1	27.5 ± 5.5	28.0 ± 6.2	29.2 ± 6.6	<.001
History of hypertension or cardiovascular disease ^b	31.5	33.0	30.0	31.7	.72
History of diabetes mellitus	6.8	5.3	4.3	10.7	.003
Smoking, pack-y	39.0 ± 20.1	40.4 ± 21.6	38.7 ± 19.5	38.0 ± 19.2	.10
Current smoking	50.1	50.1	47.9	54.3	.24
FEV ₁ , % predicted	88.3 ± 17.6	91.2 ± 18.9	89.4 ± 15.6	84.2 ± 17.7	<.001
Annualized rate of absolute change in FEV ₁ , mL/y	−13.5 ± 51.8	−64.7 ± 37.1	−14.2 ± 8.7	36.6 ± 39.3	<.001
Spirometrically defined COPD ^c	25.4	26.1	23.2	26.9	.79
Baseline CMH	29.7	32.7	28.2	28.2	.17
SGRQ score					
Total	19.7	20.2	17.9	21.0	.5
Symptom	28.4	28.3	27.2	29.7	.35
Impacts	10.3	10.8	9.0	11.2	.64
Activity	29.0	29.7	26.5	30.7	.55

Data are presented as mean ± SD or No. (%). Unless otherwise indicated, the data were obtained at the baseline visit; spirometric values were postbronchodilator. The analysis was restricted to subjects with three or more visits. Rapid, normal, and nondecliner categories were defined by an annualized absolute decline of postbronchodilator FEV₁ ≥ 30 mL/y, 0–29.9 mL/y, and improvement in lung function, respectively. Similar results were obtained when these categories of decline were defined by tertiles of annualized percent decline of > 1.51% loss; 1.51% loss to 0.11% improvement; and > 0.11% improvement, respectively. Similar results were also obtained when these categories of decline were defined by an annualized absolute decline of > 40, 20–40, and < 20 mL/y, respectively. CMH = chronic mucus hypersecretion (ie, chronic bronchitis); SGRQ = St. George's Respiratory Questionnaire.

^aP values for comparison across three categories for frequencies are based on Jonckheere-Terpstra test for ordered alternatives and for means based on general linear models with multivariate analysis of variance.

^bCardiovascular disease was defined by the presence of self-reported hypertension, myocardial infarction, or congestive heart failure.

^cCOPD was defined by postbronchodilator FEV₁/FVC < 70% at baseline examination.

inhibitor use at baseline was protective against rapid decline (OR, 0.55; 95% CI, 0.33–0.93; *P* = .03) (Table 4). This association was independent of hypertension (Table 4) and diabetes mellitus in separate models (data not shown). Similarly, ACE inhibitor use at baseline was protective against incident COPD (OR, 0.34; 95% CI, 0.15–0.78; *P* = .01) (e-Table 3). In the adjusted models, male sex was also associated with a greater likelihood of rapid decline, whereas high BMI at baseline was protective. Hispanic ethnicity, however, was no longer a statistically significant predictor.

The multivariable analyses were repeated after stratifying all subjects by the presence of comorbidities that indicated ACE inhibitor use for diabetes mellitus, hypertension, and cardiovascular disease at the baseline examination. The association between ACE inhibitor use at baseline and rapid FEV₁ decline was possibly stronger among participants with these comorbidities (Table 5), although the interaction terms between ACE inhibitor use and comorbidity on FEV₁ decline category were not statistically significant for any analyses (*P* = .10, .18, and .18, respectively). In alternate sensitivity analyses, univariate and multivariable models showed similar results when the pre-

viously defined alternative definitions of the rapid decline category were studied (data not shown). An additional sensitivity analysis in the subset of participants without a self-reported history of asthma (e-Tables 4–6) showed largely similar results.

DISCUSSION

This longitudinal observational study presents three major findings. First, it shows that the rate of FEV₁ decline is not uniform among ever smokers, and rapid decline is seen in a minority of subjects at risk. Second, rapid decline determined over a minimum of 36 months is a clinically significant biomarker because it predicts the future development of COPD among ever smokers without baseline lung disease. This finding was replicated for different definitions of decline and for a subset of subjects without a history of asthma. Third, the use of ACE inhibitors among ever smokers may be protective against rapid FEV₁ decline.

The FEV₁ value is useful in the diagnosis and staging of COPD,¹⁰ and a low value is a predictor for all-cause and respiratory mortality.^{3,13} Studies have documented

Table 2—Multivariable Analyses of the Predictors for Incident COPD Among Smokers (n = 809)

Characteristic	OR (95% CI)	P Value
Male sex	0.98 (0.56-1.69)	.93
Age	1.06 (1.03-1.08)	< .001
Hispanic ethnicity	0.55 (0.30-0.99)	.046
BMI	0.92 (0.88-0.95)	< .001
Pack-y of smoking at baseline	1.02 (1.01-1.03)	.003
Current smoking status	1.21 (0.79-1.83)	.38
Baseline FEV ₁ % predicted	0.94 (0.92-0.96)	< .001
Rapid decline	1.88 (1.24-2.83)	.003

Unless otherwise indicated, the data were obtained at the baseline visit; spirometric values were postbronchodilator. The analysis was restricted to subjects with three or more visits without prevalent obstructive and nonobstructive spirometric abnormality at baseline examination. The rapid decline category was defined by an annualized absolute decline of postbronchodilator FEV₁ of ≥ 30 mL/y. Similar results were obtained when the rapid decline category was defined by the highest tertile of annualized percent decline of $> 1.51\%$ loss or by an annualized absolute decline of > 40 mL/y. Incident COPD was defined by the new development of postbronchodilator FEV₁/FVC $< 70\%$ at baseline examination (n = 151 subjects). Unadjusted analysis showed that rapid decline was associated with an OR of 1.57 (95% CI, 1.09-2.26; $P = .02$).

that the rate of FEV₁ decline varies widely in patients with COPD.^{13,14,16} In the current study, we demonstrate that the same is true for subjects at risk for COPD, whereby about one-third of ever smokers have a rapid FEV₁ decline, whereas another one-third may actually have improved lung function over time. Although in general the reported presence of three groups (rapid, normal, and nondecliners) among ever smokers in this cohort is similar to that reported for patients with COPD,^{13,16} the actual proportion of each group is not, with the proportion of nondecliners among ever smokers being substantially higher than that reported in studies of patients with COPD.

Perhaps the most important practical finding in the current study is that a rapid FEV₁ decline pattern among at-risk ever smokers appears to be an intermediate biomarker that signals an increased risk for

developing clinical COPD. On the surface, this finding appears to be a tautology, especially because both COPD status and rapid decline status depend on FEV₁ levels. To our knowledge, however, rapid FEV₁ decline pattern as a risk factor for incident COPD has not been previously established, the risk has not been estimated in a cohort of otherwise healthy ever smokers, and the actual time and number of tests required to establish the pattern of FEV₁ change has never been studied. This finding has clinical implications such that rapid decliners can receive intense pharmacologic and nonpharmacologic interventions that may mitigate their risk for clinically relevant COPD. Furthermore, associated biomarkers that predict rapid decline susceptibility among smokers could be used to effectively shorten the time required to establish FEV₁ decline status and to detect progression or response to therapy. The data also suggest that ever smokers should have repeated spirometry tests for a minimum period of 3 years to establish their pattern of FEV₁ decline. We propose that patients demonstrating rapid decline on these tests should receive intense primary and secondary prevention based on the assumption that their rate of decline can be altered, an assumption that is true for smoking cessation³¹ and possibly for pharmacotherapy.³²

Studying the effect of non-COPD medications on decline pattern was also possible in the present cohort because there was careful supervision of the drugs taken by the subjects. The finding that ACE inhibitors but not other drugs may be protective against rapid FEV₁ decline as well as incident COPD among smokers, particularly for those with comorbid conditions, is both interesting and hypothesis generating. That ACE inhibitors may play a protective role in the course of COPD has been suggested by several database reviews,^{33,34} but its relationship in prospective studies among ever smokers has been inadequately explored. One possible explanation may be that these agents decrease pulmonary vascular congestion from left ventricular dysfunction or ameliorate pulmonary artery hypertension or pulmonary fibrosis and thereby improve the associated restrictive defect. However, this explanation is unlikely because cardiovascular disease at baseline was uniformly distributed among the decline categories. Furthermore, pulmonary arterial hypertension in COPD is usually a complication of severe stages, and only about one-fourth of the subjects met the GOLD definition of COPD, primarily of mild severity (Table 1). As well, none of the subjects reported an established diagnosis of pulmonary fibrosis, and this disease is relatively uncommon. We noted with interest that ACE inhibitor use is associated with a stronger protective effect on decline in FEV₁ than on decline in FVC (data not shown), suggesting that ACE inhibitors were more likely to be

FIGURE 2. Kaplan-Meier survival curve showing incident COPD by rapid decline status. The numbers of NDs and RDs at the various months of follow-up time are indicated. ND = nondecliner; RD = rapid decliner.

Table 3—Univariate Analyses of the Association Between Use of Non-COPD Medications at Baseline Examination Visit and Categories of FEV₁ Decline Among Smokers (N = 1,170)

Use of Non-COPD Medications at Baseline Examination	All Subjects (N = 1,170)	Rapid Decliners (n = 379)	Normal Decliners (n = 397)	Nondecliners (n = 394)	P Value ^a
ACE inhibitors (n = 116)	9.9	7.4	10.3	11.9	.04
Angiotensin receptor blockers (n = 37)	3.2	4.2	1.8	3.6	.62
β-Blockers (n = 53)	4.5	5.0	5.3	3.3	.25
Calcium channel blockers (n = 47)	4.0	4.7	3.8	3.6	.40
Statins (n = 246)	21.0	19.8	19.9	23.4	.22
Insulin (n = 2)	0.3	0.6	0.0	0.0	.10
Oral hyperglycemic agents (n = 16)	2.0	1.6	2.6	2.3	.53

Data are presented as %. Spirometric values were postbronchodilator. The analysis was restricted to subjects with three or more visits. Rapid, normal, and nondecliner categories were defined by an annualized absolute decline of postbronchodilator FEV₁ ≥ 30 mL/y; 0–29.9 mL/y, and improvement in lung function, respectively. Similar results were obtained when these categories of decline were defined by tertiles of annualized percent decline of > 1.51% loss, 1.51% loss to 0.11% improvement, and > 0.11% improvement, respectively. Similar results were also obtained when these categories of decline were defined by an annualized absolute decline of > 40, 20–40, and < 20 mL/y, respectively. ACE = angiotensin-converting enzyme.

^aP values for comparison across three categories for frequencies are based on Jonckheere-Terpstra test for ordered alternatives.

effective in preventing the development of obstructive rather than nonobstructive lung diseases among smokers.

We believe that a more likely explanation for the protective ACE inhibitor effect relates to its antiinflammatory effects. Angiotensin II, known primarily for its physiologic role in modulating BP, intravascular volume, and sodium balance, is also a proinflammatory molecule.³⁵ Angiotensin II is cleaved from angiotensin I by the action of the ACE, which is present in high concentrations in lung tissue. Although the physiologic role of angiotensin II in the lung is not well established, it has proinflammatory effects that may increase the recruitment of inflammatory and immune cells into the lung and thereby contribute to lung function decline in cigarette smokers.³⁶ Blocking

angiotensin II effects attenuates cigarette smoke-induced lung injury and rescues lung architecture in mice.³⁷ The present finding may also be related to the mitigation of progressive endothelial damage that could result from inflammation. It is known that even in subjects with mild COPD, there is pulmonary vascular inflammatory infiltration and remodeling.³⁸ Study findings from our group¹³ showed that about 30% of patients with COPD exhibit microalbuminuria, a marker for systemic vascular endothelial dysfunction. It is possible that the administration of ACE inhibitors to subjects with a clinical indication for its use may have had an unexpected beneficial effect on vascular endothelial dysfunction and lung parenchymal destruction. In addition to the ACE inhibitor effect, we observed an association of lower values of BMI and older age with rapid FEV₁ decline in ever smokers; both factors have been previously described to be similarly associated in patients with COPD.^{13,16}

The strengths of the present study include its prospective nature, the use of postbronchodilator spirometry to define decline in FEV₁, strict adherence to American Thoracic Society guidelines in the performance of spirometry,²⁸ and a longitudinal study design. We also recognize several limitations that merit comments. First, we did not exclude α₁-antitrypsin deficiency, the severe form of which accounts for only 1% to 2% of cases of COPD³⁹ and is unlikely to have influenced these results. Second, it is difficult to account for factors such as type of cigarettes, depth of inhalation, or number of puffs per cigarette, which may have differed among the groups. However, there is no reason to expect that these variables would be differentially distributed between the smokers taking and not taking ACE inhibitors. Furthermore, because the participants in the LSC were recruited from the community through newspaper and radio advertisements, the study cohort may not be representative of

Table 4—Multivariable Analyses of the Predictors for Rapid Decline in FEV₁ Among Smokers (N = 1,170)

Characteristic	OR (95% CI)	P Value
Male sex	1.39 (1.02–1.89)	.04
Age	1.01 (0.99–1.02)	.29
Hispanic ethnicity	0.84 (0.59–1.20)	.34
BMI	0.97 (0.95–0.99)	.003
Pack-years of smoking at baseline	1.00 (1.00–1.01)	.31
Current smoking status	1.01 (0.77–1.32)	.97
History of hypertension ^a	1.27 (0.94–1.70)	.12
Baseline COPD	0.85 (0.63–1.16)	.32
Baseline ACE inhibitor use	0.55 (0.33–0.93)	.03

Unless otherwise indicated, data were obtained at the baseline visit; spirometric values were postbronchodilator. The analysis was restricted to subjects with three or more visits. The rapid decline category was defined by an annualized absolute decline of postbronchodilator FEV₁ ≥ 30 mL/y. Similar results were obtained when the rapid decline category was defined by the highest tertile of annualized percent decline of > 1.51% loss or by an annualized absolute decline of > 40 mL/y. See Table 3 legend for expansion of abbreviation.

^aSubstitution of the hypertension variable with either diabetes mellitus or cardiovascular disease variables did not materially change the results.

Table 5—Multivariable Analyses of the Association Between Baseline ACE Inhibitor Use and Rapid Decline in FEV₁ Among Smokers, Stratified by Systemic Comorbidity at Baseline Examination

Comorbid Disease Stratification	OR (95% CI)	P Value
With cardiovascular disease or hypertension (n = 85 of 369)	0.48 (0.27-0.85)	.01
Without cardiovascular disease or hypertension (n = 11 of 801)	1.33 (0.37-4.78)	.66
With diabetes mellitus (n = 22 of 79)	0.12 (0.02-0.68)	.02
Without diabetes mellitus (n = 74 of 1,091)	0.76 (0.44-1.30)	.31

Rapid decline was defined by an annualized absolute decline of postbronchodilator FEV₁ $\geq$ 30 mL/y. Similar results were obtained when rapid decline was defined by the highest tertile of annualized percent decline of $>$ 1.51% loss or by an annualized absolute decline of $>$ 40 mL/y. Analysis was restricted to subjects with three or more visits. Models were adjusted for age, sex, ethnicity, baseline BMI, pack-y smoking history, baseline smoking status, and baseline COPD. Cardiovascular disease was defined by the presence or history of hypertension, congestive heart failure, or myocardial infarction at the baseline examination. Similarly, hypertension and diabetes mellitus are self-reported at the baseline examination. A similar analysis was performed with a more encompassing definition for cardiovascular disease (self-report of either hypertension, myocardial infarction, congestive heart failure, arrhythmia, coronary artery bypass procedure, valvular heart disease, or rheumatic heart disease at baseline examination visit), which yielded nearly identical results to the limited definition of cardiovascular disease. In the nonstratified adjusted analyses, there were no significant interactions between ACE inhibitor use and either diabetes mellitus, cardiovascular disease, or hypertension on absolute decline in FEV₁ (interaction $P = .10, .18,$ and $.18$, respectively). See Table 3 legend for expansion of abbreviation.

all smokers in New Mexico and in other parts of the United States. However, smoking behaviors in this study are consistent with those observed in representative state surveys of smokers.⁴⁰ Third, we recognize the variability inherent in longitudinal studies of FEV₁ decline. We have minimized this variability by using postbronchodilator FEV₁ values, longer observation periods, and an upstream cohort of relatively healthy ever smokers recruited from the community compared with other studies of FEV₁ decline. Fourth, it could be argued that the present results may be influenced by the cohort comprising primarily women given that another cohort has shown that women demonstrate a greater absolute FEV₁ decline than men.⁴¹ However, this explanation is unlikely because male smokers in this study were more (not less) likely than female smokers to experience a greater decline in FEV₁ (Table 4). In addition, no sex differences have been found in such studies as Towards a Revolution in COPD Health (TORCH), Understanding Potential Long-Term Impacts on Function With Tiotropium (UPLIFT), and Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE).^{25,32,42} Finally, we cannot rule out treatment selection bias resulting from nonrandomized groups differing in observed and unobserved characteristics. An adequate test of this hypothesis can likely only be accomplished by conducting randomized controlled clinical trials.

In summary, this study shows that rapid FEV₁ decline is present in a minority of smokers but leads to the development of incident COPD. Thus, identification of rapid decliners over a period of 36 months may help with the implementation of primary and secondary prevention strategies against COPD development. The finding of ACE inhibitor use being protective against rapid FEV₁ decline among smokers needs to be confirmed by future randomized placebo-

controlled blinded clinical trials and may open up newer preventive and therapeutic strategies for COPD.

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Mr Petersen: contributed to the data acquisition, analysis, and interpretation and drafting, critical review for important intellectual content, and final approval of the manuscript.

Dr Sood: contributed to the study conception and design; interpretation of data; and drafting, critical review for important intellectual content, and final approval of the manuscript.

Dr Meek: contributed to the study conception and design; interpretation of data; and drafting, critical review for important intellectual content, and final approval of the manuscript.

Ms Shen: contributed to the data acquisition, analysis, and interpretation and drafting, critical review for important intellectual content, and final approval of the manuscript.

Ms Cheng: contributed to the data acquisition, analysis, and interpretation and drafting, critical review for important intellectual content, and final approval of the manuscript.

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