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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S<sup>®</sup>



## Statins in COPD A Systematic Review

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**Background:** The 3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitors (*ie*, statins) are widely used for the treatment of patients with hypercholesterolemia and cardiovascular disease. Emerging evidence suggests a beneficial effect of statins on the morbidity and mortality of patients with COPD. The objective of this study was to perform a systematic review of the literature evaluating the effect of statin therapy on outcomes in patients with COPD.

**Methods:** Medline, Excerpta Medica Database, PapersFirst, and the Cochrane collaboration and Cochrane Register of controlled trials were searched. Randomized controlled trials (RCTs), observational cohort studies, case-control studies, and population-based analyses were considered for inclusion.

**Results:** Nine studies were identified for review (four retrospective cohorts, one nested case-control study of a retrospective cohort, one retrospective cohort and case series, two population-based analyses, and one RCT). All studies showed a benefit from statin therapy for various outcomes in COPD patients, including the number of COPD exacerbations ( $n = 3$ ), the number of and time to COPD-related intubations ( $n = 1$ ), pulmonary function (*eg*, FEV<sub>1</sub> and FVC) [ $n = 1$ ], exercise capacity ( $n = 1$ ), mortality from COPD ( $n = 2$ ), and all-cause mortality ( $n = 3$ ). No studies describing a negative or neutral effect from statin therapy on outcomes in COPD patients were identified.

**Conclusions:** The current literature collectively suggests that statins may have a beneficial role in the treatment of COPD. However, the majority of published studies have inherent methodological limitations of retrospective studies and population-based analyses. There is a need for prospective interventional trials designed specifically to assess the impact of statins on clinically relevant outcomes in COPD. (CHEST 2009; 136:734–743)

**Abbreviations:** adj = adjusted; CI = confidence interval; CRP = C-reactive protein; CV = cardiovascular; HR = hazard ratio; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk

COPD is an inflammatory disease of the lungs characterized by progressive bronchial airflow limitation.<sup>1</sup> Due to the resulting impairment in lung function, COPD leads to a decline in functional capacity, frequent hospitalizations, and early death.<sup>2</sup>

The mortality rate from COPD has increased since the 1990s, and it is projected to become the third most common cause of death in Western countries by the year 2020.<sup>3</sup> Currently, COPD is the fourth most common cause of death in the United States and is responsible for > 100,000 deaths annually.<sup>2</sup> COPD-related health-care costs remain high due to frequent clinic visits, hospitalizations due to exacer-

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bations, and long-term therapy. According to estimates by the National Heart, Lung, and Blood Institute,<sup>4</sup> in 2007 the annual cost in the United States for COPD was \$42.6 billion, which included \$26.7 billion in direct health-care expenditures, \$8 billion in indirect morbidity (illness-related) costs, and \$7.9 billion in indirect mortality (death-related) costs.

COPD increasingly is being recognized as a systemic inflammatory disease not limited to the pulmonary system. Cigarette smoking has been shown to induce an inflammatory process in the lungs<sup>5,6</sup> that is characterized by the recruitment and activation of inflammatory cells such as neutrophils, eosinophils, alveolar macrophages, and lymphocytes.<sup>5</sup> Furthermore, evidence now shows that long-term smoking leads to systemic inflammation, possibly through spillover from the pulmonary inflammatory process. It has been shown that long-term smokers have higher total levels of circulating WBCs, polymorphonuclear leukocytes, and band cell counts than nonsmokers.<sup>7</sup> Patients with COPD also have higher baseline levels of several circulating systemic inflammatory markers, including C-reactive protein (CRP), fibrinogen, tumor necrosis factor, leukocytes, interleukin 8, and interleukin 6.<sup>8</sup> Furthermore, it appears that the acute pulmonary and systemic inflammatory response induced by smoking can progress to a chronic persistent inflammatory process, even after the cessation of smoking.<sup>9</sup>

The 3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitors (statins) are used extensively in medical practice as cholesterol-lowering agents. By competitively inhibiting 3-hydroxy 3-methylglutaryl coenzyme A reductase activity, statins reduce cholesterol synthesis directly and lead to negative-feedback, low-density lipoprotein receptor up-regulation, resulting in a further reduction in total serum cholesterol levels. Statin therapy has been shown to decrease coronary and cerebrovascular events and to decrease mortality from coronary artery disease.<sup>10</sup>

In addition to their cholesterol-lowering ability, statins have been shown to have pleiotropic anti-inflammatory and immune modulatory effects. Recent studies<sup>1</sup> have demonstrated that statins are capable of reducing neutrophil numbers, reducing T-cell activation and differentiation, and of increasing apoptosis of eosinophils. Mechanistic studies<sup>11</sup> have shown that statins also regulate inflammation by enhancing phagocytosis of apoptotic cells via blockade of rho guanosine triphosphatase prenylation. Given the increasing evidence that COPD is an inflammatory disease, it has been postulated that the pleiotropic effects of statins may have a beneficial effect on the progression and sequelae of COPD.<sup>12</sup> In support of this postulate, animal studies<sup>13,14</sup> have

shown that statins inhibit the progression of emphysema in both murine and rat models. Very recently, several studies<sup>15–23</sup> were published that also evaluated the effect of statins on COPD outcomes in human populations. The purpose of our study was to conduct a systematic review of the published literature evaluating the effect of statin therapy on COPD in humans.

## MATERIALS AND METHODS

We decided *a priori* to examine the published evidence of statin therapy in patients with COPD. Searches were conducted on Medline (inception to December 2008), Excerpta Medica Database (inception to December 2008), PapersFirst (inception to December 2008), and the Cochrane collaboration and Cochrane Register of controlled trials for relevant trials. The following key terms were used: “statins”; “fluvastatin”; “simvastatin”; “atorvastatin”; “rosuvastatin”; “lovastatin”; “pravastatin”; “hydroxymethylglutaryl-coA reductase inhibitors”; “COPD”; “chronic obstructive airways disease”; “emphysema”; “chronic bronchitis”; and “chronic airflow obstruction.” All searches were limited to articles published in the English language and conducted in humans. We identified additional studies by searching the bibliographies of retrieved articles. Two independent reviewers (S.J. and K.P.) performed the literature search, identified all studies for full review, and selected independently studies for inclusion in the systematic review. Disagreement between these reviewers was resolved by a review of the study by a third author (J.S.), and the decision to include the study was reached by consensus. Randomized, double-blinded or single-blinded, placebo-controlled studies, observational cohort studies (retrospective and prospective), case-controlled studies, and population-based analyses were included. Experimental or laboratory-based studies were excluded.

We extracted data regarding the number of patients included in the study, study design, sample size, country of study origin, age, gender, comorbidity (*ie*, coronary artery disease, congestive heart failure, diabetes, hypertension, hypercholesterolemia, malignancy, stroke, and peripheral vascular disease), clinical outcomes (*ie*, hospitalization due to COPD exacerbation, pulmonary function, exercise capacity, mortality from COPD, and all-cause mortality), and cardiovascular (CV) drugs concurrently being administered (*ie*, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers,  $\beta$ -blockers, and aspirin). Because no universal scale is available for measuring the quality of observational studies, we followed the recommendations of the meta-analysis of observational studies in epidemiology guidelines,<sup>24</sup> assessed the quality of key design components separately, and then generated a single aggregate score. Study quality for the cohort studies was assessed with a scale comprising four questions to adjudicate the methodological quality of the studies, with higher scores indicating a higher quality study (see “Appendix”). The four questions addressed cohort inclusion criteria, exposure definition, clinical outcomes, and adjustment for confounding variables. Each question was scored on a scale of 0 to 2, with higher numbers representing better quality scores (maximum quality score, 8).

## RESULTS

We identified nine studies<sup>15–23</sup> that described the use of statins and their potential clinical effects in

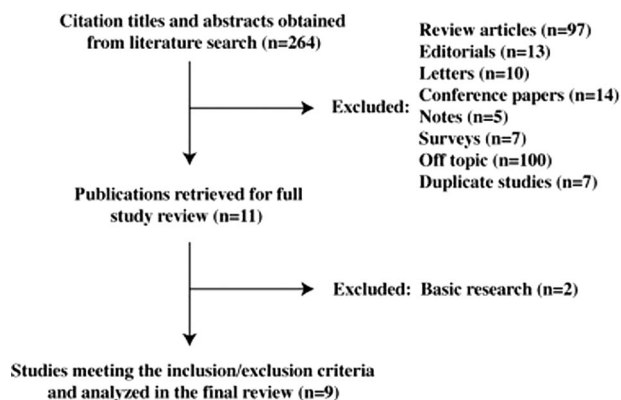


FIGURE 1. Flowchart for identification of studies.

patients with COPD (Fig 1). Of these evaluable studies, four were retrospective cohort studies, one was a nested case-control study of a retrospective cohort, one was a combination retrospective cohort study, two were case-control studies, one was a randomized controlled trial (RCT), and two were population-based analyses (Table 1). The end points that were evaluated in the identified studies included all-cause mortality, COPD-related mortality, the time to and number of COPD exacerbations, the time to and number of COPD-related intubations, exercise capacity, and pulmonary function ( $FEV_1$  and FVC) [Table 2].

Accepting the limitations of the study designs, the methodological quality of the studies was generally high. For the retrospective cohort studies, study quality was assessed using the quality score previously described (Table 1). The average score was 7 out of 8. The lowest score of 5 was given to the study by Blamoun et al<sup>15</sup> because it did not define clearly the statin-exposed group, validate the outcomes of COPD exacerbations and intubations secondary to COPD exacerbations, and account sufficiently for important confounders. The RCT by Lee et al<sup>19</sup> was well conducted and reported by the following RCT standards: randomization was concealed; blinding was adequate; few study withdrawals occurred; and the analysis was by intention to treat. Finally, the two population-based analyses<sup>17,21</sup> were well reported but were subject to the inherent limitations of this type of study design.

Three studies<sup>20,22,23</sup> showed the benefit of statin therapy in reducing all-cause mortality. Mancini et al<sup>20</sup> was a time-matched, nested case-control study of two population-based retrospective cohorts of patients with COPD (one cohort with high CV risk and one cohort with low CV risk), which included 946 case patients and 18,774 control subjects. The odds ratio (OR) for all-cause mortality in statin users (0.53; 95% confidence

interval [CI], 0.43 to 0.65) was significantly lower than that in nonusers (0.49; 95% CI, 0.41 to 0.58) in both the high-CV risk and low-CV risk groups. The retrospective cohort study by Soyseth et al,<sup>22</sup> with 118 statin users and 730 nonstatin users discharged from the hospital for a COPD exacerbation, showed a significant reduction in all-cause mortality in statin users compared to nonusers over a median follow-up period of 1.9 years (hazard ratio [HR] adjusted [adj], 0.57; 95% CI, 0.38 to 0.87). Furthermore, they found that although almost 30% of the patients with COPD had known ischemic heart disease, there did not appear to be effect modification on statin therapy by this comorbidity. The retrospective cohort study by van Gestel et al<sup>23</sup> involved 3,371 patients with peripheral arterial disease undergoing peripheral vascular surgery. In a subgroup of patients with COPD, it was shown that statin users had lower short-term mortality (30-day) and long-term mortality (10-year) than nonstatin users (OR adj, 0.48 [95% CI, 0.23 to 1.00] vs HR adj, 0.67 [95% CI, 0.52 to 0.86], respectively).

Two studies<sup>16,17</sup> showed a decrease in COPD-related mortality. The first part of the study by Frost et al<sup>16</sup> was a retrospective cohort study with 76,232 patients with COPD that compared a group of nonstatin users to a group of low-dose statin users (< 4 mg/d) and a group of moderate-dose statin users (> 4 mg/d). The second part of the study consisted of a case-control study involving COPD deaths, with 207 case patients and 9,622 control subjects. Both the retrospective cohort and the case-control analyses showed a statistically significant decrease in the number of COPD-related deaths in statin users compared to nonstatin users. This difference was dose dependent, as the moderate-dose statin users had a lower number of COPD-related deaths than the low-dose statin group (Table 2). The second study was a population-based analysis from Japan by Ishida et al<sup>17</sup> that obtained data on statin use from marketing surveys and on mortality data from government databases. The study showed that annual sales of statins negatively correlated with COPD mortality, with a correlation coefficient of 0.574 ( $p < 0.001$ ).

Three studies<sup>15,18,20</sup> showed the benefit of statin therapy in reducing the number of COPD exacerbations resulting in hospitalization. The first study by Blamoun et al<sup>15</sup> was a retrospective cohort study that observed 185 patients with COPD for 1 year. The authors found an increased risk of COPD exacerbations for nonstatin users (OR adj, 2.35; 95% CI, 1.01 to 5.50) and showed a significant reduction in the time to COPD exacerbations, time to COPD-related intubation, and number of COPD-related intubations in statin users (Table 2). The second study by

**Table 1—Summary of Various Study Characteristics of Each Study Included in the Systematic Review**

Study	Study Design	Cohort Definition	Sample Size	Disease Severity	Statin Exposure	Statin Subclass	Quality Score
Blamoun et al <sup>15</sup>	RC	COPD diagnosis based on hospital coding*	95 unexposed; 90 exposed	Baseline mean FEV <sub>1</sub> : statin users, 37.3 ± 8.8% predicted; nonusers, 38.2 ± 9.0% predicted	≥ 1 yr	A, 52%; S, 24%; O, 24%	5
Frost et al <sup>16</sup>	RC	COPD diagnosis based on HMO registry coding*	54,174 unexposed; 7,475 exposed to < 4 mg/d; 11,583 exposed to > 4 mg/d	NR	≥ 90 d	NR	7
Ishida et al <sup>17</sup>	PBA	COPD diagnosis based on HMO registry coding* COPD death based on ICD coding in a government database*	207 case patients; 9,622 control subjects 47 prefectures in Japan with total population 2.4 × 10 <sup>7</sup>	NR	Statin regional sales	NR	NA
Keddissi et al <sup>18</sup>	RC	Veterans Affairs hospital patients with ≥ 2 PFTst ≥ 6 mo apart (excluding those with normal baseline spirometry and history of asthma, and nonsmokers)	215 exposed; 203 unexposed	Baseline mean FEV <sub>1</sub> : statin users, 51.9 ± 17.1% predicted; nonusers, 51.2 ± 18.6% predicted	≥ 3 mo	A, 6%; S, 81%; O, 13%	7
Lee et al <sup>19</sup>	RCT	COPD diagnosis based on FEV <sub>1</sub> < 80% predicted and FEV <sub>1</sub> /FVC ratio < 70% (excluding history of allergic rhinitis, periodic wheezing, pulmonary embolism, improvement of FEV <sub>1</sub> of > 15% after bronchodilator inhalation)	62 in pravastatin arm; 63 in placebo arm	Baseline mean FEV <sub>1</sub> : pravastatin users, 51 ± 18% predicted; control subjects, 56 ± 13% predicted	6 mo	Pravastatin, 40 mg	NA
Mancini et al <sup>20</sup>	RC (nested CC)	High CVD risk COPD (COPD diagnosis based prescription pattern)  Low CVD risk COPD	1,028 hospital case patients and 20,429 control subjects; 1,092 death case patients and 21,692 control subjects 5,344 hospital case patients and 106,852 control subjects; 2,368 death case patients and 47,240 control subjects	NR	One or more prescriptions for statins within 60 d before index date	NR	8

(Continued)

Table 1—Continued

Study	Study Design	Cohort Definition	Sample Size	Disease Severity	Statin Exposure	Statin Subclass	Quality Score
Melbye et al <sup>21</sup>	PBA	Population survey respondents with COPD based on age > 60 yr and airflow limitation (FEV <sub>1</sub> /FVC ratio < 70); self-reported COPD	535 exposed; 3,342 unexposed	GOLD 1, 10.06%; GOLD 2, 12.00%; GOLD 3 and 4, 3.01%	Self-reported	NR	NA
Soyseth et al <sup>22</sup>	RC	COPD diagnosis based on hospital discharge ICD-10 coding (J44.0, J44.1, or J13-18.9 + J44x)	118 exposed; 736 unexposed	Baseline mean FEV <sub>1</sub> : statin users, 77.4 ± 20.4% predicted; nonusers, 71.1 ± 23.1% predicted	Not stated	NR	7
van Gestel et al <sup>23</sup>	RC	Vascular surgery patients with COPD based on symptoms, FEV <sub>1</sub> < 80% predicted, and FEV <sub>1</sub> /FVC ratio < 70	330 statin users; 980 nonstatin users	NR	Any prescription at the time of surgery	NR	7

A = atorvastatin; CC = case control; CVD = cardiovascular disease; GOLD = Global Initiative on Obstructive Lung Disease; hosp = hospitalization; HMO = health maintenance organization; ICD = *International Classification of Diseases*; ICD-10 = *International Classification of Diseases*, 10th edition; NA = quality score only done for retrospective cohort studies because there was only one RCT and two population-based analyses; NR = not recorded; O = other statin; PBA = population-based analysis; PFT = pulmonary function test; RC = retrospective cohort; S = simvastatin.

\*COPD diagnosis criteria not specified.

†Subgroup with only obstructive lung disease.

**Table 2—Summary of the Outcomes, Results, and Conclusions of the Nine Studies Included in the Systematic Review**

Study	Comparison	Outcomes	Results	Conclusions	
Blamoun et al <sup>15</sup>	No statins vs statin use	Exacerbation episodes	OR adj, 2.35 (95% CI, 1.01–5.50)	Use of statins may be associated with lower incidence of both exacerbations and intubations in individuals with COPD	
	No statins vs statin use	Intubations	OR adj, 10.36 (95% CI, 2.77–38.76)		
	Statin use vs nonuse	Time to exacerbation	HR, 0.19 (95% CI, 0.06–0.14)		
	Statin use vs nonuse	Time to intubation	HR, 0.14 (95% CI, 0.10–0.30)		
Frost et al <sup>16</sup>	Retrospective cohort	Statins, < 4 mg/d, vs nonuse	COPD hospital mortality	OR adj, 0.58 (95% CI, 0.17–0.92)	There was a significantly reduced risk of mortality from COPD in statin users that was more pronounced with moderate-dose statin use
		Statins, > 4 mg/d, vs nonuse	COPD hospital mortality	OR adj, 0.17 (95% CI, 0.07–0.42)	
	Case-control study	Statins, < 4 mg/d, vs nonuse	COPD hospital mortality	OR adj, 0.60 (95% CI, 0.26–1.36)	
		Statins, > 4 mg/d, vs nonuse	COPD hospital mortality	OR adj, 0.19 (95% CI, 0.08–0.47)	
Ishida et al <sup>17</sup>	Across prefecture correlation; statin sales and COPD mortality	COPD mortality	Annual statin sales negatively correlated with mortality from COPD ( $R = 0.574$ ; $p < 0.001$ )	Statin use correlated with decreased mortality from COPD	
Keddissi et al <sup>18</sup>	No statin use vs statin use	Respiratory-related ED visits	$0.17 \pm 0.31$ vs $0.11 \pm 0.26$ pt/yr, respectively ( $p = 0.01$ )	In smokers and ex-smokers, statins are associated with a slower decline in pulmonary function and reduced respiratory-related ED visits	
	Statin use vs nonuse	Decline in FEV <sub>1</sub>	$-5 \pm 207$ vs $86 \pm 168$ mL/yr ( $p < 0.0001$ )*		
	Statin use vs nonuse	Decline in FVC	$-33 \pm 452$ vs $150 \pm 328$ mL/yr ( $p < 0.0001$ )†		
Lee et al <sup>19</sup>	Placebo vs pravastatin	Increase in exercise time on treadmill	Pravastatin arm ( $599 \pm 323$ to $922 \pm 328$ s; $p < 0.0001$ ); placebo arm no change	Treatment with 6 mo of pravastatin increased exercise capacity in patients with COPD	
	Placebo vs pravastatin	Change in CRP levels	Pravastatin arm ( $3.94 \pm 3.54$ to $2.66 \pm 2.49$ mg/L; $p < 0.005$ ); Placebo arm no change		
Mancini et al <sup>20</sup>	High-CV risk cohort	Statin use vs nonuse	COPD hospitalization	RR adj, 0.71 (95% CI, 0.56–0.91)	In patients with COPD, statin use is associated with reduced COPD hospital and death irrespective of CV risk profile
		Statin use vs nonuse	Death (all cause)	RR adj, 0.53 (95% CI, 0.43–0.65)	
	Low-CV risk cohort	Statin use vs nonuse	COPD hospitalization	RR adj, 0.71 (95% CI, 0.64–0.77)	
		Statin use vs nonuse	Death (all cause)	RR adj, 0.49 (95% CI, 0.41–0.58)	
Melbye et al <sup>21</sup>	Normal lung function vs airflow limitation, as follows:	Mild (GOLD 1)	CRP level	1.64 vs 1.74 mg/L ( $p = \text{NS}$ )	High CRP levels correlate with increased bronchial airflow limitation; no association between statin use and CRP levels in COPD without CVD
		Moderate (GOLD 2)	CRP level	1.64 vs 2.21 mg/L ( $p < 0.001$ )	
		Severe (GOLD 3 and 4)	CRP level	1.64 vs 3.15 mg/L ( $p < 0.001$ )	
		Statin use vs nonuse (COPD without CVD)	CRP level	1.89 vs 2.36 mg/L ( $p = \text{NS}$ )	
Soyseth et al <sup>22</sup>	Statin use vs nonuse	All-cause mortality	HR adj, 0.57 (95% CI, 0.38–0.87)	Treatment with statins was associated with improved survival after COPD exacerbation	
van Gestel et al <sup>23</sup>	Statin use vs nonuse	Short-term (30 d) mortality	Low-dose OR adj, 0.77 (95% CI, 0.34–1.74)	Statin use was associated with improved short- and long-term survival in patients with PAD with COPD	
			Intensified dose OR adj, 0.08 (95% CI, 0.01–0.64)		
			Total OR adj, 0.48 (95% CI, 0.23–1.00)‡		
		Long-term (10 yr) mortality	Low dose HR adj, 0.66 (95% CI, 0.48–0.91)		
Intensified dose HR adj, 0.58 (95% CI, 0.40–0.83)					
			Total HR adj, 0.67 (95% CI, 0.52–0.86)‡		

NS = not significant; PAD = peripheral arterial disease; pt = patient; R = correlation coefficient; RR = relative risk. See Table 2 for other abbreviations.

\*Negative value for rate of decline indicates an increase in FEV<sub>1</sub> per year.

†Negative value for rate of decline indicates an increase in FVC per year.

‡Combination of low dose and intensified dose.

Keddissi et al<sup>18</sup> was a retrospective cohort study that included 418 patients who were either smokers or ex-smokers. The authors showed that a mean ( $\pm$  SD) of  $0.17 \pm 0.31$  patients per year presented with COPD exacerbations and were receiving therapy with statins vs  $0.11 \pm 0.26$  patients per year with COPD exacerbations who did not receive therapy with statins ( $p = 0.01$ ). Interestingly, this study found a significantly lower rate of decline in FEV<sub>1</sub> and FVC in statin users compared to nonusers. The final study by Mancini et al<sup>20</sup> also showed a statistically significant benefit of statins for reducing COPD-related hospitalizations in both high-CV risk and low-CV risk groups (relative risk [RR] adj: 0.71 [95% CI, 0.56 to 0.91] vs 0.71 [95% CI, 0.64 to 0.77], respectively).

The only RCT<sup>19</sup> of statin use in patients with COPD that has been reported to date compared therapy with pravastatin to placebo and evaluated the effect of therapy on exercise capacity and CRP levels. The study found a 54% increase in exercise capacity in patients who received 40 mg of pravastatin compared to placebo over a 6-month follow-up period. Furthermore, there was a correlation between the increase in exercise time and the decrease in CRP, even after adjustment for lipid profiles and hemodynamics. The cross-sectional study by Melbye et al<sup>21</sup> surveyed 3,877 Norwegians who were > 60 years of age and found a positive correlation between the severity of airflow limitation and CRP levels, but did not find an association between statin use and CRP levels in those participants who self-reported COPD but not CV disease.<sup>21</sup>

## DISCUSSION

Statins not only have a proven role in treating CV patients, primarily through their cholesterol-lowering ability, but also possess antiinflammatory and immunomodulatory pleiotropic effects postulated to be beneficial to patients with COPD. We identified nine studies that evaluated the effect of statins on various outcomes in COPD. Eight of the studies were retrospective cohorts, case-control studies, or epidemiologic analyses. Only one interventional study specifically designed to address the effect of statins in COPD has been reported. All studies that we identified reported a benefit from the use of statins in patients with COPD on a range of clinical outcomes.

A major strength of the collective literature regarding the effects of statins on COPD lies in the benefit seen in a number of different COPD-specific outcomes, including lung function and exercise capacity, COPD exacerbation rates, COPD-related hospitalizations and intubations, and COPD-related

mortality. A reduction in the frequency of COPD exacerbations, hospitalizations, and mortality by statin therapy may be a result of a direct pulmonary effect, an impact on the systemic consequences of COPD, or both. The reduction in the rate of decline in FEV<sub>1</sub> and FVC demonstrated by Keddissi et al<sup>18</sup> suggests that statins exert a protective effect on the pulmonary system directly and abrogate the adverse effects of smoking on lung function, even in those patients who no longer smoke. Similarly, Alexeeff et al<sup>25</sup> conducted a retrospective analysis of serial lung function data prospectively collected over a 10-year period from 803 men participating in the Veterans Administration Normative Aging Study. For the entire cohort of men with and without a smoking history, the researchers found a significantly lower rate of decline in lung function in statin users compared to nonusers (FEV<sub>1</sub>, 10.9 vs 23.9 mL/yr, respectively [ $p < 0.001$ ]; FVC, 14.0 vs 36.2 mL/yr, respectively [ $p < 0.001$ ]). Although not confirmed statistically, the difference in the rate of decline between statin users and nonusers appeared to be most prominent in patients with a smoking history.

In support of these clinical findings, a direct benefit from statins on the pulmonary system in COPD also has been reported in animal models.<sup>14</sup> Takahashi et al<sup>14</sup> induced pulmonary emphysema in C57BL/6 mice with intratracheal elastase followed by treatment with simvastatin or saline solution. The study found that, compared to control subjects, simvastatin inhibited the development of elastase-induced emphysema, with a decrease in inflammatory markers in the lungs and the promotion of alveolar epithelial cell proliferation. Similarly, Lee et al<sup>13</sup> exposed Sprague-Dawley rats to cigarette smoke for 16 weeks and found that simvastatin inhibited the destruction of lung parenchyma and the development of pulmonary hypertension. These findings are encouraging because they suggest that statins may be capable of directly modulating disease progression within the lungs.

A number of epidemiologic studies<sup>26</sup> have demonstrated an increased incidence of coronary artery disease in patients with COPD compared to the general population as well as an increase in CV mortality in this population. With the exception of the study by Lee et al,<sup>19</sup> all of the studies identified in this review were noninterventional; therefore, the evaluated patients with COPD were presumably receiving statins, based on the presence of risk factors for or the presence of vascular disease. As such, it could be argued that the reduction in all-cause mortality described in the studies by Mancini et al,<sup>20</sup> Soyseth et al,<sup>22</sup> and van Gestel et al<sup>23</sup> may have been due to an effect on CV-related outcomes rather than COPD-related outcomes. Although van Gestel et al<sup>23</sup> found an all-cause mortality reduction in patients

with COPD who were receiving therapy with statins, even after adjusting for CV and cerebrovascular disease, all patients in their cohort had known peripheral vascular disease. However, Mancini et al<sup>20</sup> identified a similar reduction in mortality in both the high-CV risk and low-CV risk groups, suggesting that statins may not be exerting a purely vascular-protective effect. In defense of this possibility, the study by Soyseth et al<sup>22</sup> did not find a significant degree of effect modification on statin therapy by a history of ischemic heart disease. Furthermore, Frost et al<sup>16</sup> and Ishida et al<sup>17</sup> specifically reported a reduction in COPD-related mortality. Although the study by Ishida et al<sup>17</sup> was a population-based analysis, the study by Frost et al<sup>16</sup> was well designed, and the results were obtained from both retrospective cohort and case-control analyses. Thus, based on the current evidence, it appears that statins have a positive impact on mortality from COPD outside of their vascular-protective effects.

The most significant limitation to the current data regarding the effect of statins on outcomes in COPD patients relates to study design. All reported studies, with the exception of Lee et al<sup>20</sup>, were noninterventional and, therefore, subject to confounding and bias. The only interventional study<sup>20</sup> was designed to evaluate changes in exercise capacity and CRP levels and, therefore, did not address major negative outcomes of COPD, such as hospitalization rates or mortality. Six of the remaining studies were observational analyses of a retrospective design. Cohort studies have a limited ability to control for confounding variables, and the retrospective designs in particular must be cautiously interpreted, with attention to the cohort and exposure definitions. Although most of the studies adequately defined the population from which the cohorts were derived, the diagnosis of COPD remains a concern. Four of the studies<sup>15-17,22</sup> defined their COPD cohort by registry or hospital coding, two studies<sup>21,23</sup> did so by spirometric data alone, two studies<sup>18,19</sup> did so by spirometric data and partial clinical data, and one study<sup>20</sup> did so by analysis of prescription data (Table 2). Reliance on incomplete information or unvalidated diagnoses may result in the misdiagnosis of COPD.<sup>27-29</sup> Random misclassification of the diagnosis of COPD would most likely lead to an underestimation of the overall effect of statins; however, it is impossible to know how significantly the risk estimates are affected by this error.

Whether the reported effects of statins on outcomes in COPD patients differ depending on disease severity cannot be ascertained from the studies presented in this review. Four of the studies<sup>16,17,20,23</sup> did not report disease severity in any way, whereas four studies<sup>15,18,19,22</sup> reported only a mean FEV<sub>1</sub> for the cohorts (Table 2). Only one study<sup>21</sup> stratified the

cohort by severity (based on the Global Initiative for Chronic Obstructive Lung Disease criteria); however, this analysis only looked at CRP levels and did not compare the effects across severity stages. Determining the differential effects of statins in various disease severity categories of COPD is important because it may be that patients with more or less severe disease are affected differently by statin therapy. Further elucidating this variable will require either the evaluation of COPD populations that are homogeneous in their disease state or a stratified analysis that subclassifies patients based on disease severity.

Exposure definition was found to be quite variable across studies (Table 2). Only three studies<sup>15,18,19</sup> defined the type of statin that their cohort was exposed to. The benefits of statins are largely assumed to be a class effect; however, whether the pleiotropic effects of statins are similar across subclasses remains to be determined.<sup>30</sup> Furthermore, the degree of exposure to statins (*ie*, dose and duration) varied significantly among the studies; therefore, it is impossible to draw any conclusions from the current literature regarding the adequate exposure to statins required to achieve a clinically meaningful outcome.

All reported studies that we identified in this review showed a positive effect of statin therapy on outcomes in patients with COPD. Although this consistently positive trend is encouraging, it also raises the concern of publication bias. The complete absence of negative studies in the literature suggests that publication bias likely exists. It is well known that positive studies are more likely to be published, and this is particularly true for those of a noninterventional design. However, whether data showing a lack of benefit from statins in COPD populations exist cannot be ascertained, and the current literature is, at the very least, supportive of further investigation.

Four clinical trials<sup>31-34</sup> addressing the effects of statin therapy in COPD patients had been listed in the US National Institutes of Health trials registry as of January 1, 2009. All four trials are randomized, double-blinded, placebo-controlled designs. The first study<sup>31</sup> is a parallel-group pilot study comparing therapy with atorvastatin, 40 mg, to placebo in patients with COPD with a primary outcome of change in peak flow. Two studies<sup>32,33</sup> are comparing therapy with simvastatin, 40 mg, to placebo in patients with COPD and evaluating CRP level as the primary outcome. The fourth study<sup>34</sup> is comparing therapy with lovastatin, 40 mg, to placebo in patients with COPD with the primary outcome being apoptosis and efferocytosis in pulmonary macrophages. Although all four studies are evaluating surrogate or intermediate end points, they will shed further

## Appendix—Quality Scores for Cohort Studies

Scores	Cohort Entry	Exposure Definition	Outcome	Confounding Assessment
2	Clear definition ( <i>ie</i> , specific time and description of those entering the cohort)	Well defined with good description of exposure ( <i>eg</i> , definition of current, past use; any dose response)	Clear definition ( <i>ie</i> , including validity of outcome assessment using different methods and reporting of specificity or positive predictive value)	Good methodology used to assess both known and unknown confounders, including propensity scores, regression calibrations, sensitivity analysis, simulation, and imputation for unknown confounders
1	Cohort entry described but not well defined	Brief description of exposure but not explicit	Specific description but no validity	Only accounts for known confounders using matching or standard regression
0	No definition for cohort or cohort entry given	No description of exposure	Only a general description	Only adjusts for a few potential confounders ( <i>ie</i> , age and gender)

light on the effects of statin therapy in COPD patients, and, if their results are positive, they will justify larger clinical trials evaluating clinically meaningful morbidity and mortality outcomes, such as disease progression, hospitalization, and death.

The current collective evidence suggests that statins have a positive impact on outcomes in patients with COPD. Despite the encouraging results, all studies reported to date have limitations and should be considered, even collectively, as hypothesis generating only. The true effect of statin therapy on outcomes in COPD patients remains to be elucidated, as does the dose and duration required to achieve any such effect, the optimal disease severity population to target, and the relative efficacies of the various statins available. The evidence is compelling but currently insufficient to justify a clinical indication for statins therapy in patients with COPD outside of vascular protection. The body of literature does, however, justify and support the need for well-designed RCTs to evaluate the effect of statins on outcomes in COPD populations. Whether the benefits of statin therapy in COPD patients are due to pulmonary, systemic, or CV effects, or some combination of the three, rationalization of the use of statin therapy in patients with COPD ultimately will be based on clinical outcomes, such as lung function, disease control, and mortality. A therapeutic intervention that positively affected outcomes, such as hospitalization and mortality rates in patients with COPD, potentially could have a huge beneficial impact on the individual, social, and economic consequences of this disease.

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