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Statins, systemic inflammation and risk of death in COPD: The Rotterdam study

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ABSTRACT

Background: Studies suggest that statins decrease mortality in COPD patients but it is unknown which patients might benefit most.
Objectives: We investigated whether statins were associated with reduced mortality in COPD patients and whether effects differed according to baseline high-sensitivity C-reactive protein (hsCRP) concentration, a marker of systemic inflammation.
Methods: This nested case–control study was part of the Rotterdam Study, a prospective population-based cohort study among 7983 subjects $\geq$ 55 years. Using automated pharmacy records, we evaluated statin use of 363 cases (COPD patients who died during follow-up of 17 years) with 2345 age and sex matched controls (COPD patients who survived the follow-up period of the index case).
Results: Compared to never use, long-term statin use (>2 years) was associated with a 39% decreased risk of death in COPD patients. Stratified according to the level of systemic inflammation, long-term statin use was associated with a 78% reduced mortality if hsCRP level > 3 mg/L, versus a non significant 21% reduced mortality if hsCRP level $\leq$ 3 mg/L.
Conclusions: Statin use is associated with a beneficial effect on all-cause mortality in COPD, depending on the baseline level of systemic inflammation.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of morbidity and mortality worldwide. In industrialized countries about 400,000 COPD deaths occur each year and the mortality is expected to increase further [1]. The disease is characterized locally by a chronic inflammation of small airways and destruction of alveoli and systemically, in a subset of COPD patients, by increased markers of inflammation, including high-sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL6) [2–4]. The subset of COPD patients with persistent systemic inflammation has recently been shown to be associated with poor clinical outcomes despite similar lung impairment [5]. The chronic low-grade inflammation might be the key link to the occurrence of various comorbidities in COPD including cardiovascular diseases and lung cancer. Moreover, these comorbidities are the main causes of death in mild to moderate COPD; therefore, with the increased recognition of the prognostic role of comorbidities in COPD, all-cause mortality has become one of the major endpoints in the evaluation of novel therapies [6].

Recent observational studies suggest that statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors] may reduce morbidity and mortality in COPD patients [7–9]. Statins are a class of drugs mainly used to treat hypercholesterolemia and to prevent cardiovascular events. Statins reduce cholesterol synthesis by inhibition of HMG-CoA reductase in the liver and increase low density lipoprotein-cholesterol uptake from the circulation. In addition to their lipid-lowering effect, statins also possess pleiotropic anti-inflammatory and immunomodulating properties, and are able to reduce levels of inflammatory markers such as CRP [10].

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CRP is a validated biomarker of systemic inflammation in COPD and increased CRP levels in patients with COPD are associated with increased mortality [11,12]. Lee et al. recently showed in a randomized controlled trial with COPD patients, that pravastatin treatment significantly decreased CRP and IL6 levels compared to placebo and that the improvement of exercise tolerance was greater in those with a greater decrease of hsCRP levels and higher baseline CRP levels [13]. However, to our knowledge, studies exploring whether the beneficial effect of statins on all-cause mortality in COPD is greater in those with increased systemic inflammation, have not yet been published.

Therefore, the objective was to investigate whether statins have a beneficial effect on mortality in COPD patients with increased baseline hsCRP-levels in the Rotterdam Study, a large prospective population-based cohort study with long-term follow-up.

2. Methods

2.1. Study population and design

We performed a nested case–control analysis in all COPD cases within the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence of and risk factors for chronic diseases in the elderly [14]. The Rotterdam study cohort includes 7983 participants aged $\geq$ 55 years, living in Ommoord, a well-defined suburb of Rotterdam, the Netherlands. Almost all participants (99.8%) are of Caucasian descent. Baseline data were collected from 1989 until 1993 and each participant visits the research centre every 2–3 years. In addition, participants are continuously monitored for the onset of major events which occur during follow-up through automated linkage with files from general practitioners. Nearly all participants (99.7%) are registered at one or more of seven automated pharmacies serving the Ommoord area. From these pharmacies, records of all filled prescriptions were available as of January 1st, 1991. The medical ethics committee of the Erasmus Medical Centre, Rotterdam, and the review board of The Netherlands Ministry of Health, Welfare and Sports, approved the study. Participants gave written informed consent.

2.2. Definition of cases and controls

Cases and controls were nested in all participants of the source population of whom hsCRP was measured at baseline and of whom COPD was diagnosed by an obstructive spirometry [proportion of the forced vital capacity exhaled in the first second (FEV_1/FVC) < 0.7] during the research centre or pulmonologist visits or by a general practitioner. Physician diagnosed asthma patients were excluded. The incident COPD date was defined as the date of COPD diagnosis in the medical records, or the date of a first COPD medication prescription or the date of obstructive lung function examination, whichever came first. To ensure at least three months medication history for every subject, participants of whom study follow-up started before April 1st, 1991 were excluded. Cases were COPD subjects who died between April 1st, 1991 and January 1st, 2008. The mortality date was taken as the index date. Controls were COPD subjects matched on sex and age ($\pm$1 year) who were still alive on the same day of follow-up as their matched case. The duration of COPD was determined as the time between the incident COPD date and the index date.

2.3. Statin exposure

Complete information on all filled prescriptions on a day-to-day basis was obtained in automated format from the pharmacies. Subjects were classified as statin users if they had received at least one prescription for statins between start and index date. The duration of a prescription was calculated as the total number of delivered units divided by the prescribed daily number of units. The studied statins were simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin and rosuvastatin. All drugs under study are only available on prescription in the Netherlands.

2.4. All-cause mortality & primary cause of death

Information on vital status of the Rotterdam Study participants was obtained from general practitioners and from municipal records. Mortality follow-up started at baseline and was complete until January 1st, 2008. Causes of death during follow-up in the Rotterdam Study were coded according to the International Classification Of Diseases (ICD)-10 [15]. The following categories were applied for description in the text: cardiac mortality (ICD-10: I21-I73, R96), pulmonary mortality (ICD-10: J15-J44), death from bronchial carcinoma (ICD-10: C34), death from other malignancies (ICD-10: C15-C96 except C34) and other causes of death (ICD-10: all other used codes).

2.5. Covariables

The nested case–control approach makes it possible to account for age and gender by matching and to adjust for other drug use at the index date. Therefore, we adjusted mortality risk estimates for use of cardiovascular drugs (antihypertensives, diuretics, β-blockers, calcium channel blockers and agents acting on the renin-angiotensin system, ATC C02, C03, C07, C08 & C09 respectively), antidiabetics (ATC A10) and corticosteroids for systemic use (ATC H02) on the index date. Furthermore, the duration of COPD at index date and the following covariables at baseline were considered as potential confounders: pack-years of cigarette smoking, total serum cholesterol, hsCRP, systolic blood pressure, body-mass index (BMI), diabetes mellitus and cardiovascular covariables (myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, atrial fibrillation and heart failure); and their assessment has been described previously [2,3]. One prerequisite to be a confounder is that the variable is associated with the exposure, here statin use. Therefore, the relationship between the potential confounder and statin use (yes/no) was evaluated for categorical variables with a Chi Square test and for continuous variables with a Mann–Whitney *U* test.

2.6. Statistical analysis

Crude and adjusted odds ratios for mortality were estimated using conditional logistic regression. All models were adjusted for covariates that were significantly related to the exposure and changed the point estimate by more than 10%. Statin drug use was categorized as no use (0 days), short-term (1–30 days), mid-term (31 days-2 year) and long-term use ($\geq$2 year). Because every participant should have the opportunity to be a long-term user, COPD subjects with an incident date from January 1st, 2006 onwards, were excluded from analyses. Never use of statins was the reference category in all analyses. To gain power in the subdivided cause-specific mortality analyses, the groups mid-term and long-term use were combined. hsCRP serum levels were categorized as high versus average and low, based on the American Heart Association classification [16]. Total serum cholesterol levels were categorized as high versus borderline and desirable, based on the Adults Treatment Panel III classification [17]. All statistical analyses were performed using SPSS version 18 (SPSS Inc, Chicago, IL). *P* values below the conventional level of significance ($p < 0.05$) were considered as statistically significant.

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3. Results

3.1. Baseline characteristics of the study population

Within the source population of 7983 subjects, hsCRP was successfully measured in 6658 participants at baseline (Fig. 1). Of these, 758 COPD patients were identified with a study start date after April 1st, 1991 to ensure at least three months of medication history. The vast majority (82.5%) of COPD patients was confirmed by an obstructive spirometry. Seventy-one patients with an incident COPD date after January 1st, 2006 were excluded from analyses because at least two years of follow-up between incident COPD and death were required to study the association of long-term statin use on mortality. During the potential follow-up of 17 years (1991–2008), 363 COPD patients deceased and were determined as cases. For each case, an average of six age- and sex-matched controls with COPD who survived the follow-up period of their matched case, were selected for a total of 2345 controls. Because non-deceased participants with COPD could serve as a control in several case–control sets, the total number of controls is larger than the total number of incident cases of COPD. Table 1 shows the baseline characteristics of cases and controls. Cases were more frequently current smokers and had a higher prevalence of cardiovascular disease at baseline in comparison to the controls. Although age- and sex-matched, cases seem older and less often males as a consequence of the fact that there were more controls for males and lower age-categories.

3.2. Mortality in COPD patients

The cumulative survival of COPD patients ($n = 758$) was worse in those with a baseline hsCRP of more than 3 mg/L than in those with an hsCRP of 3 mg/L or less (Fig. 2; log-rank: $p < 0.0001$). In contrary, COPD patients with a total cholesterol of 240 mg/dL or more had a better survival than those with less than 240 mg/dL at baseline (data not shown; log-rank: $p = 0.008$). The most frequent causes of death in COPD patients are listed in Table 2. Most cases died due to cardiovascular causes (38.3%), followed by pulmonary complications of COPD (COPD exacerbations, emphysema or pneumonia; 19.6%) and bronchial carcinoma (10.5%).

3.3. Statin use and the risk of mortality in COPD

Table 3 shows the association between statin use and the risk of all-cause mortality in COPD in a first model which is already adjusted for age and sex by matching and in a second model adjusted for all confounders related to the exposure which changed the point estimate by more than 10%. Baseline hsCRP-level was ruled out as confounder because it was not associated with statin

Table 1
Baseline characteristics.

		Cases	Controls
Number of participants		363	2345
Age at index date (years)		81 (75–85)	78 (74–81)
Male		249 (69%)	1722 (73%)
Smoking behaviour			
Never smoker		39 (11%)	252 (11%)
Current smoker		145 (40%)	820 (35%)
Former smoker		164 (45%)	1170 (50%)
Missing		15 (4%)	103 (4%)
Median pack-years		30 (14–50)	28 (13–47)
Body mass index (kg/m^2)		25 (23–28)	26 (24–28)
Diabetes		43 (12%)	161 (7%)
Systolic blood pressure (mmHg)		139 (123–155)	137 (124–152)
Cardiovascular covariables[a]		163 (45%)	724(31%)
hsCRP (mg/L)		2.1 (1.1–4.0)	2.7 (1.3–4.8)
hsCRP categories[b]	≤3 mg/L	202 (56%)	1524 (65%)
	>3 mg/L	161 (44%)	821 (35%)
Total serum cholesterol (mmol/L)		6.4 (5.6–7.2)	6.4 (5.7–7.3)
Total cholesterol categories[b]	<240 mg/dL	166 (46%)	1055 (45%)
	≥240 mg/dL	197 (54%)	1290 (55%)
Drug use at index date			
Antidiabetics		41 (11%)	194 (8%)
Cardiovascular drugs[c]		209 (58%)	1249 (53%)
Oral corticosteroids		138 (38%)	303 (13%)
Duration of statin use			
None		299 (82%)	1856 (79%)
1–30 days		5 (1%)	22 (1%)
31 days-2 years		18 (5%)	197 (8%)
>2 years		41 (11%)	270 (12%)
Duration of COPD at index date (years)		7 (3–11)	5 (2–8)

Categorical variables are expressed as count (percentage). Values of continuous variables are expressed as median (25–75 percentiles). Cases: COPD patients who deceased during follow-up; controls: COPD patients who survived the follow-up period of the index case.

[a] Cardiovascular covariables included myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, atrial fibrillation and heart failure.

[b] hsCRP categories based on the American Heart Association [16], total cholesterol categories based on the Adults Treatment Panel III classification [17].

[c] Cardiovascular drugs include antihypertensives, diuretics, β-blockers, calcium channel blockers and agents acting on the renin-angiotensin system.

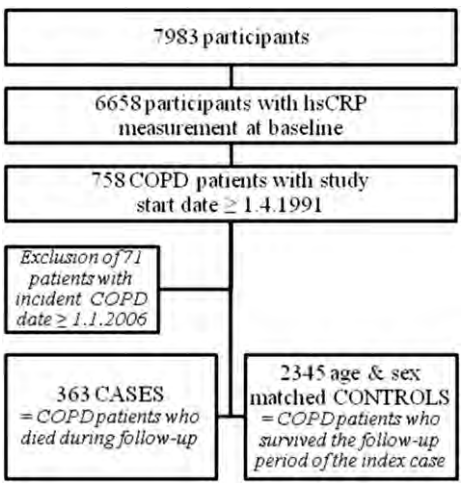

Fig. 1. Study flowchart.

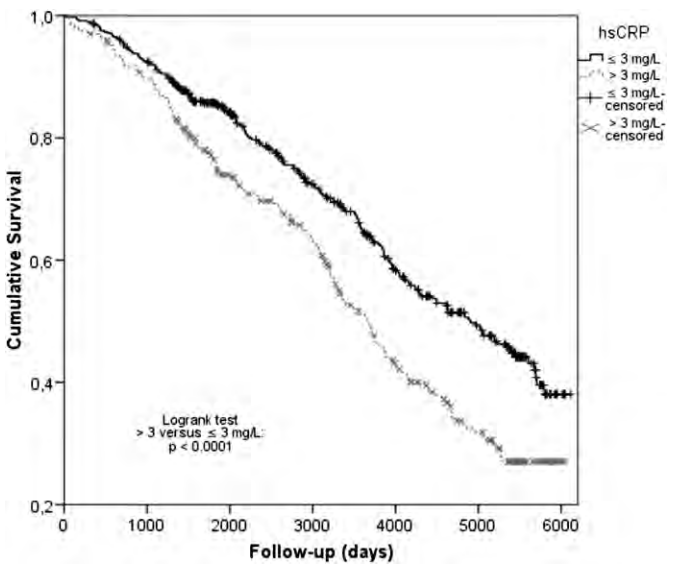

Fig. 2. Kaplan–Meier survival curve of COPD patients ($n = 758$) according to the hsCRP level (at baseline).

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Table 2
Causes of death in the COPD study population.

	n	% of total
Pulmonary	71	19.6
COPD	59	16.3
Pneumonia	12	3.3
Cardiovascular	139	38.3
Mainly		
Heart failure	31	8.5
Stroke	30	8.3
Sudden (cardiac) death	30	8.3
Cardiac arrest	18	5.0
Acute myocardial infarction	12	3.3
Chronic ischaemic heart disease	6	1.7
Cancer	88	24.2
Mainly		
Malignant neoplasm of bronchus and lung	38	10.5
Malignant neoplasm of colon	8	2.2
Malignant neoplasm of pancreas	6	1.7
Malignant neoplasm of prostate	6	1.7
Other	65	17.9
Mainly		
Other ill-defined and unspecified causes of mortality	19	5.2
Dementia	8	2.2
Fracture of femur	7	1.9
Total	363	

prescriptions (nor as categorical variable neither continuously); however, hsCRP was evaluated as a potential effect modifier. Compared to never use, long-term statin use (>2 years) was associated with a 39% decreased risk of (all-cause) death in COPD patients (95%CI, 0.38–0.99) independent of age, sex, other drug use, duration of COPD, pack-years, total serum cholesterol, BMI and cardiovascular covariables.

Regarding cause-specific mortality in COPD, statin use (>30 days) compared to never use was associated with a significant 64% decrease in risk of pulmonary mortality (95%CI, 0.13–0.97) (Table 4). In the adjusted model, there was a trend of decrease in risk of pulmonary and cardiovascular mortality. Statin use did not affect cancer mortality in both, crude and adjusted analyses.

3.4. Statin use and the risk of (all-cause) death in COPD according to the level of systemic inflammation

When stratified according to the level of systemic inflammation, long-term statin use was associated with a 78% reduced risk of death in COPD patients with a hsCRP level > 3 mg/L (95% CI, 0.06–0.74), versus a non significant 21% reduced risk of death in COPD patients with a hsCRP level ≤ 3 mg/L (95% CI, 0.41–1.55) (Table 5).

Table 3
Association between statin use and the risk of (all-cause) death in COPD.

	Crude model[a]				Adjusted model[b]			
	OR	95% CI		*p*-value	OR	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
No statin use	Reference				Reference			
1–30 days	1.34	0.49	3.67	0.572	1.61	0.48	5.48	0.443
31 days–2 years	0.68	0.40	1.16	0.156	0.64	0.35	1.15	0.136
>2 years	0.82	0.55	1.22	0.331	**0.61**	**0.38**	**0.99**	**0.045**

Abbreviations: CI, confidence interval; OR, Odds ratio. Bold values indicate statistical significant values (with *p* value below the conventional level of significance ($p < 0.05$)).
[a] Crude model: adjusted for age and sex by matching.
[b] Adjusted model: adjusted for age and sex by matching; adjusted in the analyses for the use of cardiovascular drugs, antidiabetics, oral corticosteroids and duration of COPD at index date, and pack-years of cigarette smoking, total serum cholesterol, body-mass index and cardiovascular covariables at baseline.

Table 4
Association between statin use and the risk of cause-specific mortality in COPD.

Pulmonary mortality	Crude model[a]				Adjusted model[b]			
	OR	95% CI		*p*-value	OR	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
No statin use	Reference				Reference			
>30 days of statin	**0.36**	**0.13**	**0.97**	**0.044**	0.37	0.13	1.08	0.068
Cardiovascular mortality								
No statin use	Reference				Reference			
>30 days of statin	0.87	0.54	1.41	0.579	0.58	0.33	1.01	0.053
Cancer mortality								
No statin use	Reference				Reference			
>30 days of statin	0.89	0.49	1.61	0.700	0.92	0.48	1.75	0.790

Abbreviations: CI, confidence interval; OR, Odds ratio. Bold values indicate statistical significant values (with *p* value below the conventional level of significance ($p < 0.05$)).
[a] Crude model: adjusted for age and sex by matching.
[b] Adjusted model: adjusted for age and sex by matching; adjusted in the analyses for the use of cardiovascular drugs at index date, and total serum cholesterol and cardiovascular covariables at baseline.

When we excluded COPD patients exclusively diagnosed by GP, the point estimator did not change substantially (OR 0.49 in the crude model and OR 0.31 in the adjusted model, investigating the effect of long-term statin use compared to no use in COPD subjects with hsCRP > 3 mg/L). A sensitivity analysis restricting the subjects to smoking COPD patients with a hsCRP level > 3 mg/L, confirmed that long-term statin use compared to no use was associated with an 85% reduced risk of death (95% CI, 0.04–0.61, adjusted model). In Table 6, analyses were stratified according to the total serum cholesterol level at baseline. The reduced risk of death in COPD patients by long-term statin use was significant in both categories (<240 mg/dL and ≥240 mg/dL).

4. Discussion

This is the first prospective study in a general population showing that the beneficial effect of long-term statin use on the risk of mortality in COPD patients is modified by the baseline level of systemic inflammation. The results suggest that the subset of COPD patients characterized by increased markers of systemic inflammation might benefit most from long-term statin therapy. One in three COPD patients in our study died from cardiovascular causes – figures which have also been described by other authors [6,18]. Although the protective effect of statins in COPD patients could represent solely an indirect effect on the cardiovascular comorbidities associated with COPD, our results also suggest an effect on respiratory mortality by statin use compared to never use.

Increasing insights into the pleiotropic effects of statins unravel several possible mechanisms for the beneficial effects seen in COPD patients. Beyond their known ability to inhibit endogenous cholesterol synthesis, statins exert immunomodulating effects in both systemic and pulmonary cytokine driven inflammation by inhibiting guanosine triphosphatase proteins [19]. Statins down regulate the expression of adhesion molecules involved in the recruitment of inflammatory cells, and of chemokines which are increased in COPD, such as CCL2 and CXCL8 [20]. Furthermore, simvastatin reduces the expression of matrix metalloproteinases (MMPs) involved in COPD matrix remodelling, such as MMP2, MMP9 and MMP12 [21,22]. In support of a direct effect of statins in COPD, Lee et al. demonstrated in a rat model of smoking-induced emphysema that simvastatin

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Table 5
Association between statin use and the risk of death in COPD, stratified according to the serum level of hsCRP (at baseline).

		Crude model[a]				Adjusted model[b]			
		OR	95% CI		p-value	OR	95% CI		p-value
			Lower	Upper			Lower	Upper	
hsCRP ≤ 3 mg/L	No statin use	Reference				Reference			
	1–30 days	0.66	0.14	3.16	0.606	0.77	0.14	4.09	0.756
	31 days–2 years	0.70	0.35	1.43	0.335	0.60	0.27	1.34	0.212
	>2 years	0.87	0.51	1.50	0.620	0.79	0.41	1.55	0.496
hsCRP > 3 mg/L	No statin use	Reference				Reference			
	1–30 days	1.83	0.29	11.49	0.520	*NA*			
	31 days–2 years	0.77	0.30	1.96	0.584	0.95	0.33	2.73	0.917
	>2 years	**0.44**	**0.20**	**0.97**	**0.042**	**0.22**	**0.06**	**0.74**	**0.015**

Abbreviations: hsCRP, high-sensitivity CRP; CI, confidence interval; OR, Odds ratio; NA, Not applicable (due to low numbers). Bold values indicate statistical significant values (with p value below the conventional level of significance ($p < 0.05$)).
[a] Crude model: adjusted for age and sex by matching.
[b] Adjusted model: adjusted for age and sex by matching; adjusted by model for the use of cardiovascular drugs, antidiabetics, oral corticosteroids and duration of COPD at index date, and pack-years of cigarette smoking, total serum cholesterol, body-mass index and cardiovascular covariables at baseline.

ameliorated the structural and functional derangements of the lungs partly by suppressing inflammation and matrix MMP9 induction [23]. Statins may even reduce oxidative stress, related to their ability to scavenge oxygen derived free radicals [24].

The 39% reduced risk of death in COPD patients by using (long-term) statin therapy is consistent with findings of previous (retrospective) observational studies [8,9]. Similar to the retrospective study of Frost et al., we found a protective effect of statin use on the risk of pulmonary mortality in COPD [25]. Furthermore, our results showed that having an hsCRP baseline level of more than 3 mg/L was associated with increased mortality and therefore we expected, if statins were effective, that the pre-specified subset of COPD patients with high hsCRP levels would benefit most of treatment. Surprisingly but consistent with other prospective population-based studies in the elderly, we found that COPD patients with a total cholesterol of 240 mg/dL or more had a better survival [26,27]. Selective survival or changes in the arterial wall by aging might yield individuals resistant to the effects of high cholesterol concentrations in the blood or high cholesterol levels might be associated with less frailty.

Importantly, we demonstrate a significant interaction between statin use and the degree of systemic inflammation because the protective effect of statins was only significant in COPD patients with the highest hsCRP serum level. There was no significant effect in COPD patients with a low-to-moderate degree of systemic inflammation, which cannot be explained due to lack of power as numbers were even higher in this stratum. The same phenomenon has also been reported in cardiovascular studies and one RCT in COPD patients. Kinjo et al. described a decreased hazard by statin therapy for 1-year mortality in patients with a CRP level above 2.9 mg/L who had an acute myocardial infarction [28]. In addition, the JUPITER trial of apparently healthy persons without hyperlipidemia but with elevated hsCRP levels, demonstrated that rosuvastatin significantly reduced the incidence of all cause mortality and was associated with a 60% decreased risk for cardiovascular endpoints [29]. However, a recent RCT in persons at high risk of vascular events, could not confirm that these vascular benefits of statin therapy were affected by the baseline CRP concentration [22]. The RCT in COPD patients by Lee et al. demonstrated that the improvement in exercise time by statin treatment is modified by plasma hsCRP-levels [13]. Because both the inflammation and therapeutic interventions in COPD have been studied merely in (ex) smoking subjects, we furthermore restricted the analyses to smoking COPD patients, which confirmed the beneficial effects of long-term statin use in the subgroup with greater inflammation.

Because of its observational character, a possible limitation of our study is that treatment with statins was not randomly assigned. Our results could therefore be flawed by confounding by indication. However, because statins are selectively prescribed in subjects who have substantial comorbidities such as diabetes mellitus and cardiovascular disease, this kind of confounding would only underestimate the protective effect of statins on the risk of death. Consequently, this would mean that the true protective effect is even stronger than we measured. Secondly, we cannot exclude a healthy user bias if statins are prescribed more readily in health-conscious, medical-attention-seeking patients or in those patients who are expected to live long enough to benefit from statin treatment. Importantly, however, this would not explain effect modification by baseline hsCRP as this measurement was not used for usual patient care. Finally, of a minority of COPD patients diagnosed

Table 6
Association between statin use and the risk of death in COPD, stratified according to the total serum cholesterol level (at baseline).

		Crude model[a]				Adjusted model[b]			
		OR	95% CI		p-value	OR	95% CI		p-value
			Lower	Upper			Lower	Upper	
Total cholesterol < 240 mg/dL	No statin use	Reference				Reference			
	1–30 days	1.99	0.36	10.85	0.428	5.68	0.38	84.61	0.208
	31 days–2 years	0.32	0.07	1.40	0.130	0.17	0.02	1.42	0.102
	>2 years	0.41	0.13	1.30	0.129	**0.16**	**0.03**	**0.91**	**0.039**
Total cholesterol ≥ 240 mg/dL	No statin use	Reference				Reference			
	1–30 days	1.24	0.22	7.01	0.806	1.22	0.07	21.19	0.891
	31 days–2 years	0.69	0.37	1.32	0.266	0.65	0.32	1.33	0.238
	>2 years	0.79	0.47	1.31	0.355	**0.50**	**0.26**	**0.95**	**0.034**

Abbreviations: CI, confidence interval; OR, Odds ratio. Bold values indicate statistical significant values (with p value below the conventional level of significance ($p < 0.05$)).
[a] Crude model: adjusted for age and sex by matching.
[b] Adjusted model: adjusted for age and sex by matching; adjusted by model for the use of cardiovascular drugs, antidiabetics oral corticosteroids and duration of COPD at index date, and pack-years of cigarette smoking, body-mass index and cardiovascular covariables at baseline.

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by GP (17.5%), we do not have the certainty that diagnosis was confirmed by an obstructive spirometry. However, exclusion of this subgroup did not change the point estimator substantially.

The strengths of this study are the high quality information available about exposures prior to outcome with a prospective data collection, the general population based setting, the large number of subjects that participated in the Rotterdam Study and the long duration of follow-up. The high response rate and virtually complete follow-up for every participant makes information and selection bias for these data unlikely. An important advantage is the availability of continuous pharmacy dispensing data with complete pharmacy records of all filled prescriptions on practically all members of the cohort, providing very specific and detailed information on drug use and thus minimizing the risk of exposure misclassification. Furthermore, the nested case–control approach made it possible to account for other drug use at index date, a major confounder in the association between statins and mortality. It is important that these results should be further investigated in randomized controlled trials before recommending widespread statin use in COPD patients. According to Clinicaltrials.gov, several randomized clinical trials are ongoing.

In conclusion, statin use is associated with a decreased risk of all-cause mortality in patients with COPD, depending on the degree of systemic inflammation. These results suggest that in an older population of COPD patients, CRP levels might guide the clinician better than total cholesterol levels in his decision to start lipid lowering therapy. This study may provide a rationale for undertaking more definitive randomized clinical trials to confirm the impact of statin use on the outcome of COPD and to elucidate the mechanisms by which they may work.

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Conflict of interest

None of the authors had any conflict of interest to declare with respect to this paper.

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References

[1] Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006;27:397–412.
[2] van Durme Y, Verhamme KMC, Aarnoudse A, Van Pottelberge GR, Hofman A, Witteman JCM, et al. C-reactive protein levels, haplotypes, and the risk of incident chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;179:375–82.
[3] van Durme YM, Lahousse L, Verhamme KM, Stolk L, Eijgelsheim M, Loth DW, et al. Mendelian randomization study of interleukin-6 in chronic obstructive pulmonary disease. Respiration 2011.
[4] Brusselle GG, Joos GF, Bracke KR. New insights into the immunology of chronic obstructive pulmonary disease. Lancet 2011;378:1015–26.
[5] Agusti A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PLoS One 2012;7:e37483.
[6] Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. Eur Respir J 2006;28:1245–57.
[7] Janda S, Park K, FitzGerald JM, Etminan M, Swiston J. Statins in COPD a systematic review. Chest 2009;136:734–43.
[8] Dobler CC, Wong KK, Marks GB. Associations between statins and COPD: a systematic review. BMC Pulm Med 2009;9:32.
[9] Lawes CM, Thornley S, Young R, Hopkins R, Marshall R, Chan WC, et al. Statin use in COPD patients is associated with a reduction in mortality: a national cohort study. Prim Care Respir J 2012.
[10] Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005; 352:20–8.
[11] Man SF, Connett JE, Anthonisen NR, Wise RA, Tashkin DP, Sin DD. C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. Thorax 2006;61:849–53.
[12] Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG. C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007;175:250–5.
[13] Lee TM, Lin MS, Chang NC. Usefulness of C-reactive protein and interleukin-6 as predictors of outcomes in patients with chronic obstructive pulmonary disease receiving pravastatin. Am J Cardiol 2008;101:530–5.
[14] Hofman A, van Duijn CM, Franco OH, Ikram MA, Janssen HL, Klaver CC, et al. The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol 2011;26:657–86.
[15] WHO. Tenth Revision. International statistical classification of diseases and related health problems, vol. 1. Geneva: World Health Organization; 1992. Tabular list (1992); vol. 2: Instruction Manual (1993); vol. 3: Index (1994).
[16] Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon 3rd RO, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499–511.
[17] Third Report of the National Cholesterol Education Program (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. Circulation; 2002, 106: 3143–421.
[18] Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775–89.
[19] Young RP, Hopkins R, Eaton TE. Pharmacological actions of statins: potential utility in COPD. Eur Respir Rev 2009;18:222–32.
[20] Barnes PJ. Future treatments for chronic obstructive pulmonary disease and its comorbidities. Proc Am Thorac Soc 2008;5:857–64.
[21] Criner GJ, Scharf SM, Falk JA, Gaughan JP, Sternberg AL, Patel NB, et al. Effect of lung volume reduction surgery on resting pulmonary hemodynamics in severe emphysema. Am J Respir Crit Care Med 2007;176:253–60.
[22] Emberson J, Bennett D, Link E, Parish S, Danesh J, Armitage J, et al. C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20,536 patients in the Heart Protection Study. Lancet 2011;377:469–76.
[23] Lee JH, Lee DS, Kim EK, Choe KH, Oh YM, Shim TS, et al. Simvastatin inhibits cigarette smoking-induced emphysema and pulmonary hypertension in rat lungs. Am J Respir Crit Care Med 2005;172:987–93.
[24] Wagner AH, Kohler T, Ruckschloss U, Just I, Hecker M. Improvement of nitric oxide-dependent vasodilatation by HMG-CoA reductase inhibitors through attenuation of endothelial superoxide anion formation. Arterioscler Thromb Vasc Biol 2000;20:61–9.
[25] Frost FJ, Petersen H, Tollestrup K, Skipper B. Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. Chest 2007;131: 1006–12.
[26] Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. Lancet 1997;350:1119–23.
[27] Krumholz HM, Seeman TE, Merrill SS, Mendes de Leon CF, Vaccarino V, Silverman DI, et al. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. JAMA 1994;272:1335–40.
[28] Kinjo K, Sato H, Sakata Y, Nakatani D, Mizuno H, Shimizu M, et al. Relation of C-reactive protein and one-year survival after acute myocardial infarction with versus without statin therapy. Am J Cardiol 2005;96:617–21.
[29] Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. Circulation 2003;108:2292–7.

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