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Statin use is associated with reduced mortality in chronic obstructive pulmonary disease

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Abstract:

Patients with chronic obstructive pulmonary disease (COPD) have an increased risk of ischemic heart disease (IHD). Statins reduce mortality and morbidity in IHD. We hypothesised that statin treatment is associated with reduced long-term mortality in patients with COPD.

Using a retrospective cohort design**,** 854 consecutive patients (mean age 70.8 years, 51.5% female) with a diagnosis of COPD exacerbation were included in the study at discharge from a Norwegian teaching hospital

Median follow-up was 1.9 years, during which 333 patients died. The crude mortality rate per 1000 person-years was 110 in patients treated with statins, and 191 in patients not treated with statins. After adjustment for gender, age, smoking, pulmonary function and comorbidities, the hazard ratio for statin users vs. statin non-users was 0.57 (95% confidence interval 0.38-0.87**, p=0.009**). When subdividing statin-users and statin non-users into groups according to concomitant treatment with inhaled corticosteroids (ICS) the following hazard ratios were found: 0.75 (0.58-0.98) for ICS only, 0.69 (0.36-1.3) for statins only, and 0.39 (0.22-0.67) for the combined treatment with statin and ICS compared to no such treatment (p-trend <0.001).

Treatment with statins was associated with improved survival after COPD exacerbation. ICS appeared to increase the survival benefit associated with statin use.

Chronic obstructive pulmonary disease (COPD) is characterised by chronic airflow limitation that is usually progressive (1). During the past decades the mortality from COPD has increased, and COPD is expected to become the third greatest cause of mortality in Western countries by year 2020 (2). The majority of the patients are current or former smokers (1,3). Thus, patients with COPD are likely to develop other smoking-related diseases as well, predominantly symptomatic or asymptomatic ischemic heart disease (IHD) (4,5).

Chest pain and dyspnea are the most common symptoms in patients with IHD **(6)**. The likelihood of these symptoms increases with increasing intensity of the exercise. Likewise, patients with COPD frequently experience dyspnea or even chest pain on exertion or during an exacerbation. Thus, in COPD patients these symptoms may be misinterpreted as COPD related symptoms even if the origin is cardiac. Moreover, exercise capacity may be limited by impaired lung function concealing the coronary symptoms. Unfortunately, exercise testing and pharmacological stress testing for detection of myocardial ischemia is often poorly suited for patients with COPD. Hence, IHD among COPD patients may persist undiagnosed even though cardiovascular disease is increasingly being recognised as a leading cause of death in COPD (7).

After an exacerbation of COPD the median survival is only 3-5 years (8,9). **The prognosis is particularly serious in patients with hypercapnia and the presence of several comorbidities.** Except from long-term oxygen treatment, which is restricted to patients with chronic respiratory failure, no current therapies for COPD are known to alter long-term prognosis **(3)**. Whether inhaled corticosteroids (ICS) improve the prognosis is still a matter of controversy (10). By contrast, several drugs have been shown to improve prognosis after acute coronary events during the past decades, among them hydroxymethylglutaryl CoA reductase inhibitors (statins) in particular (11)

We hypothesised that many COPD patients might have subclinical IHD and that use of statins might be associated with improved survival. Moreover, we wanted to explore whether concurrent use of ICS would modify outcome.

Methods

Patients and design

In the present study we included consecutive patients discharged from Akershus University Hospital from 01-Jan-2000 through 31-Dec-2003 after a COPD exacerbation. **At discharge from the hospital the diagnoses of each patient was stored in a database using codes from the International Classification disease version 10 (ICD-10). Our patients were selected from this database. The following criteria for the selection of patients were used: *i*) a primary diagnosis of COPD exacerbation with (J44.0) or without lower tract infection ((J44.1), or *ii*) a main diagnosis of pneumonia (J13-J18.9) combined with an unspecified diagnosis of COPD (J44.x). Frequently, it is difficult to decide if COPD exacerbations are accompanied with pneumonia or not. Thus, we included patients coded with pneumonia as the main diagnosis and COPD as the underlying diagnosis.** Discharge diagnoses **were made by clinical assessment of each patient, and** had been verified by a physician specialised in internal medicine or chest medicine. Information on medications, co-morbidity, concomitant treatment and smoking history was obtained from the medical records of each patient. **No information of compliance of the statin treatment after discharge was available.** We considered the patients to have established IHD if there was a previous diagnosis of myocardial infarction, hospitalisation for unstable angina; they had undergone percutaneous coronary intervention, or coronary artery bypass surgery. Spirometry results in a stable state, i.e. at least one week prior to hospitalisation or one month after discharge, were available in 72.4 % of the patients. **A total of 592 patients had spirometry prior to the current hospitalisation. Among these patients 521 (88%) had FEV_1/FVC-ratio < 0.7.** Date of death was obtained from the Central National Register, which is based on a unique personal identification number for all Norwegian inhabitants. Characteristics of the patients at discharge from hospital are shown in table 1.

Table 1
Characteristics of the patients at discharge from the hospital.

	Statin user		
	Yes (n=118)	No (n=736)	Total (n=854)
Pneumonia n (%)			
Yes	53 (44.9)	322 (43.8)	375 (43.9)
No	65 (55.1)	414 (56.3)	479 (56.1)
Gender n (%)			
Male	70 (59.3)	344 (46.7)	414 (48.5)
Female	48 (40.7)	392 (52.1)	440 (51.5)
Age in yrs., mean (SD)	68.5 (8.4)	71.1 (11.6)	70.8 (11.2)
Spirometry, mean (SD)			
FVC in litres	2.50 (0.81)	2.21 (0.83)	2.25 (0.83)
FVC, % of predicted	77.4 (20.4)	71.1 (23.1)	72.1 (22.8)
FEV_1 in litres	1.36 (0.51)	1.16 (0.56)	1.19 (0.56)
FEV_1, % of predicted	52.4 (16.6)	46.7 (20.2)	47.6 (19.8)
Spirometry missing n (%)	24 (20.3)	212 (28.8)	236 (27.6)
Smoking habits n (%)			
Never smoker	10 (8.5)	49 (6.7)	59 (6.9)
Former smoker	43 (36.4)	277 (37.5)	320 (37.5)
Current smoker	60 (50.9)	382 (51.9)	442 (51.8)
Missing	5 (4.2)	28 (3.8)	33 (3.9)
Comorbidity n (%)			
Lung cancer	6 (5.1)	26 (3.5)	32 (3.8)
Cancer, other sites	7 (5.9)	64 (8.7)	71 (8.3)
Ischemic heart disease	73 (61.9)	170 (23.1)	243 (28.5)
Congestive heart failure	29 (24.6)	140 (19.0)	169 (19.8)
Atrial fibrillation	20 (16.7)	147 (20.0)	167 (19.6)
Cerebrovascular disease	16 (13.6)	51 (6.9)	67 (7.9)
Peripherial vascular disease	17 (14.4)	40 (3.0)	28 (3.0)
Arterial hypertension	44 (37.3)	135 (18.3)	179 (21.1)
Diabetes	25 (21.2)	77 (10.5)	102 (11.9)
Venous thrombembolism	3 (2.5)	18 (2.5)	21 (2.5)
Concomitant treatment n (%)			
ACEI or ARB	37 (31.6)	142 (19.3)	179 (21.0)
Beta-blockers	44 (37.6)	67 (9.1)	111 (13.0)
Acetyl salicylate	59 (50.0)	165 (22.5)	224 (26.3)
Warfarin	16 (13.7)	68 (9.3)	84 (9.9)
Inhaled corticosteroids	79 (67.0)	462 (62.8)	541 (63.4)
Long term oxygen-therapy	5 (4.3)	65 (8.9)	70 (8.3)

ACEI: Angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker

Data analyses

All-cause mortality after discharge from the hospital was used as the outcome measure. First, the age-adjusted relative mortality was assessed using Mantel-Haenszel test for incidence density data. Second, a multivariate analysis was performed using Cox proportional hazards regression. The covariates listed in table 2 were included in the initial multivariate model. If the age-adjusted association between statin use and mortality deviated meaningfully from the age-adjusted mortality of statin, a product-term between the corresponding covariate and statin was included in the initial multivariate model**.** Backward elimination of covariates was performed if the covariate was not significant and the removal of the covariate did not cause a meaningful change of the association between mortality and treatment with statins. Time after discharge from the hospital was used as the underlying time variable. The proportional hazard assumption was tested using Schoenfeld's residuals on partial likelihood **(12)**. Results are reported as rate ratio (RR) for stratified analyses, or hazard ratio (HR) for Cox analyses, with 95 % confidence intervals in parentheses.

Statistical analyses were performed using Stata/SE version 8.2 software (StataCorp LP, Texas, USA).

Results

The study comprised 854 patients. The median follow-up was 1.9 years. Cumulative survival was 75.4 %, 65.0 %, 59.6 % and 55.6 % at one, two, three and four years after discharge. The crude relative mortality ratio among statin-users versus non-users was 0.58 (0.39-0.84), whereas the age-adjusted relative mortality ratio was 0.66 (0.45-0.96). The age-adjusted relative mortality for separate covariates is shown in table 2. Bivariate analyses indicated that the adjusted mortality was lower in statin-users than non-users in almost all the subgroups (table 2). The following covariates were included as product-terms with statin in the initial multivariate Cox model: IHD, congestive heart failure, cerebrovascular disease and treatment with acetyl salicylate. A product-term with ICS was also added.

Table 2
Number of deaths (n), mortality rate (MR) in 1000^{-1} $year^{-1}$, age-adjusted and age-specific* mortality rate ratio (MRR) with 95% confidence interval (95% CI).

	Statin user: n (MR)		
	Yes	No	MRR 95% CI
Gender			
Male	19 (121)	160 (228)	0.58 (0.36-0.94)
Female	12 (98)	142 (162)	0.70 (0.38-1.3)
Age in yrs.			
< 60	1 (17)	25 (67)	0.25* (0.01-1.6)
60 – 69	8 (121)	35 (97)	1.3* (0.50-2.7)
70 – 79	20 (146)	111 (202)	0.72* (0.43-1.2)
≥ 80	2 (105)	131 (450)	0.23* (0.03-0.86)
FEV_1 % of predicted			
< 30	5 (500)	63 (320)	1.5 (0.61-3.9)
30 – 49	10 (124)	105 (214)	0.48 (0.25-0.92)
≥ 50	16 (86)	134 (150)	0.81 (0.42-1.6)
Missing	4 (98)	59 (167)	0.74 (0.27-2.0)
Smoking habits			
Never smoker	0 (0.0)	18 (168)	0.00 (0-0.70)
Former smoker	18 (202)	125 (224)	1.2 (0.75-2.4)
Current smoker	11 (75)	149 (174)	0.49 (0.26-0.91)
Comorbidity			
Ischemic heart disease	20 (120)	105 (357)	0.43 (0.26-0.72)
Congestive heart failure	10 (156)	99 (550)	0.29 (0.15-0.55)
Atrial fibrillation	8 (182)	97 (458)	0.52 (0.25-1.1)
Cerebrovascular disease	4 (111)	29 (345)	0.36 (0.12-1.1)
Peripherial vascular disease	6 (177)	24 (429)	0.43 (0.17-1.1)
Arterial hypertension	16 (172)	55 (194)	1.1 (0.59-2.0)
Diabetes	10 (208)	49 (395)	0.81 (0.41-1.6)
Venous thrombembolism	1 (250)	13 (650)	1.1 (0.19-6.5)
Lung cancer	3 (375)	21 (808)	0.96 (0.31-3.0)
Cancer, other sites	4 (444)	44 (579)	0.85 (0.29-2.5)
Concomitant treatment			
ACEI or ARB	14 (194)	71 (261)	1.1 (0.61-2.1)
Beta-blockers	11 (106)	35 (252)	0.57 (0.28-1.2)
Acetyl salicylate	13 (88)	85 (259)	0.44 (0.24-0.82)
Warfarin	6 (231)	42 (362)	0.80 (0.32-2.0)
Inhaled corticosteroids	19 (98)	175 (170)	0.65 (0.40-1.1)
Long term oxygen-therapy	1 (91)	37 (407)	0.33 (0.05-2.1)

ACEI: Angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker

The results of the Cox regression analysis are presented in table 3. The presence of IHD, congestive heart failure, atrial fibrillation, diabetes, venous thromboembolism, lung cancer, and cancers other than lung cancer, were all associated with increased mortality (table 3). The HR for pneumonia was, however, not higher than in the non-pneumonia group (HR=0.98, p=0.99). Moreover, the HR for females was not significantly different from that of males (HR=0.89, p=0.38), and we found no significant association between current smoking and mortality (HR=1.2, p=0.32).

Table 3
Multivariate Cox-regression analyses of mortality after discharge from the hospital.

Covariate	Hazard-ratio	95 % confidence interval	p-value
Gender: female *vs*. male	0.89	0.70-1.2	0.4
Age in years			
< 60	1		
60-69	1.6	0.93-2.8	0.09
70-79	2.5	1.5-4.1	<0.001
≥ 80	4.5	2.7-7.6	<0.001
Current smoking: yes vs. never	1.2	0.89-1.7	0.2
FEV_1 % of predicted + 10%	0.80	0.74-0.86	<0.001
Comorbidity: yes *vs*. no			
Ischemic heart disease	1.3	1.0-1.7	0.03
Congestive heart failure	1.6	1.2-2.2	0.001
Atrial fibrillation	1.6	1.2-2.1	0.002
Diabetes	1.8	1.3-2.5	<0.001
Venous thromboembolism	2.0	1.0-3.7	0.04
Lung cancer	4.6	2.8-7.5	<0.001
Cancer: other sites	2.3	1.6-3.3	<0.001
Treatment			
Statins	0.57	0.38-0.87	0.009
Inhaled corticosteroids	0.73	0.57-0.94	0.01

The HR for patients treated with statins was 0.57 (0.38-0.87) compared with non-statin users (table 3). **None of t**he product terms **between statins and IHD, congestive heart failure, cerebrovascular disease, acetyl salicylate, or ICS** were significant (p=0.20, **0.16, 0.33, 0.57,** and 0.48, respectively), suggesting no effect modification on statins **by any of these covariates**. Concomitant treatment with ACE inhibitors or angiotensin receptor blockers (HR 1.0 (0.73-1.4)), aspirin (HR 0.94 (0.68-1.3)), beta-blockers (HR 0.92 (0.61-1.4)), warfarin

(HR 1.0 (0.67-1.6)) did not affect the mortality risk. However, treatment with ICS was associated with improved survival (HR 0.73 (0.57-0.94)).

Finally, we stratified statin users and statin non-users into ICS users and ICS non-users. Cox regression analysis, employing the same covariates as in Table 3, revealed that the relative mortality among ICS users only, statin users only, and those using a combination of statins and ICS was 0.75 (95% CI 0.58-0.98), 0.69 (95% CI 0.36-1.3), and 0.39 (95% CI 0.22-0.67), respectively, compared with patients receiving none of these treatments (p-trend <0.001). For the trend test, the coefficients from the corresponding Cox-analysis were used as scores.

The final model did not violate the proportional hazard assumption for any of the covariates or the global test (p=0.63).

Discussion

We have found that the mortality among COPD patients after discharge from hospital was lower among those who were taking a statin as compared to those who did not. Furthermore, combined use of statins and ICS was associated with a more favourable prognosis than use of statin alone.

In our study nearly 30 % of the patients had diagnosed IHD. Additionally, it is likely that several of the patients had unrecognised IHD. In an autopsy study at our hospital 106/144 of the patients with COPD diagnosis (74 %) had coexisting heart disease (13). Moreover, in a pilot study of 30 COPD patients hospitalised for exacerbations 30 patients had an elevated level of troponin T. During five months after discharge from the hospital 3 of the patients (50 %) with elevated troponin T died, whereas only 1 patient (4 %) died among the remaining 24 patients (p=0.03, age-adjusted log-rank (14). High prevalence of troponin elevation during exacerbation of COPD has also been described by others (15). Nevertheless, only 12 % of these patients got a diagnosis of acute coronary syndrome Thus, it appears a considerable proportion of COPD patients may have an undiagnosed IHD.

Treatment with statins is now a cornerstone-therapy for patients with IHD (11). A meta-analysis of 90056 patients in 14 randomised trials showed 12 % proportional reduction in all-cause mortality, and 19 % for coronary, and 18 % for respiratory mortality (16). The latter relation was, however, not significant. As symptoms of cardiac ischemia may be

misinterpreted as pulmonary symptoms, and many COPD patients have too low exercise capacity to provoke coronary symptoms it is difficult to identify COPD patients with concomitant IHD. Thus, it appears likely that COPD patients should benefit from statin treatment.

Recently, Mancini and co-workers reported that statin treatment reduces mortality among COPD in a register-based retrospective cohort study (17). Interestingly, they also found a decreased number of hospitalisation due to COPD exacerbation. In an experimental study in rat lungs it was found that simvastatin had a suppressing effect on the inflammatory process induced by cigarette smoking (18). Thus, the beneficial effect of statins may be mediated by an anti-inflammatory effect in the lungs and the airways. In these regards statin treatment may increase the anti-inflammatory effect on the airways that has been observed with ICS treatment (19). **In our study there was no effect modification by ICS on the association between statins and mortality, in agreement with Mancini and co-workers (15).**

There is growing evidence that COPD is associated with a systemic inflammatory component, the intensity of which relates to the severity of the underlying disease (20). It is conceivable that this systemic component may exacerbate the inflammatory process that is associated with atherosclerosis and atherothrombosis. An association between airways inflammation and cardiovascular events has previously been suggested in studies of the effects of air pollution (21)

There is still controversy concerning a possible survival benefit from long-term use of ICS in COPD. A recent systematic review and meta-analysis found a pooled RR of 0.81 (95% CI: 0.60-1.08) for mortality (10). We found that ICS use was associated with reduced mortality, and an additive benefit from concurrent statin use. Even though ICS do not seem to alter the rate of decline in lung function, there is strong evidence that they reduce the frequency of exacerbations, which are both related to mortality in COPD (22, 23). A recent observational study by Huiart and colleagues showed that use of ICS was associated with significant decrease in the risk of myocardial infarction among patients with COPD (24). Whether ICS can suppress systemic inflammation in COPD is not clear at present, but there are studies suggesting such an effect (25).

The overall mortality rate in our study was comparable with the long-term mortality rate in previous studies of patients hospitalised with COPD exacerbation (26,27). A physician specialised in internal medicine or pulmonary medicine verified the diagnoses. Thus, the study population was well defined. Mortality data were gathered from the Central National Register, which is based on a unique personal identification number for all Norwegian inhabitants. This ensured complete follow up of the cohort, and makes misclassification of the outcome highly unlikely.

The main limitation of this study is its non-randomised design. Thus, statin treatment could have been restricted to patients with inherently better prognosis than patients who were not offered this treatment. Even though many important determinants of mortality were adjusted for in multivariate analyses, we cannot completely rule out the possibility that important prognostic factors might have been imbalanced between the groups. **Moreover, the results should be interpreted with caution due to the limited number of patients.** Consequently, our results should be considered to be hypothesis-generating, and not definitive.

In conclusion, this study shows that use of statins is associated with improved survival after COPD exacerbation, regardless of whether or not the patients have a diagnosis of IHD. Concurrent medication with inhaled corticosteroids appears to further enhance this beneficial effect. If these findings can be confirmed in prospective randomized clinical trials, which are now warranted, it may lead to a paradigm shift in the treatment of this large patient population.

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