Can simvastatin reduce COPD exacerbations? A randomised double-blind controlled study

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Shareable abstract (@ERSpublications)
Acute exacerbations of COPD cause a lot of suffering and healthcare burden. In this study, *p.o.* simvastatin 40 mg·day^{-1} reduced time to first exacerbation and exacerbation frequency in a double-blind, randomised controlled trial. https://bit.ly/3nHINet

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Abstract

Background Several studies have shown that statins have beneficial effects in COPD regarding lung function decline, rates and severity of exacerbation, hospitalisation and need for mechanical ventilation.

Methods We performed a randomised double-blind placebo-controlled single-centre trial of simvastatin at a daily dose of 40 mg *versus* placebo in patients with Global Initiative for Chronic Obstructive Lung Disease criteria grades 2–4 at a tertiary care pulmonology department in Austria. Scheduled treatment duration was 12 months and the main outcome parameter was time to first exacerbation.

Results Overall, 209 patients were enrolled. In the 105 patients taking simvastatin, time to first exacerbation was significantly longer compared to the 104 patients taking placebo: median 341 *versus* 140 days (log-rank test p<0.001). Hazard ratio for risk of first exacerbation for the simvastatin group was 0.51 (95% CI 0.34–0.75; p=0.001). Rate of exacerbations was significantly lower with simvastatin: 103 (41%) *versus* 147 (59%) (p=0.003). The annualised exacerbation rate was 1.45 events per patient-year in the simvastatin group and 1.9 events per patient-year in the placebo group (incidence rate ratio 0.77, 95% CI 0.60–0.99). We found no effect on quality of life, lung function, 6-min walk test and high-sensitivity C-reactive protein. More patients dropped out in the simvastatin group compared to the placebo group (39 *versus* 29).

Conclusion In our single-centre RCT, simvastatin at a dose of 40 mg daily significantly prolonged time to first COPD exacerbation and reduced exacerbation rate.

Introduction

COPD is an enormous challenge for healthcare systems all over the world, with an estimated 328 million people being affected worldwide; within the next decade, COPD is expected to become the leading cause of death worldwide [1]. While 20–30% of deaths in patients with COPD are attributed to cardiovascular disease, acute exacerbations are associated with worsened quality of life, decreased lung function, increased hospitalisations, costs of care and mortality [2–5]. However, effective therapies for prevention of COPD exacerbations are limited [6].

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors that are widely used in clinical practice for lowering cholesterol serum levels in patients. They play an important role in secondary prophylaxis of cardio- and cerebrovascular events and long-term treatment proved to improve outcome and reduce coronary heart disease related mortality [7, 8]. In extension to their lipid-lowering therapy, statins show anti-inflammatory, immunomodulatory and antioxidative effects [9]. This includes beneficial effects in COPD regarding lung function decline, need for mechanical ventilation, rates of hospitalisation

and mortality in several, mostly retrospective, studies [10–15]. To clarify the role of statins for prevention of COPD exacerbations, we conducted a prospective double-blind placebo-controlled randomised study (RCT).

Methods

Study design

In this single-centre randomised, parallel-group, placebo-controlled trial, participants were randomly assigned in a 1:1 ratio to receive simvastatin orally at a dosage of 40 mg or an identical-looking placebo drug once daily. Participants were recruited from the pulmonology department at Landesklinikum Hochegg (Grimmenstein, Austria). Written informed consent was obtained from all study participants and the institutional review board approved the study protocol. Study reporting complies with Consolidated Standards of Reporting Trials guidelines [16].

Study population

Patients aged between 40 and 85 years with a diagnosis of COPD defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 2–4 were enrolled according to lung function criteria: ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) <70% and FEV_1 <80% predicted after bronchodilator use. They were current or former smokers with ⩾20 pack-years lifetime cigarette consumption.

Exclusion criteria were as follows. Other diagnosed lung diseases except COPD; suspected or diagnosed coronary artery, cerebrovascular and peripheral artery disease; valvular heart disease; significant arrhythmic and conductance heart disease; left and right heart insufficiency or uncontrolled arterial hypertension; patients already receiving statins; statin therapy within the past 4 weeks; allergy against statins; taking drugs that are contraindicated together with statins; active liver disease including unclear and repetitive elevation of serum transaminases or serum transaminases greater than three-fold level of upper normal value; chronic renal impairment (glomerular filtration rate <30 $mL \cdot min^{-1}$); known myopathy or elevated risk for myopathy; galactose intolerance; Lapp-lactase deficit; and glucose-galactose malabsorption.

Study participants filled out a patient medication diary daily and noted every change of medication.

Study visits

Spirometric measurements post-bronchodilator (FVC and FEV_1), 6-min walk test, St George's Respiratory Questionnaire (SGRQ) and blood samples (total cholesterol, high-density (HDL) and low-density lipoprotein (LDL), triglyceride, high-sensitivity C-reactive protein (hsCRP)) were performed at baseline, 3, 6 and 12 months.

Spirometry was performed according to American Thoracic Society and European Respiratory Society guidelines [17]. All study visits were performed at the pulmonology department at Landesklinikum Hochegg.

Intervention

Study patients took encapsulated simvastatin (Genericon Pharma, Graz, Austria) at a dosage of 40 mg or placebo orally once daily for a treatment period of 1 year.

Randomisation and blinding of study medication

Randomisation was performed using sealed, opaque envelopes, which were produced before the start of the study with the help of an open randomisation generator (www.randomisation.com) and with block sizes of four by a person not otherwise involved in patient care. Study drugs (simvastatin and placebo) were prepared and supplied by JF (Landesklinikum Mödling, Mödling, Austria). Hard gelatine capsules were filled with simvastatin 40 mg tablets (verum) or lactose (placebo), so that the capsules had the same appearance, size and mass (0.51 g). All study staff in direct contact with participants (*i.e.* nurses, principal investigator, subinvestigators) and all study patients themselves were blinded for the treatment. Study medication for each patient was prepared for the period until the next study visit (at 3, 6 and 12 months) and identified by numbers on the medication box. Patients' adherence to the study medication was assessed by interview the study visits, inspection of the drug container and the patient's study diary.

Outcomes

The predefined primary outcome variable was time to first moderate-to-severe COPD exacerbation. The most relevant secondary outcome variable was the rate of COPD exacerbations. Moderate exacerbation was

defined as impairment of respiratory symptoms necessitating systemic corticosteroids and/or antibiotics [18, 19]. Severe exacerbation additionally needed hospitalisation [19].

Further secondary outcome variables were SGRQ, 6-min walk test, FVC, FEV_1 and laboratory values (cholesterol, HDL, LDL, triglyceride, hsCRP).

Statistical analysis

Sample-size calculation was based on a case–control study [11] which showed that mean time to first COPD exacerbation was 5 months longer in the statin group. We assumed that a clinical significant benefit would be a difference of ⩾2 months. For a two-sided log-rank test a sample size of 83 per group was calculated, given a power of 80% at a Type I error rate of 5%. To account for potential loss to follow-up the total study size was increased by 25% to an overall sample size of 208 participants.

We present categorical data as absolute count and relative frequency, and continuous data as mean±SD. We compared baseline variables between the simvastatin group and the placebo group by tabulation and tested the null hypothesis of no difference using Fisher's exact test or the Mann–Whitney U-test, as appropriate. The primary outcome was defined as time to first exacerbation within 1 year. Observation time was censored at the first event, end of follow-up, death or at 365 days. Following the intention-to-treat principle, we analysed patients as randomised.

We analysed data as available and did not use any missing-data imputation methods. We used survival analysis acknowledging the time to first event, ignoring subsequent events.

We calculated 95% confidence intervals for the treatment effects. In a *post hoc* sensitivity analysis we tested for interaction of the main effect by recruitment period and dropout status by including these as interaction terms into the main model separately. We used the log-rank test to compare survivor functions between the study groups. Using the Kaplan–Meier method, we plotted probabilities of at least one exacerbation, allowing for censoring.

As an explanatory analysis we analysed the number of exacerbations. We used the Mann–Whitney U-test to test the null hypothesis of no difference in exacerbations between the intervention groups. To estimate the effect of simvastatin *versus* placebo on the annual exacerbation rate we used a Poisson regression model and calculated the incidence rate ratio (IRR) with a 95% confidence interval.

We compared mortality using Fisher's exact test, and reasons for withdrawal from the study between treatment groups by tabulating data. We used logistic regression models with treatment allocation as the covariable for each outcome to calculate odds ratios with 95% confidence intervals. Spirometry, 6-min walk test, SGRQ and laboratory parameters were measured on three occasions after baseline (3, 6 and 12 months). We considered these as panel data with longitudinally repeated measurements. To allow for this we used a random-effects linear regression model with these outcomes as dependent variables, the patient identifier as the cluster specification and treatment allocation as the covariable to calculate linear coefficients with 95% confidence intervals. For data management and analyses we used MS Excel and Stata 14 for Mac (Stata Corp, College Station, TX, USA). Generally, we considered a two-sided p-value <0.05 statistically significant.

Results

Enrolment and follow-up

Screening, enrolment and randomisation as well as follow-up are presented in figure 1. Enrolment began in August 2012 and was finished in April 2017. Among the 520 patients screened, 209 were eligible for our study and were enrolled. 105 patients were randomly allocated to the simvastatin group and 104 patients to the placebo group.

More patients in the simvastatin group withdrew from the study than from the placebo group (39 *versus* 29). Most dropouts occurred within the first 6 months (35 with simvastatin and 27 with placebo). 25 patients wished to discontinue study medication (13 in the simvastatin group and 12 in the placebo group) and 20 patients did not come to the scheduled study visits (11 in the simvastatin group and nine in the placebo group).

In the simvastatin group, 12 patients withdrew from the study due to medical reasons: four developed myopathy; four received a new diagnosis of coronary artery disease after study entry and therefore had a clear indication to take a statin; one patient experienced respiratory worsening; two patients developed worsening of general condition; and one patient stopped medication because of hair loss.

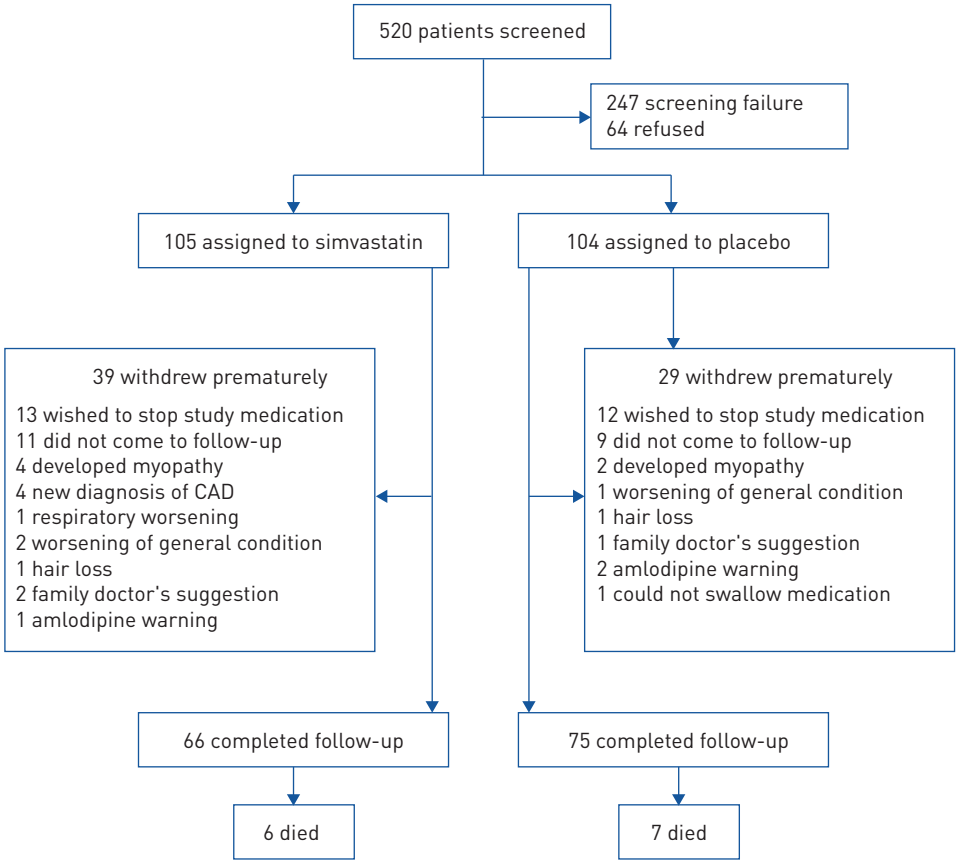


FIGURE 1 Enrolment, randomisation and study completion. CAD: coronary artery disease.

In the placebo group, four patients withdrew from study treatment: two patients because of myopathy, one patient because of worsening of general condition and one patient because of hair loss.

In three patients (two in the simvastatin group and one in the placebo group), the family doctor (general physician or pulmonologist) suggested stopping the study drug without contacting the study investigators.

Due to the 2014 World Health Organization warning of concomitant use of amlodipine with simvastatin, three patients (one in the simvastatin group and two in the placebo group) discontinued the study drug. In other patients, amlodipine was stopped or substituted with an alternative antihypertensive drug. One patient in the placebo group withdrew because he could no longer swallow the medication.

Characteristics of the study population

Demographic and baseline characteristics are presented in table 1. Mean age was 64±8 years; 79 (38%) were female. Spirometry showed a mean FEV_1/FVC of 45.4±14.2% and FEV_1 of 1.2±0.6 L and 39.4±17% pred. Overall, 38 patients were current smokers and 171 were former smokers with a total smoking history of 49±30 pack-years. 6-min walk distance was 249±116 m. The majority of our patients (80%) were on a triple inhalation therapy containing a long-acting muscarinic antagonist (LAMA), a long-acting β-agonist (LABA) and an inhaled corticosteroid (ICS) followed by LAMA monotherapy (8%), LABA+ICS (6%) and LAMA+LABA (5%). One patient was on short-acting muscarinic antagonist+short-acting β-agonist and one was on LAMA+ICS. 13 (6%) patients took an oral theophylline and 11 (5%) an oral roflumilast, in addition to inhaled treatment. Demographic characteristics were comparable in both groups except smoking history: pack-years were significantly ($p=0.048$) higher in the simvastatin group.

COPD exacerbations

The median number of days to the first moderate-to-severe exacerbation was significantly higher in the simvastatin group compared to the placebo group: 341 *versus* 140 days (log-rank test $p<0.001$). Hazard ratio

TABLE 1 Demographic characteristics

	Simvastatin	Placebo	p-value
Patients	105	104	
Age years	65±7.6	63.5±8.2	NS
Male	66 (63)	64 (61.5)	NS
Current smoking	20 (19)	18 (17)	NS
Smoking history pack-years	52±30	47±31	0.048
COPD stage[#]			NS
GOLD 2	32	23	
GOLD 3	40	38	
GOLD 4	33	43	
FEV_1 L	1.2±0.6	1.2±0.6	NS
FEV_1 % pred	40.9±17.5	37.9±16.5	NS
FVC L	2.3±0.8	2.2±0.8	NS
FVC % pred	63±18.9	59.3±17	NS
FEV_1/FVC %	46.1±14.2	44.6±14.2	NS
6MWD m	258±113	241±118	NS
COPD medication			
LAMA+LABA+ICS	81	86	NS
LAMA+LABA	6	5	NS
LAMA+ICS	1	0	NS
LAMA	9	7	NS
LABA+ICS	8	5	NS
SABA+SAMA	0	1	NS
Theophylline	6	7	NS
Roflumilast	5	6	NS

Data are presented as n, mean±SD or n (%), unless otherwise stated. GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; 6MWD: 6-min walk distance; LAMA: long-acting muscarinic antagonist; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroids (glucocorticoids); SABA: short-acting β_2-agonist; SAMA: short-acting muscarinic antagonist; NS: nonsignificant. [#]: GOLD staging system is used to assess the severity of lung disease, with grade 4 indicating the most severe disease.

for first exacerbation for the simvastatin *versus* placebo was 0.51 (95% CI 0.34–0.75; p=0.001). Figure 2 presents the Kaplan–Meier curve of time to first exacerbation.

250 COPD exacerbations occurred during the study period (table 2): 103 (41%) among the 105 patients in the simvastatin group and 147 (59%) among the 104 patients in the placebo group (p=0.003). Severe exacerbations occurred more frequently in the placebo group compared to the simvastatin group (45 *versus* 35; p=0.07) as did moderate exacerbations (102 *versus* 68; p=0.02).

The annualised COPD exacerbation rate was 1.45 events per patient-year in the simvastatin group and 1.9 in the placebo group, which means a relative reduction of 23% (IRR 0.77, 95% CI 0.60–0.99) for patients taking simvastatin *versus* placebo.

In a *post hoc* analysis we found no interaction of the main effect with recruitment period (p=0.63) and dropout status (p=0.69) Further details on the dropout status are provided in the supplementary material.

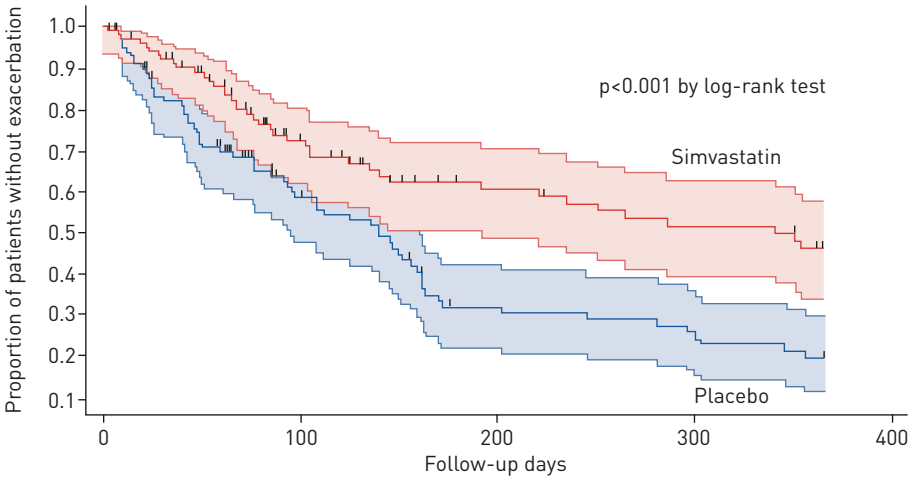
Secondary outcomes

There was no effect of simvastatin on quality of life (SGRQ), spirometry or 6-min walk test (table 3).

Six patients died in the simvastatin group and seven in the placebo group during the 12-month follow-up (p=0.78).

Lipid levels and hsCRP

Simvastatin treatment significantly reduced total cholesterol and LDL at 3, 6 and 12 months' visits compared to placebo. In addition, triglyceride levels were significantly lower under simvastatin treatment (table 4). There was no significant treatment effect on HDL.



At risk n					
Placebo	104	44	21	17	0
Simvastatin	105	53	35	29	0

FIGURE 2 Effect of simvastatin on the time to the first exacerbation of COPD. There was a significant between-group difference in the time to the first exacerbation. The median time to the first exacerbation was 341 (95% CI 192–not applicable) days in the simvastatin group and 140 (95% CI 95–161) days in the placebo group.

Simvastatin had no influence on hsCRP.

Adverse events

Myopathy occurred in four patients with simvastatin and two patients with placebo; alopecia developed in one patient in each group.

Discussion

In this double-blind, placebo-controlled RCT we found that 12 months of treatment with 40 mg simvastatin daily significantly prolonged the time to first moderate-to-severe COPD exacerbation. The median time to first exacerbation was doubled compared to placebo. In addition, the overall frequency of exacerbations was significantly lower in the simvastatin group; dividing exacerbations into moderate and severe, only moderate exacerbations were significantly lower with simvastatin.

Accordingly, the annualised COPD exacerbation rate showed a 23% relative reduction in the simvastatin compared to the placebo group. This is in the range of the effect of ICS: ICS/LABA combinations reduced annual exacerbation rates by approximately 25–35% compared with LABA monotherapy [20] whereas triple therapy (ICS+LABA+LAMA) also showed a reduction of the exacerbation rate by 15–25% in IMPACT and TRIBUTE [21, 22].

Adherence to study medication was documented as well as possible during the study visits by counting the remaining medication and control of the patient's diary. In addition, the significant lowering of total cholesterol and LDL in the simvastatin group supports a good study drug adherence.

TABLE 2 Number of COPD exacerbations

	Simvastatin	Placebo	p-value
Exacerbations	103	147	0.003
Severe	35	45	0.068
Moderate	68	102	0.02

Data are presented as n, unless otherwise stated.

TABLE 3 Effect of simvastatin on quality of life, lung function and 6-min walk distance (6MWD)

	Simvastatin				Placebo				p-value
	Baseline	3 months	6 months	12 months	Baseline	3 months	6 months	12 months	
SGRQ	43.5±121	35.7±15.3	35.1±15.4	34.1±15.4	46.1±12.6	37.3±13.9	39±14.6	37.8±14.6	0.37
FEV_1 % pred	41.5±18.6	42.1±20.3	41.9±22.5	43.5±22.3	37.9±16.5	38.5±19.6	39.1±21.3	39.8±22.6	0.38
FVC % pred	63±18.9	62.9±21.8	65.6±21.8	64.5±23.3	59.3±17	60.2±18.8	60.6±20.6	60.5±21.3	0.93
FEV_1/VC %	46.1±14.2	50.8±15.7	49.8±15.6	51.6±15.2	44.6±14.2	49.2±14.5	50.3±15	50.2±15.3	0.67
6-MWD m	258±113	257±127	255±138	256±125	241±118	248±131	230±120	234±144	0.59

Data are presented as mean±SD, unless otherwise stated. SGRQ: St George's Respiratory Questionnaire; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; VC: vital capacity.

Several previous human studies have shown that statins may be beneficial for COPD patients. In COPD patients, simvastatin decreased biomarkers in sputum that are associated with airway inflammation and remodelling [23]. Alexeeff *et al.* [10] showed in 803 males that statin use attenuated lung function decline. In a double-blind RCT, Lee *et al.* [14] observed that statin use improved exercise tolerance and dyspnoea in 53 COPD patients. In a retrospective cohort study, Blamoun *et al.* [11] showed that statin treatment reduced exacerbations and requirement for intubation in 185 COPD patients. A large retrospective database analysis showed that statin use was associated with reduced hospitalisation and mortality in COPD [15]. Likewise, reduction of mortality in COPD has been shown by a population-based Japanese analysis [24], a retrospective analysis in Norway [25], a large matched US cohort study with 76 232 patients [12] and a case–control study from Rotterdam [26]. In a systematic review, Dobler *et al.* [27] found that statin intake in COPD was associated with reduced morbidity and mortality. A large Danish study (>5000 patients) found that statin use was associated with a reduced risk for COPD exacerbation (OR 0.67 in a multivariable conditional logistic regression analysis) [28]. Our study was started before publication of the multicentre RCT STATCOPE by Criner *et al.* [29] with a total of 885 enrolled COPD patients. In this study, 40 mg of simvastatin had no benefit on frequency of exacerbations and on time to first exacerbation. In addition, the authors found no effect on lung function and quality of life. The study population was similar to our study regarding the parameters age, percentage male and COPD severity stage. Likewise, baseline lung function was similar in both studies (mean FEV_1 was 1.2 L in both arms of both studies, but more patients in our study used ICS (87% in both arms) compared to STATCOPE (72% and 75% for simvastatin and placebo, respectively).

The differences in outcome of the observational studies and STATCOPE are highlighted in the review by Young *et al.* [30].

One reason for the different results of our RCT as well as the smaller RCT by Lee *et al.* [14] and the observational studies mentioned earlier may be the different selection criteria: in STATCOPE [29], patients with diabetes and subclinical cardiovascular risk/disease (termed "unhealthy untreated" in the Young *et al.* [30] review) were excluded, in contrast to the current study. Thus, our population may be nearer to the "real world", reflecting the high comorbidity rate in COPD patients.

Cardiac diseases play an important role within the comorbidity scale [6]. Heart failure and ischaemic heart disease contribute to COPD exacerbations and increase the risk of frequent exacerbations and mortality in

TABLE 4 Lipid levels and high-sensitivity C-reactive protein (hsCRP) at baseline and 3, 6 and 12 months by treatment group

	Simvastatin				Placebo				p-value
	Baseline	3 months	6 months	12 months	Baseline	3 months	6 months	12 months	
Total cholesterol $mg \cdot dL^{-1}$	206.7±43.2	158.7±29.2	165.3±35.1	169.8±33.8	212.6±39.5	213.7±34.8	213.4±34.2	215±41.3	<0.00001
HDL $mg \cdot dL^{-1}$	64.7±20.4	68±20.5	69.3±22.7	66.3±20.5	62.1±21.8	64.8±19.3	66.2±21.6	66.3±20	0.41
LDL $mg \cdot dL^{-1}$	113.4±38.3	67.5±23	73.4±32	79.3±32.6	119.5±34.2	121±27.4	118.8±29.2	120.1±31.9	<0.00001
Trigycerides $mg \cdot dL^{-1}$	142.9±71.5	124±79.6	123.6±82.3	120.4±58.6	154.5±66.6	139.3±63.8	141±71.1	141.6±78.4	0.03
hs-CRP $mg \cdot dL^{-1}$	1.3±2.7	0.7±1.1	0.7±1.8	0.8±1.7	1.2±2.6	0.8±1.5	0.7±1	0.7±1.1	0.46

Data are presented as mean±SD, unless otherwise stated. HDL: high-density lipoprotein; LDL: low-density lipoprotein.

patients with COPD [31]. Statins reduce the incidence and mortality of ischaemic heart disease [7]. This may be one reason for statins improving exacerbations.

We chose simvastatin as one of the most effective and widely used HMG-CoA reductase inhibitors for reducing cardiovascular risk. It is easily available and affordable as a generic drug and several publications have described its pleiotropic effects aside from the main lipid-lowering action [32–36]. Simvastatin is considered to exhibit its pleiotropic effects *via* several pathways: adhesion molecules, cell migration, proliferation, endothelial function, matrix degradation, apoptosis, thrombosis and a list of inflammatory mediators [35]. We chose to measure hsCRP, which can be analysed easily and affordably. CRP has been shown to be influenced by statin administration [34, 36]. In our study, no effect of simvastatin on the hsCRP results could be observed compared to placebo. hsCRP was higher in both groups at baseline compared to the follow-up visits at 3, 6 and 12 months. This can be explained by the fact that our study is hospital-based and most of our patients were asked at the end of their hospital stay to participate in the study, and the reason for most of hospitalisations were exacerbations. But even if baseline hsCRP levels were excluded from analysis, there was no statistical difference in the follow-up values between the two groups. One explanation may be that treatment with ICS may reduce serum CRP levels [37]: 90 (86%) patients in the simvastatin group and 91 (87%) in the placebo group regularly used ICS.

It is well known that the rate and intensity of exacerbations are linked to morbidity and mortality of COPD patients. One main treatment focus of GOLD initiative is to minimise the negative impact of a current exacerbation and to prevent subsequent events [6]. Beside the main factor of smoking cessation, several other factors could help to achieve that goal: pharmacotherapy and correct inhaler technique; influenza and pneumococcal vaccinations; pulmonary rehabilitation; long-term oxygen therapy; and nocturnal long-term noninvasive ventilation in chronic hypercapnic patients [6].

The economic burden of COPD is high: in the European Union the total direct costs of respiratory diseases are estimated to be ∼6% of the total healthcare budget with COPD accounting for 56% of these costs (3% of the healthcare budget = EUR 38.6 billion per year) [6]. Exacerbations account for the greatest proportion of COPD burden, calculated to cause 50–75% of direct COPD costs [38]. As expected, costs differ with exacerbation severity. In the review by Toy *et al.* [39] costs for moderate exacerbations were below EUR 900 per case in five countries (Canada, Belgium, the Netherlands, Sweden and UK), whereas they increased to EUR 3700–8600 per case for severe exacerbations, with differences between national healthcare systems. Considering the high morbidity/mortality and the enormous economic burden of COPD exacerbations, all efforts for avoiding these distressing events should be supported.

Our study has some limitations. First, it was a single-centre study with a long recruitment time. However, the treatment effect did not change over the recruitment period. Enrolment was difficult because of several exclusion criteria. Second, withdrawal of participants was relatively high due to the already described factors. Whilst we cannot exclude selection bias due to differential loss to follow-up, one main reason for these dropouts might have been the long-distance drive to our hospital (up to 100 km, and in some cases even more) located in the alpine area of Lower Austria for the scheduled study follow-up visits. To cover at least the travel costs for our patients a reimbursement programme was started after 2 years of study enrolment.

In conclusion, simvastatin at a dose of 40 mg daily significantly prolonged time to first COPD exacerbation and significantly reduced exacerbation rate in our double-blind RCT. There was no effect on spirometry, quality of life, 6-min walk distance and hsCRP. Our data could inform a revived discussion about statin treatment of COPD after the previously negative results of the large multicentre RCT by Criner *et al*. [29].

This clinical trial is registered with EUDRACT number 2011-004166-16. Individual patient data are available. The study protocol and the informed consent form are available.

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