Adherence of Elderly Patients with Cardiovascular Disease to Statins and the Risk of Exacerbation of Chronic Obstructive Pulmonary

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ORIGINAL RESEARCH ARTICLE

Adherence of Elderly Patients with Cardiovascular Disease to Statins and the Risk of Exacerbation of Chronic Obstructive Pulmonary Disease: Evidence from an Italian Real-World Investigation

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Abstract

Objective The objective of this study was to investigate the relationship between adherence to statin therapy and the risk of exacerbation among elderly individuals affected by chronic obstructive pulmonary disease and cardiovascular disease.

Methods Using the healthcare utilisation databases of five Italian territorial units accounting for nearly 35% of the Italian population, we recruited a cohort of 6263 elderly persons (i.e. aged 65 years or older) with co-existing chronic obstructive pulmonary disease and cardiovascular disease who initiated statin therapy. Exposure was adherence to statins measured by the proportion of days of follow-up covered. Outcome was the first hospital admission for chronic obstructive pulmonary disease occurring in the period of observation. A proportional hazards model was used to estimate the hazard ratio and 95% confidence intervals for the exposure–outcome association, after adjusting for several covariates. A set of sensitivity analyses was performed to account for sources of systematic uncertainty.

Results During an average follow-up of about 4 years, 1307 cohort members experienced the outcome. Compared with patients with low adherence (proportion of days of follow-up covered ≤ 40%), those with intermediate (proportion of days of follow-up covered 41–80%) and high (proportion of days of follow-up covered > 80%) adherence exhibited a lower risk of exacerbation of 16% (95% confidence interval 3–27) and 23% (95% confidence interval 10–34).

Conclusions In a real-world setting, we observed evidence that adherence to statin therapy markedly reduced the risk of chronic obstructive pulmonary disease exacerbations in elderly patients with co-existing chronic obstructive pulmonary disease and cardiovascular disease. Given the limited and controversial evidence from trials, more randomised controlled trials are urgently needed to better examine the potential benefits of statins as adjunct therapy in chronic obstructive pulmonary disease.

Key Points

Evidence exists of the beneficial action of statins on pulmonary inflammation as well as on systemic inflammation in chronic obstructive pulmonary disease (COPD)

A large investigation was conducted based on a large cohort of new users of statins among elderly patients with COPD hospitalised for cardiovascular events

Compared with patients with low adherence, those with intermediate and high adherence to statin therapy exhibited a lower risk of exacerbation for COPD among patients with elevated cardiovascular risk

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1 Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health issue worldwide owing to its associated high morbidity, mortality and economic burden [1, 2]. Chronic obstructive pulmonary disease exacerbations are major determinants of high disease burden and costs, especially when hospitalisation is required [3]. Underlying chronic and systemic inflammation plays an important role in the pathophysiology of COPD and its progression [4, 5]. It is therefore reasonable to hypothesise that patients with COPD might benefit from treatments that counteract this systemic process [6].

The hydroxy-methyl-glutaryl-CoA reductase inhibitors, known as statins, are used in the therapy of hypercholesterolemia. Besides the well-established effect in reducing cardiovascular (CV) morbidity and mortality [7], other pleiotropic effects have been described, e.g. anti-inflammatory properties [8, 9]. At the lung level, statins influence bronchial remodelling and recruitment of inflammatory cells, in turn having an effect on emphysema development [6]. Although it has been postulated that patients with COPD might benefit from the anti-inflammatory effects of statins, conflicting results have been reported on this issue [10]. A systematic review and meta-analysis of observational studies showed a clear benefit of statins in patients with COPD [11]. Conversely, both the STATCOPE trial (Prospective Randomized Placebo-Controlled Trial of Simvastatin in the Prevention of COPD Exacerbations) and a meta-analysis of randomised controlled trials did not offer any evidence of a risk reduction in mortality or exacerbation among statin users [12, 13].

With the aim of generating new evidence for this ongoing debate, we conducted an extensive investigation based on a large cohort of new users of statins among elderly patients with COPD hospitalised for CV events. The rationale of our investigation is based on the assumption that the higher the adherence to therapy with statins, the better their anti-inflammatory action. Consequently, a reduction in the risk of exacerbation is then expected among patients with COPD who are highly adherent compared with those who have low adherence. Controlling for sources of systematic uncertainty was of particular concern in this study. This article is part of an Italian project of the Italian Group for Appropriate Drug prescription in the Elderly (I-GrADE) consortium [14] and promoted from the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA).

2 Methods

2.1 Data Sources

The entire Italian population is covered by the National Health Service (NHS) providing universal and free of charge coverage for most healthcare services. The programme is administered by an automated system of healthcare utilisation databases that collect a variety of standard information, including at least (1) demographic and administrative data on NHS beneficiaries (virtually the entire resident population); (2) medical diagnoses and procedures of inpatients admitted to public and private hospitals, coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification and (3) dispensing information of outpatient drug prescriptions reimbursable by the NHS, coded according to the Anatomical Therapeutic Chemical classification system. Further details on these databases and their utilisation in the I-GrADE project have been reported elsewhere [15].

The data used for the present study were retrieved from the healthcare utilisation databases of five Italian territorial units corresponding to three regions (Lombardy, Lazio and Tuscany) and two local health units (Caserta and Treviso). Approximately 21 million residents were recorded in the corresponding databases, accounting for nearly 35% of the Italian population.

Separately for each of the five territorial units, we performed a deterministic record linkage to identify healthcare supplied to each NHS beneficiary of the corresponding territorial units. Record linkage was based on the unique individual identification code (regional health code), which is consistently reported in all archives. As required by the Italian regulations on data privacy, the original identification code was replaced by its digest, which is the image of the code through a cryptographic hash function, the Secure Hash Algorithm (SHA-256). The specific hash function used (SHA-256) was incorporated into the data extraction-transformation-load software provided by the University of Milano-Bicocca.

All data were extracted from databases by means of standardised queries, which were developed after the discussion and consensus of investigators in the study Steering Committee. Table S1 of the Electronic Supplementary Material provides the specific diagnostic and drug codes used in our study.

2.2 Cohort Selection and Follow-Up

National Health Service beneficiaries who (1) were aged 65 years or older, (2) were resident in the participating healthcare territorial units, (3) were hospitalised for CV

disease during 2002–7 (Lombardy), 2005–7 (Tuscany), 2008 (Lazio) or 2008–10 (Caserta and Treviso) [the corresponding hospital admission being defined as index hospitalisation], (4) received at least two prescriptions of statins within 1 year following the CV disease hospital admission and (5) were hospitalised with a primary or secondary diagnosis of COPD within the 2 years before the index hospitalisation were identified and considered for inclusion into the cohort. Eligible patients who received at least a statin or an antineoplastic agent or who were hospitalised for cancer or asthma within the 2 years before the index hospitalisation were excluded.

The remaining patients were included in the final cohort whose members accumulated person-years of follow-up from the date of the second statin prescription until the date of the outcome onset (i.e., first hospital admission for COPD [16] in the period of observation) or censoring (i.e. first hospital admission for cancer, death, emigration or the end of follow-up), whichever came first. The study period ended on 31 December, 2012 for Lombardy, Tuscany and Caserta, 31 December, 2011 for Lazio and 31 December, 2014 for Treviso.

Patients were not recruited in the same time window among the territorial units because of different data availability. The length of the enrolment window was established with the aim to maximise the follow-up period.

2.3 Adherence to Statin Therapy and Covariates

For each cohort member, all statin prescriptions dispensed during follow-up were identified. The period covered by each prescription was calculated from the number of tablets in the dispensed canister, assuming a treatment schedule of one tablet per day [17]. Adherence to statin therapy was assessed by the ratio between the number of days in which the drug was available and the days of follow-up, a measure known as "proportion of days covered" (PDC) [18]. For exposure–response relationship analyses, three categories of PDC were considered: low ($\leq$40%), intermediate (41–80%) and high (> 80%).

Additional information included initial drug treatment strategy (class and potency of statins), co-morbidities (respiratory failure, pulmonary infections, hypertension, diabetes mellitus, depression and dementia), concomitant drugs (antihypertensive drugs, antidiabetic drugs, cardiac therapy, antiplatelet, anti-arrhythmic drugs and antidepressants), hospital admission with COPD as the main diagnosis and the Charlson Comorbidity Index [19] (assessed in the 2-year period before the index prescription), and adherence to bronchodilators during follow-up.

2.4 Data Analysis

The Cox proportional hazard regression model was used to estimate the hazard ratio and 95% confidence interval (CI), for the association between categories of adherence to statins and the time of outcome onset. As adherence may change over time, assessment of its effect requires consideration of its cumulative and varying nature. This was achieved by fitting the Cox model including dummy factors for adherence categories expressed as time-dependent covariates. Adjustments were made for the above-listed additional covariates. Factors measured during the follow-up were included in the model as time-dependent covariates. Trends in the hazard ratio were tested, when feasible, according to the statistical significance of the regression coefficient of the recoded variable obtained by scoring the corresponding categories. The effect of adherence to statins on COPD hospitalisation was stratified according to CV disease experience at cohort entry (i.e. ischaemic heart disease, stroke, heart failure or arrhythmia) and initial drug strategy (i.e. low or high potency). To take into account the clustered structure of the data (i.e. patients nested into territorial units), a shared frailty model was also fitted.

2.5 Sensitivity Analysis

To verify the robustness of our findings, five sensitivity analyses were performed. First, we adopted a different criterion to identify patients with COPD: subjects were included not only if they were hospitalised for COPD, as in the main analysis, but also if they received at least two consecutive prescriptions per year of one of the following drugs: short-acting muscarinic antagonists, long-acting beta agonists or long-acting muscarinic antagonist. Second, because the adopted categorisation was arbitrary, we used alternative PDC categories of < 80 and $\geq$ 80%. Third, the adherence to drug therapy was assessed by a different measure, i.e. the Medication Possession Ratio [18]. Fourth, because we had no information on drug prescriptions for inpatients, with the aim of avoiding immeasurable time bias [20], we classified those patients as users who were covered by statin doses at the time of hospitalisation. Fifth, the rule-out approach was applied to investigate the potential bias associated with unmeasured confounders (e.g. smoking status), detecting the extension of the confounding required to fully account for the exposure–outcome association [21]. We set the possible generic unmeasured confounder: (1) to have a 15% or 30% prevalence in the study population; (2) to increase hospitalisation for COPD up to 10-fold more in patients exposed to the confounder than in those unexposed to the confounder and (3) to be up to 10-fold less common in high-adherent than low-adherent patients.

The Statistical Analysis System Software (Version 9.4; SAS Institute, Cary, NC, USA) was used for the analyses. For all hypotheses tested, two-tailed p values < 0.05 were considered to be significant.

3 Results

3.1 Patients

The selection of the final cohort is detailed in Fig. 1. The 6263 patients fulfilling the inclusion criteria accumulated 25,061 person-years of observation (on average 4 years per patient) and generated 1307 first hospital admissions for COPD in the period of observation (5 cases every 100 person-years).

Selected features of cohort members are shown in Table 1. At baseline, the mean age was 75 years and 70% of patients were men. Most patients started drug therapy with atorvastatin or simvastatin and were discharged with a diagnosis of ischaemic heart disease. Overall, patients exhibited a high burden of co-morbidities (Charlson Comorbidity Index score). Four out of ten patients showed high adherence to statin therapy during follow-up.

3.2 Adherence to Statin Therapy and the Risk of Chronic Obstructive Pulmonary Disorder Hospitalisation

The risk of hospitalisation for COPD exhibited a clear and significant reduction as adherence to statins increased. Compared with patients with low adherence, those with intermediate and high adherence exhibited a lower risk of exacerbation of 16% (95% CI 3–27) and 23% (95% CI 10–34), respectively. The same risk estimates were obtained from the shared frailty model. Analogously, significant trends were observed for patients who at index hospital admission had a diagnosis of heart failure and stroke, whereas the trend was not significant for patients with ischaemic heart disease and arrhythmia (Fig. 2). Although the benefit of drug adherence was observed in both dosage groups, the extent of the risk reduction was slightly greater among those prescribed initially high-potency statins (Fig. 3).

Table 2 shows the robustness of our findings with regard to four sensitivity analyses. The risk reduction did not change substantially by (1) adopting a different criterion to identify patients with COPD (including 8194 patients), (2) modifying the PDC categorisation, (3) using the Medication Possession Ratio as an adherence measure and (4) accounting for immeasurable time bias. Finally, the results obtained by applying the rule-out approach are shown in Fig. 4. Assuming that the confounder prevalence in the study population was 30% and patients with high adherence to statins had a three-fold lower odds of exposure to a confounder than those with low adherence, the analysis shows that exposure to the confounder should increase the outcome risk of three-fold to nullify the observed favourable effect of high adherence on hospitalisation for COPD.

4 Discussion

This large real-world investigation shows that, among elderly people with co-existing COPD and CV disease and initiating therapy with statins, those more adherent to statin therapy during follow-up exhibited a lower risk (− 23%) of hospital admissions for COPD exacerbation than those less adherent. Our study supports the hypothesis that cardiopathic patients with COPD might benefit from continuous treatment with statins.

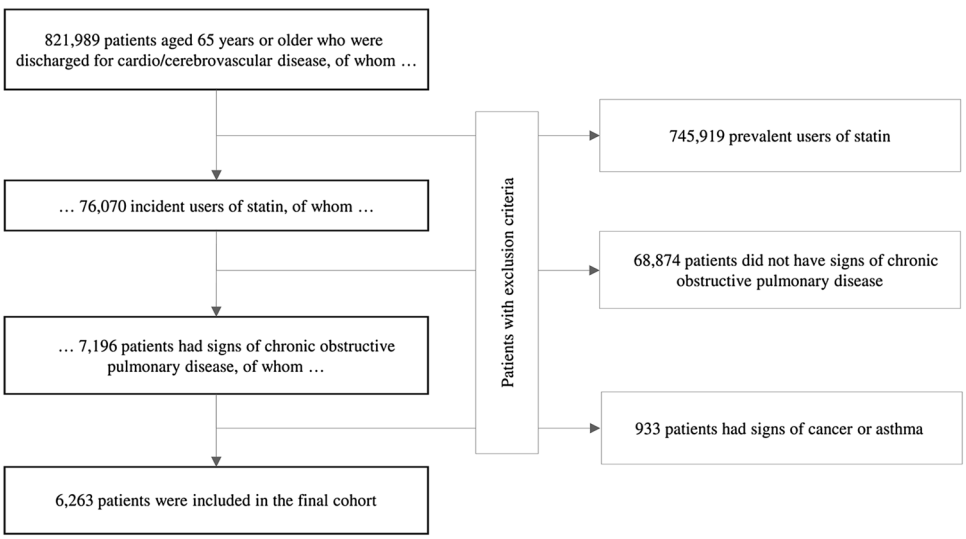

Fig. 1 Flow chart of inclusion and exclusion criteria

Table 1 Baseline characteristics of the 6263 patients included in the study cohort (I-GrADE programme, Italy, 2002–14)

Characteristics	Study cohort ($n=6263$)
Baseline	
Men	4370 (69.8)
Age, y, mean (SD)	75.0 (6.2)
Initial drug treatment strategy	
High potency	2714 (43.3)
Class	
Atorvastatin	2398 (38.3)
Fluvastatin	163 (2.6)
Lovastatin	73 (1.2)
Pravastatin	641 (10.2)
Rosuvastatin	488 (7.8)
Simvastatin	2500 (39.9)
Diagnosis at index hospitalisation	
Ischaemic heart disease	3309 (52.8)
Stroke	1214 (19.4)
Heart failure	1211 (19.3)
Arrhythmia	529 (8.5)
Co-morbidities[a]	
Respiratory failure	799 (12.8)
Pulmonary infections	307 (4.9)
Hypertension	6080 (97.1)
Diabetes mellitus	1786 (28.5)
Depression	1166 (18.6)
Dementia	145 (2.3)
Drug co-treatments[a]	
Antihypertensive agents	6059 (96.7)
Antidiabetic drugs	1630 (26.0)
Cardiac therapy	3822 (61.0)
Antiplatelet drugs	5424 (86.6)
Antiarrhythmic drugs	1306 (20.9)
Antidepressant agents	1198 (19.1)
Hospitalisation for COPD as main diagnosis[a]	1347 (21.5)
Charlson Comorbidity Index score[a]	
0 or 1	268 (4.3)
2 or 3	2131 (34.0)
≥4	3864 (61.7)
During follow-up	
Adherence to bronchodilators[b]	
Low	4843 (77.3)
Intermediate	520 (8.3)
High	900 (14.4)
Adherence to statin therapy[b]	
Low	1803 (28.8)
Intermediate	1974 (31.5)
High	2486 (39.7)

Data are presented as *n* (%) unless otherwise specified

COPD chronic obstructive pulmonary disease, *SD* standard deviation

[a]In the 2 years before the entry date

[b]Adherence was measured according to the proportion of days covered by the drug treatment. Adherence categories are low (≤40%), intermediate (41–80%) and high (>80%)

Our findings are inconsistent with those found in the STATCOPE trial [12]. In this study, 885 participants with COPD were randomly assigned to receive simvastatin at a daily dose of 40 mg per day or placebo. Although at the time of the study closeout the low-density lipoprotein cholesterol levels were lower in the simvastatin-treated patients than in those who received placebo, the two groups did not differ for several outcomes, including the mean number of exacerbations during follow-up, as well as the median number of days to the first exacerbation. However, generalisability of the STATCOPE trial has been questioned because patients taking statins, as well as those who should be taking statins based on their CV disease risk profiles, were excluded from the study [10]. Conversely, all participants in our study had a diagnosis of CV disease at the index hospitalisation.

A recent meta-analysis of randomised clinical trials reported that, although treatment with statins was not statistically associated with inflammatory markers, all-cause mortality and clinical outcomes, improved clinical outcomes were observed in the trials including patients with overt CV disease, elevated baseline C-reactive protein levels or high cholesterol levels [13]. However, statin use was not associated with beneficial effects on all-cause, CV disease, and no CV disease mortality or hospitalisation in patients with coexistent chronic heart failure and a history of COPD according to a post hoc analysis of the GISSI-HF trial [22]. Again, the exclusion of patients with a clear indication for receiving statins might explain the inconsistency of our results with those reported by this trial.

Consistent with our findings, beneficial effects of treatment with statins on COPD outcomes, including a 36% lower risk of COPD exacerbation with or without hospitalisation, have been recently reported from a meta-analysis of observational studies [11]. In addition, several observational investigations showed that, among patients with a high CV disease risk, the long-term use of statins exerts a protective role on the risk of COPD exacerbations [23–25]. A likely explanation for the beneficial effect of statins is that CV disease, especially heart failure, (1) has a leading role in the exacerbation of COPD [26] and (2) increases the systemic inflammation of COPD, thereby increasing the potential efficacy of statins [10]. In fact, evidence exists of the beneficial action of statins on pulmonary inflammation as well as systemic inflammation in COPD [27]. Indeed, statins positively affect some neutrophil functions thought central to the pathogenesis of both COPD and CV disease (e.g. improving neutrophil migratory accuracy) [28]. Nevertheless, a recent meta-analysis of randomised trials suggested that statins had only a modest effect on reducing hospitalisation for heart failure and no impact on mortality in patients with heart failure [29].

Finally, the greater beneficial effect of statin adherence observed in our study among those initially prescribed

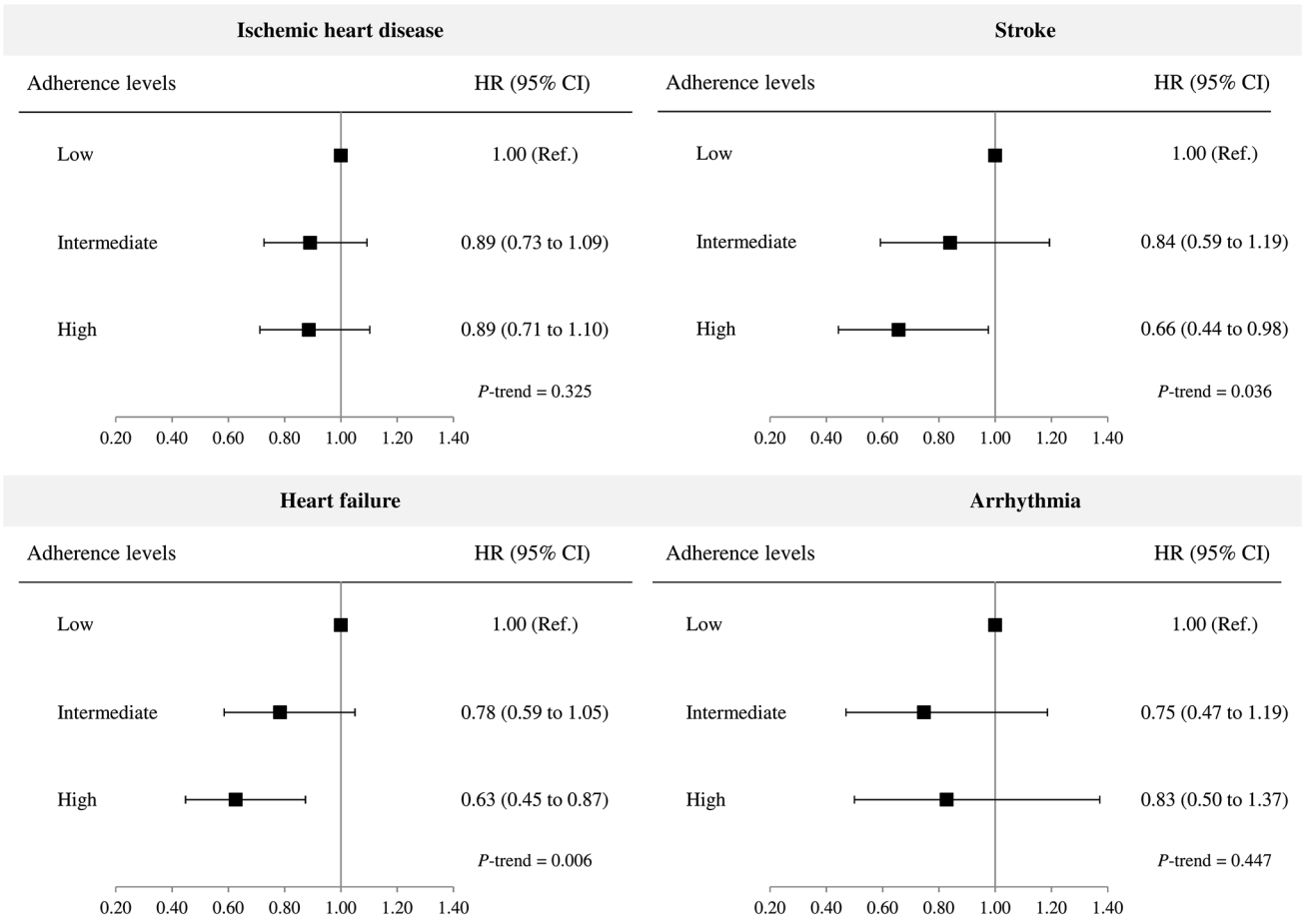

Fig. 2 Effect of adherence to statins on the hazard ratio (HR) of hospitalisation for chronic obstructive pulmonary disease exacerbation according to cardiovascular disease experienced at cohort entry (i.e. ischaemic heart disease, stroke, heart failure or arrhythmia). Adherence was measured according to the proportion of days with statins available with respect to the days of overall follow-up. Categories were as follows: low: ≤ 40%; intermediate: 41–80%; and high: > 80%. The Cox proportional hazards model was used to estimate the HR and 95% confidence interval (CI). Estimates are adjusted for the covariates listed in Table 1

high-potency statins is confirmed by a recent investigation in which only a high dose of a statin affected inflammatory outcomes [30]. This could also explain the results of the STATCOPE study, where 40 mg of simvastatin was used.

The present study is unique in several respects. First, the investigation was based on data from a large unselected population, which was made possible because in Italy a publicly funded healthcare system involves virtually all citizens. Second, the drug prescription database provided highly accurate data because pharmacists are required to report prescriptions in detail to obtain reimbursement, with legal consequences for incorrectly reported information [31]. Third, following the user-only and new-user approach, patients untreated or already treated before the index hospitalisation were excluded, thus reducing the potential for selection bias [32, 33]. Finally, the robustness of our main results was confirmed by several sensitivity analyses.

Our study has a number of potential limitations. First, the lack of useful clinical information for the identification of patients with COPD [i.e. the Global initiative for chronic Obstructive Lung Disease (GOLD) standard diagnostic criteria of spirometry plus smoking history], meaning not all patients with COPD have been included in our cohort. Second, our results should be specifically applied to patients with a severe clinical profile because all participants (1) had a diagnosis of CV disease at the index hospitalisation and (2) were hospitalised with a diagnosis of COPD within 2 years prior to the index hospitalisation. Third, adherence to statins was derived from reimbursed drug dispensing, i.e. a widely used method to estimate adherence to treatment in large populations [34], which requires the assumption that the proportion of days covered by a prescription corresponds to the proportion of days of drug use [35]. Therefore, the actual association between the use of statins and COPD exacerbations might be understated given this source of exposure

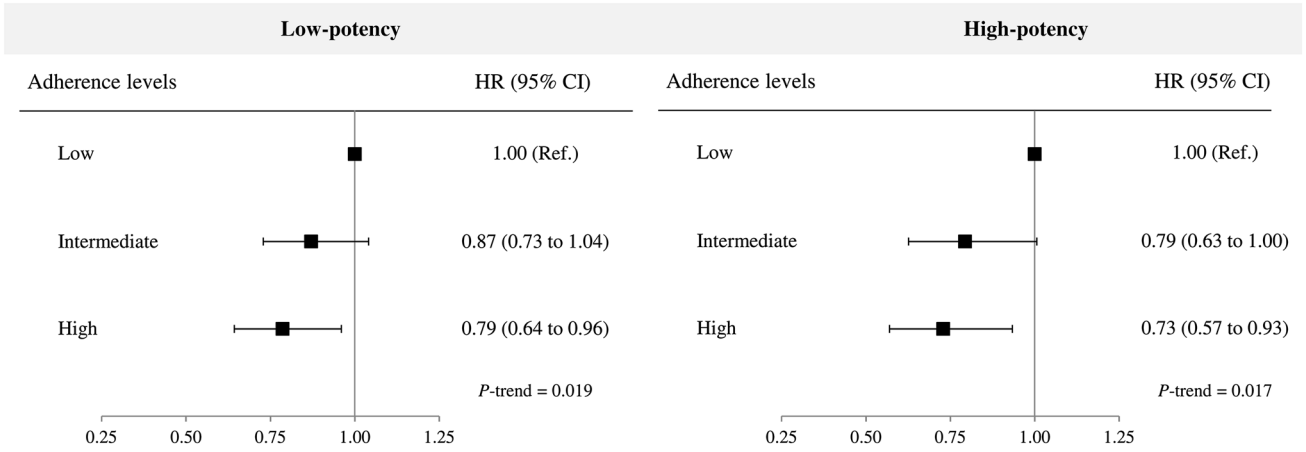

Fig. 3 Effect of adherence to statins on the hazard ratio of hospitalisation for chronic obstructive pulmonary disease exacerbation according to initial drug strategy (i.e. low or high potency). Adherence was measured according to the proportion of days with statins available with respect to the days of overall follow-up. Categories were as follows: low: ≤ 40%; intermediate: 41–80%; and high: > 80%. The Cox proportional hazards model was used to estimate the HR and 95% confidence interval (CI). Estimates are adjusted for the covariates listed in Table 1

misclassification. Four, the assumption of the adoption of the pill-count approach, which presumes that the patient takes exactly one pill per day, without any information on individually prescribed doses.

Finally, the question remains of whether the observed findings are the result of our inability to fully account for higher adherence to statin therapy in those patients with COPD at a lower risk of exacerbation. That is, the reduction in the risk of hospital admission for COPD exacerbation associated with a better adherence to statins might have been generated by other factors. However, factors such as ethnicity or socioeconomic status can be confidently ruled out because the study population is largely Caucasian and Corrao et al. previously found that in Italy income and educational differences play no role in adherence to long-term therapies [36]. Only statin users were included in the cohort comparing them according to the adherence to their statin therapy, rather than with no users. In this way, the potential for confounding is reduced by actively comparing patients with the same indication at baseline [32].

However, lower adherence might be an indication for poorer or worsening health conditions, as well as unhealthy lifestyle habits (e.g. smoking), as patients who have severe acute health problems such as COPD exacerbations are more likely to stop long-term drug treatments for other conditions. Our estimates were adjusted for a number of available demographic, therapeutic and clinical characteristics, such as comorbidities, co-treatments and adherence to bronchodilators during follow-up. However, despite these precautions, as our databases do not record lifestyle information (above all, data about smoking) and have a limited amount of clinical information, residual confounding cannot be fully ruled out. In particular, patients who adhere to statin therapy are more likely exhibit healthy behaviours than non-adherent

Table 2 Hazard ratio [and 95% confidence intervals (CIs)] for the risk of chronic obstructive pulmonary disease (COPD) hospitalisation with increasing adherence to statins according to four sensitivity analyses (I-GrADE programme, Italy, 2002–2014)

	Hazard ratio (95% CI)
Extending criteria for identification of patients with COPD	
Categories of PDC, %	
≤ 40	1.00 (Ref.)
41–80	0.90 (0.79–1.02)
> 80	0.85 (0.74–0.98)
p trend	0.022
Changing PDC categorisation	
Categories of PDC, %	
< 80	1.00 (Ref.)
≥ 80	0.86 (0.76–0.98)
p value	0.020
Adopting the MPR method	
Categories of MPR, %	
≤ 40	1.00 (Ref.)
41–80	0.83 (0.72–0.95)
> 80	0.77 (0.66–0.90)
p trend	0.002
Accounting for immeasurable time bias	
Categories of PDC, %	
≤ 40	1.00 (Ref.)
41–80	0.85 (0.74–0.98)
> 80	0.80 (0.69–0.94)
p trend	0.007

MPR Medication Possession Ratio, *PDC* proportion of days covered, *Ref.* reference

Adherence was measured according to PDC by the drug treatment. Adherence categories are low (≤ 40%), intermediate (41–80%) and high (> 80%)

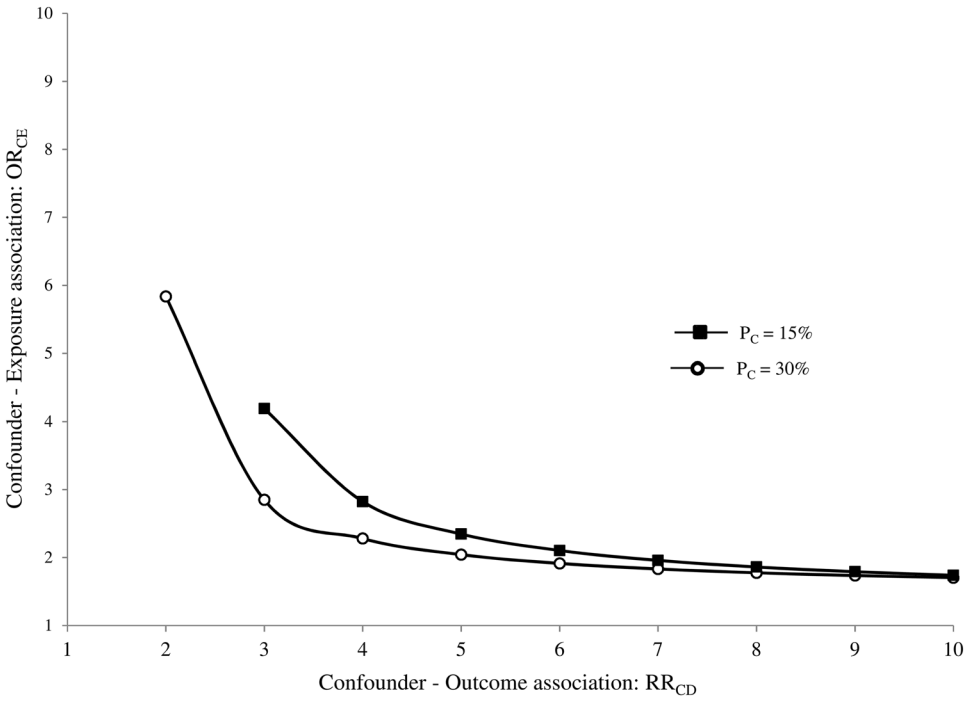

Fig. 4 Influence of a confounder on the relationship between adherence to statins (exposure) and chronic obstructive pulmonary disease hospitalisation (outcome). The graph indicates the RR_{CD}–OR_{CE} combinations (i.e. the confounder–outcome and confounder–exposure associations, respectively) required to move the observed protective effect of adherence to treatment towards the null for two possible values of the confounder's prevalence in the study population (P_c = 15% and 30%)

subjects, i.e. our findings may be biased by the well-known healthy-user effect [37].

For example, as evidence exists of a poorer quality of life among obese patients [38] and that obesity is associated with lower adherence to treatment [39], it is plausible that obesity may act as a confounder. However, we calculated that to fully account for the observed association, obesity should (1) be widespread among patients with COPD (30%) and, at the same time, (2) associated with an increased (three-fold) risk of both poor adherence and exacerbation, which makes this explanation of the results, although in principle possible, highly unlikely.

5 Conclusion

This large real-world investigation among elderly patients with CV disease and a concomitant diagnosis of COPD adds further evidence to adherence to statin therapy markedly reducing the risk of COPD exacerbations. However, given the limited and controversial evidence from trials, more randomised controlled trials are urgently needed to better examine the potential benefits of statins as adjunct therapy in COPD.

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Compliance with Ethical Standards

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Conflict of interest Alessandro Mugelli received research support from the Italian Medicines Agency (AIFA), the Italian Ministry of Education, Universities and Research (MIUR), Gilead and Menarini. In the last 2 years, he received personal fees as a speaker/consultant for the Menarini Group, IBSA, Molteni, Angelini and Pfizer Alliance. Giovanni Corrao received research support from the European Community, AIFA and MIUR. He participated in a variety of projects funded by pharmaceutical companies (i.e. Novartis, GSK, Roche, AMGEN and BMS). He also received honoraria as a member of an advisory board for Roche. Federico Rea, Giulia Calusi, Matteo Franchi, Davide Liborio Vetrano, Giuseppe Roberto, Stefano Bonassi, Ursula Kirchmayer, Alessandro Chinellato, Alessandra Bettiol and Janet Sultana have no conflicts of interest that are directly relevant to the contents of this study.

Ethics Approval This study was approved by the Ethics Committee of "Azienda Ospedaliera Universitaria di Careggi", Florence, Italy, on 26 March, 2012; Protocol Number: 2012/0012643.

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