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ORIGINAL RESEARCH

Statin Use and the Risk of Subsequent Hospitalized Exacerbations in COPD Patients with Frequent Exacerbations

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Rationale: The potential benefits of statins for the prevention of exacerbations in patients with COPD remains controversial. No previous studies have investigated the impact of statins on clinical outcomes in COPD patients with frequent exacerbations.

Objective: This study aimed to evaluate the association between the use of statins and the risk of subsequent hospitalized exacerbations in COPD frequent exacerbators.

Materials and Methods: We conducted a population-based cohort study using the Taiwan National Health Insurance Research Database. 139,223 COPD patients with a first hospitalized exacerbation between 2004 and 2012 were analyzed. Among them, 35,482 had a second hospitalized exacerbation within a year after the first exacerbation, and were defined as frequent exacerbators. 1:4 propensity score matching was used to create matched samples of statin users and non-users. The competing risk regression analysis model was used to evaluate the association between statin use and exacerbation risk.

Results: The use of statins was associated with a significantly reduced risk in subsequent hospitalized exacerbations in COPD patients after their first hospitalized exacerbation (adjusted subdistribution hazard ration [SHR], 0.89; 95% CI, 0.85–0.93, $P<0.001$). In frequent exacerbators, the SHR for subsequent hospitalized exacerbations in statins users was 0.88 (95% CI, 0.81–0.94, $P=0.001$). Subgroup analysis among frequent exacerbators demonstrated that the use of statins only provided a protective effect against subsequent hospitalized exacerbations in male patients aged 75 years and older, with coexisting diabetes mellitus, hypertension or cardiovascular disease, and no protective effect was observed in those with lung cancer or depression. Current use of statins was associated with a greater protective effect for reducing subsequent hospitalized exacerbation.

Conclusion: The use of statins was associated with a significant reduction in the risk of hospitalized exacerbations in COPD patients after a first hospitalized exacerbation and in specified COPD frequent exacerbators.

Keywords: chronic obstructive pulmonary disease, statin, exacerbation, frequent exacerbator

Summary at a Glance

The benefits of statins for the prevention of exacerbations in patients with COPD remains controversial. This is the first study to observe a reduced risk of hospitalized exacerbations with the use of statins in frequent exacerbators of COPD in a real-world setting. The use of statins was associated with a significant reduction in the risk of hospitalized exacerbations in COPD patients after the first hospitalized exacerbation and in specified COPD frequent exacerbators.

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide.[1] Exacerbations of COPD can lead to hospitalization, worsening lung function, worsening quality of life, and increased mortality.[1–4] A higher frequency of COPD exacerbations has been associated with worse disease progression, a higher risk of further exacerbations and hospitalization, and mortality.[5–8] Therefore, the "frequent exacerbator" is recognized as an important phenotype in patients with COPD. In recent years, there has been a growing understanding of systemic inflammation in patients with COPD.[9–11] Frequent exacerbators have been shown to have higher levels of serum C-reactive protein (CRP) during their exacerbation recovery period.[12] Therefore, new therapeutic strategies to reduce systemic inflammation might play a role in the prevention of recurrent exacerbations in COPD patients.

Statins have been demonstrated to have anti-inflammatory and antioxidant effects.[13–18] The use of statins has also been shown to have beneficial effects on cardiovascular outcomes.[19–21] Observational studies have demonstrated that the use of statins may reduce the risk of exacerbations,[22–25] as well as lung-related and all-cause mortality[26–29] in patients with COPD. Nevertheless, another observational study demonstrated that statins may only be associated with a decreased risk of exacerbations in patients with COPD with comorbid cardiovascular disease.[30] Although observational studies have reported that statins have a beneficial effect on the prevention of COPD exacerbations, a large randomized trial reported that simvastatin treatment had no effect on exacerbation rates or the time to a first exacerbation in patients with COPD.[31] In patients with COPD, the potential effects of statins remain controversial.

To the best of our knowledge, no previous studies have investigated the impact of statins on clinical outcomes in COPD patients with frequent exacerbations. Therefore, the aim of the current study was to evaluate the potential association between the use of statins and the risk of subsequent hospitalized exacerbations in COPD patients with frequent exacerbations in a real-world setting.

Materials and Methods

Data Source

The present population-based observational retrospective cohort study was conducted using medical claims data from the National Health Insurance Research Database (NHIRD) of Taiwan. The NHIRD contains registration files and original claims data, including details of all medical and pharmacy claims from hospitalizations, outpatient visits, and emergency services. Access to and the use of the database for the current study was approved by the National Health Research Institute. The present study was approved by the Institutional Review Board of Chang Gung Medical Foundation, Taiwan (approval number: 103-2966B).

Study Population and Design

Subjects who had a diagnosis code for COPD (ICD-9 codes 491, 492, and 496) in the NHIRD in at least six outpatient visits or one hospitalization from January 1997 to December 2010 were eligible for inclusion within the current study. These patient's data were retrieved from the NHIRD for analysis. A hospitalized exacerbation was defined as a primary discharge diagnosis code for COPD with at least one prescription for respiratory antibiotics or systemic steroids during the hospital admission. Those without a prescription for any COPD medication before enrolment, including beta agonists, ipratropium bromide, tiotropium, inhaled corticosteroids (ICS) or xanthins, were excluded from the study. Patients with a first COPD hospitalized exacerbation between January 2004 and December 2012 were selected for analysis, because the major maintenance medications for COPD, the combination of inhaled corticosteroids (ICS) plus long-acting beta-2 agonists (LABA), and the first long-acting muscarinic antagonist (LAMA), were available for prescription in Taiwan from 2001 and 2003, respectively.

Propensity score matching was performed for gender, age, urbanization, income level, comorbidities and medications with ratio matching of 1 (statin users) to 4 (statin non-users). A total of 9462 statin users and 37,848 non-users were included in the matched cohort, which was classified as cohort 1. Patients with a second hospitalized exacerbation within 1 year of their discharge from the first hospitalization were selected as frequent exacerbators. Again, 1:4 propensity score matching was used, and 2116 statin users and 8464 non-users were included the matched cohort, which was classified as cohort 2. The index dates for cohorts 1 and 2 were the dates of discharge from the first and second hospitalized exacerbations, respectively. The study cohorts were further classified into statin users and non-users. The pre-index period for each cohort was 1 year before the index date, and this was used to determine baseline characteristics and

statin exposure. The post-index period included a variable-length follow-up period to a maximum of 1 year, during which the study outcomes were assessed. These two study cohorts were followed from the index date to the occurrence of a hospitalized exacerbation, discontinuation of enrolment in the NHI program, the end of the 1-year follow-up period, or the end of the study period (December 31st 2013), whichever came first.

Exposure Measurements

Patients who received statin prescriptions for a cumulative defined daily dose (cDDD) for more than 28 days within the 365 days prior to the index date, were defined as statin users. Those who used statins for less than 28 cDDD days before the index date were defined as statin non-users. To evaluate the association between the total dosage of statins and the study outcomes, statin users were categorized into two groups according to their cDDD: 28–83, and ≥84. In addition, the use of statins was further categorized as current use (≤180 days) and past use (>180 days) according to the end of the most recent prescription before the index date.

Potential Confounders

Potential confounding risk factors for COPD were defined as the following comorbidities recorded during the enrolment period: cardiovascular disease, lung cancer and diabetes mellitus. Information on other medications that may have affected the risk of COPD exacerbation was also collected, this included LAMA, ICSs, ICS/LABA combinations, acetylcysteine, oral corticosteroids, respiratory antibiotics, beta-blockers, angiotensin converting enzyme inhibitors (ACEI), and aspirin. In addition, sociodemographic characteristics (age, sex, income, and level of urbanization) of the patients were also collected.

Statistical Analysis

The demographic factors and the proportions of comorbidities between the statin users and non-users were compared. Pearson's chi-square test was used for categorical variables and Mann–Whitney-Wilcoxon test was used for continuous variables. The incidence rates and 95% confidence intervals (CIs) for subsequent hospitalized exacerbations in each cohort were calculated for the 1-year follow-up period. The Kaplan–Meier method was used to estimate the cumulative incidence of hospitalized exacerbations. The Log rank test was performed to examine differences in the risk for subsequent hospitalized exacerbations. Death was considered to be a competing event prior to subsequent exacerbation and the competing risk regression model was applied as described by Austin and Fine,[32] to estimate the subdistribution hazard ratios (SHRs) of subsequent hospitalized exacerbation for the matched cohorts and subgroups. Adjusted SHRs were calculated by controlling for demographic data and confounding factors, including gender, age, urbanization, income, diabetes mellitus, hypertension, cardiovascular disease, lung cancer, osteoporosis, depression and medications. A two-tailed p value of 0.05 was considered to indicate a statistically significant difference. All analyses were conducted using SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA).

Sensitivity Analyses

Many medications have shown positive effects on the prevention of COPD exacerbations. To evaluate potential effect modifiers, analyses were stratified by groups with and without the use of long- or short-acting bronchodilators, ICSs, acetylcysteine, oral corticosteroids, respiratory antibiotics, cardioselective and non-cardioselective beta-blockers, ACEI, and aspirin. Outcomes were also stratified by groups according to sex, age, and those with or without diabetes mellitus, hypertension, cardiovascular disease, and lung cancer. These sensitivity analyses were used to evaluate the difference and consistency between the use of statins and the risk of COPD exacerbations.

Results

As shown in Figure 1A and B, there were a total of 139,223 patients who had their first hospitalized exacerbation between 2004 and 2012 were selected for analysis. After 1:4 propensity score matching, 9462 statin users and 37,848 non-users were included in cohort 1. Among the patients with a first hospitalized exacerbation, 35,482 patients had a second hospitalized exacerbation within 365 days after being discharged for their first exacerbation and were defined as frequent exacerbators. After propensity score matching, 2116 statin users and 8464 non-users were included in the matched cohort, which was classified as cohort 2. The basic demographic characteristics of the patients after propensity score matching are summarized in Table 1.

Statin Use and the Risk of Hospitalized Exacerbations

Table 2 shows that the use of statins was associated with a significantly reduced risk (adjusted SHR, 0.89; 95% CI,

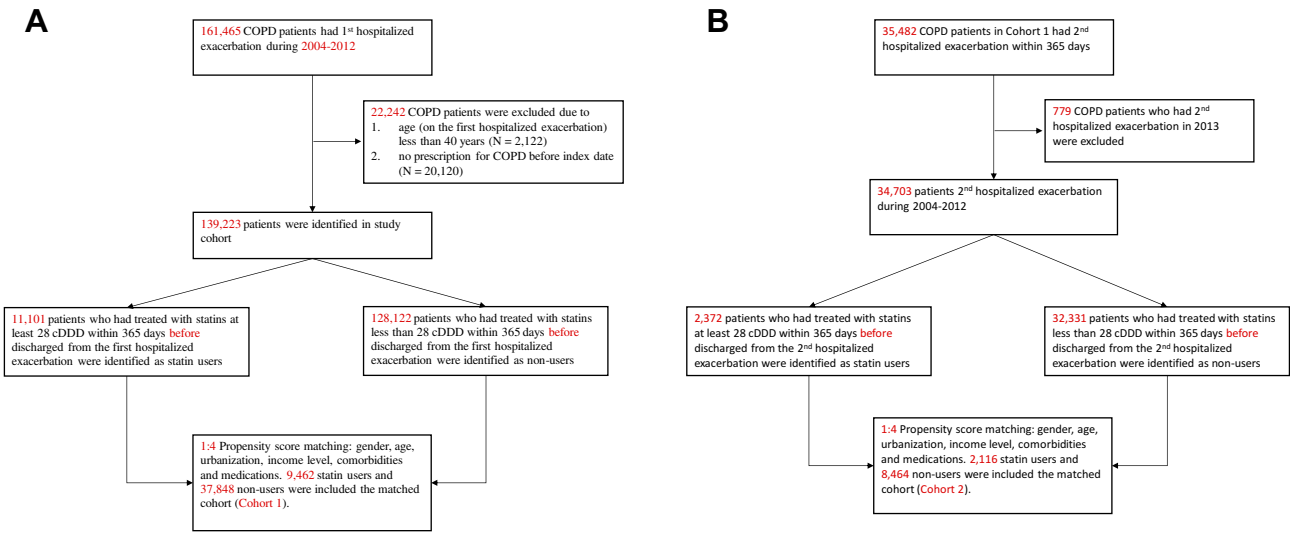

Figure 1 Study flow diagram of the patient enrollment process of the study cohort. COPD Patients with a first hospitalized exacerbation were included in the cohort 1 after propensity score matching (**A**). COPD patients with a second hospitalized exacerbation within 1 year of their discharge from the first hospitalization (frequent exacerbators) were included in the cohort 2 after propensity score matching (**B**).

0.85–0.93, $P<0.001$) of a subsequent hospitalized exacerbation after the first hospitalized exacerbation of COPD. In the frequent exacerbators of COPD group, the use of statins was associated with a significantly reduced risk (adjusted HR, 0.88, 95% CI, 0.81–0.94, $P=0.001$) of a subsequent hospitalized exacerbation. Figure 2A and B illustrate the results of the Kaplan-Meier method for cohorts 1 and 2. The Log rank test revealed a significant difference over the entire Kaplan-Meier curve.

Sensitivity Analysis

Table 3 shows the results of the sensitivity analysis adjustments; this revealed a significant association between the use of statins and a reduced risk of subsequent hospitalized exacerbations according to different models in patients in cohort 1 (with a first exacerbation), except for those with female gender, those under 55 years of age, without hypertension, and those coexisting with lung cancer or osteoporosis. In the frequent exacerbators of COPD (cohort 2), the use of statins provided a protective effect against subsequent hospitalized exacerbations only in male patients aged 75 years and older coexisting with diabetes mellitus, hypertension, or cardiovascular disease, except for those patients with lung cancer or depression. Stratified analyses revealed that the protective effect of statins remained in frequent exacerbators with and without the concomitant use of ICS/LABA combination, acetylcysteine, oral corticosteroids, cardioselective beta-blockers, ACEIs and aspirin, but did not remain for those who used Tiotropium, inhaled corticosteroids, respiratory antibiotics, or non-cardioselective beta-blockers.

Dosage and Recency of Statin Use

Table 4 demonstrates that the use of statins reduced the risk of subsequent hospitalized exacerbations in a dose-dependent manner in COPD patients with a first exacerbation (cohort 1). However, the dose-dependent effect of statins was not significant in the frequent exacerbators of COPD. Although the use of statins was associated with a reduced risk in COPD exacerbations, the decreased risk appeared to vary according to the recency of statin use. Current use of statins was associated with a greater reduced risk of subsequent hospitalized exacerbations, whereas there was no statistically significantly decreased risk for past users of statins in COPD frequent exacerbators.

Discussion

In the present population-based study, it was found that the use of statins was associated with a significant reduction in the risk of subsequent hospitalized exacerbations in patients with COPD after a first exacerbation. In the frequent exacerbators of COPD, the use of statins provided a protective effect against subsequent hospitalized exacerbations only in male patients aged 75 years and older coexisting with diabetes mellitus, hypertension, or cardiovascular disease, except for those patients with lung cancer or depression. Furthermore, current statin use was associated with a greater reduced risk of subsequent hospitalized exacerbation. To the best of our

Table 1 Demographic and Baseline Clinical Characteristics of COPD Patients After Propensity Score Matching

Variable	COPD Patients with a First Hospitalized Exacerbation (Cohort 1)					COPD Frequent Exacerbators (Cohort 2)				
	User (≧28 cDDD)		Non-User (< 28 cDDD)		p-value*	User (≧28 cDDD)		Non-User (< 28 cDDD)		p-value*
Number, n (%)	9462	(100.0%)	37,848	(100.0%)		2116	(100.0%)	8464	(100.0%)	
Gender, n (%)					0.680					0.645
Female	2908	(30.7%)	11,715	(31.0%)		559	(26.4%)	2278	(26.9%)	
Male	6554	(69.3%)	26,133	(69.0%)		1557	(73.6%)	6186	(73.1%)	
Age**					0.983					0.864
40–54 y, n (%)	336	(3.6%)	1364	(3.6%)		60	(2.8%)	224	(2.6%)	
55–64 y, n (%)	944	(10.0%)	3752	(9.9%)		191	(9.0%)	753	(8.9%)	
65–74 y, n (%)	2690	(28.4%)	10,710	(28.3%)		556	(26.3%)	2172	(25.7%)	
≧75 y, n (%)	5492	(58.0%)	22,022	(58.2%)		1309	(61.9%)	5315	(62.8%)	
Median (Q1–Q3)	76.8	(70.4–82.0)	76.9	(70.1–82.3)	0.401	77.6	(71.2–82.8)	77.8	(71.1–82.9)	0.523
Urbanization					0.923					0.919
Very High	2042	(21.6%)	8085	(21.4%)		450	(21.3%)	1779	(21.0%)	
High	4090	(43.2%)	16,386	(43.3%)		907	(42.9%)	3584	(42.3%)	
Moderate	2156	(22.8%)	8598	(22.7%)		499	(23.6%)	2023	(23.9%)	
Low	1174	(12.4%)	4779	(12.6%)		260	(12.3%)	1078	(12.7%)	
Income level					0.237					0.852
0	3628	(38.3%)	14,601	(38.6%)		790	(37.3%)	3181	(37.6%)	
1~15,840	2738	(28.9%)	11,119	(29.4%)		668	(31.6%)	2682	(31.7%)	
15,841~25,000	2888	(30.5%)	11,406	(30.1%)		618	(29.2%)	2464	(29.1%)	
≧25,000	208	(2.2%)	722	(1.9%)		40	(1.9%)	137	(1.6%)	
Comorbidities prior to cohort entry										
Diabetes mellitus, n (%)	6259	(66.1%)	25,082	(66.3%)	0.823	1409	(66.6%)	5653	(66.8%)	0.861
Hypertension, n (%)	8976	(94.9%)	36,166	(95.6%)	0.004	2024	(95.7%)	8133	(96.1%)	0.359
Cardiovascular disease, n (%)	8096	(85.6%)	32,611	(86.2%)	0.132	1876	(88.7%)	7506	(88.7%)	0.976
Lung cancer, n (%)	622	(6.6%)	2436	(6.4%)	0.627	173	(8.2%)	684	(8.1%)	0.887
Osteoporosis, n (%)	3082	(32.6%)	12,154	(32.1%)	0.392	692	(32.7%)	2792	(33.0%)	0.804
Depression, n (%)	1809	(19.1%)	7228	(19.1%)	0.963	406	(19.2%)	1639	(19.4%)	0.854
Medications within 365 days prior to cohort entry										
Tiotropium (LAMA)	1099	(11.6%)	4203	(11.1%)	0.160	432	(20.4%)	1702	(20.1%)	0.753
Inhaled corticosteroids (ICS)	1353	(14.3%)	5348	(14.1%)	0.673	457	(21.6%)	1860	(22.0%)	0.707
ICS/LABA combination	2825	(29.9%)	11,131	(29.4%)	0.394	960	(45.4%)	3863	(45.6%)	0.822
Acetylcysteine	2441	(25.8%)	9938	(26.3%)	0.363	927	(43.8%)	3747	(44.3%)	0.703
Oral corticosteroids	5811	(61.4%)	23,096	(61.0%)	0.485	1793	(84.7%)	7109	(84.0%)	0.402
Respiratory antibiotics	2687	(28.4%)	10,722	(28.3%)	0.895	1142	(54.0%)	4693	(55.4%)	0.222
Beta-blockers (Cardioselective)	1569	(16.6%)	6127	(16.2%)	0.353	285	(13.5%)	1096	(12.9%)	0.526
Beta-blockers (Non-cardioselective)	604	(6.4%)	2248	(5.9%)	0.105	114	(5.4%)	459	(5.4%)	0.949
ACEI	4864	(51.4%)	19,397	(51.2%)	0.786	1123	(53.1%)	4511	(53.3%)	0.853
Aspirin	4348	(46.0%)	17,330	(45.8%)	0.775	1058	(50.0%)	4205	(49.7%)	0.793
Follow-up time (days)										
Median (Q1–Q3)	365.0	(173.0–365.0)	365.0	(100.0–365.0)	<0.001	294.0	(53.5–365.0)	197.0	(37.0–365.0)	<0.001

Notes: *Pearson's chi-square test was used for categorical variables and Mann–Whitney-Wilcoxon test for continuous variables. **Age on index date.

Abbreviations: cDDD, cumulative defined daily dose; COPD, Chronic obstructive pulmonary disease; LAMA, Long-acting muscarinic antagonist; ICS, Inhaled corticosteroid; LABA, Long-acting beta agonist; ICS/LABA, Combination of inhaled corticosteroid and long-acting beta agonist; ACEI, angiotensin converting enzyme inhibitor.

Table 2 Adjusted Subdistribution Hazard Ratios (SHRs) for the Development of Subsequent Hospitalized Exacerbations for COPD Patients Associated with Statin Use in Propensity Score Matched Cohorts

Variable	COPD Patients with a First Hospitalized Exacerbation (Cohort 1)				COPD Frequent Exacerbators (Cohort 2)			
	Statin User (Ref: Non-User)				Statin User (Ref: Non-User)			
	SHR*	95% CI		P-value	SHR*	95% CI		P-value
Crude model	0.89	0.85	0.93	<0.001	0.88	0.81	0.95	0.001
Main model**	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001
Additional covariates								
Main model + HTN	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001
Main model + Lung cancer	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001
Main model + Osteoporosis	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001
Main model + Depression	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001
Main model + LAMA	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001
Main model + ICS	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001
Main model + ICS/LABA combination	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001
Main model + Acetylcysteine	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001
Main model + Oral corticosteroids	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001
Main model + Respiratory antibiotics	0.89	0.85	0.93	<0.001	0.88	0.81	0.95	0.001
Main model + Beta-blockers (Cardioselective)	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001
Main model + Beta-blockers (Non-cardioselective)	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001
Main model + ACEI	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001
Main model + Aspirin	0.89	0.85	0.93	<0.001	0.88	0.81	0.94	0.001

Notes: *Competing risk regression models were used to compute the subdistribution hazard ratios (SHRs) accompanying 95% CI for subsequent hospitalized exacerbation in each cohort. **Main model is adjusted for gender, age, urbanization, income, diabetes mellitus and cardiovascular disease.

Abbreviations: LAMA, Long-acting muscarinic antagonist; ICS, Inhaled corticosteroid; LABA, Long-acting beta agonist; ICS/LABA, Combination of inhaled corticosteroid and long-acting beta agonist; ACEI, angiotensin converting enzyme inhibitor.

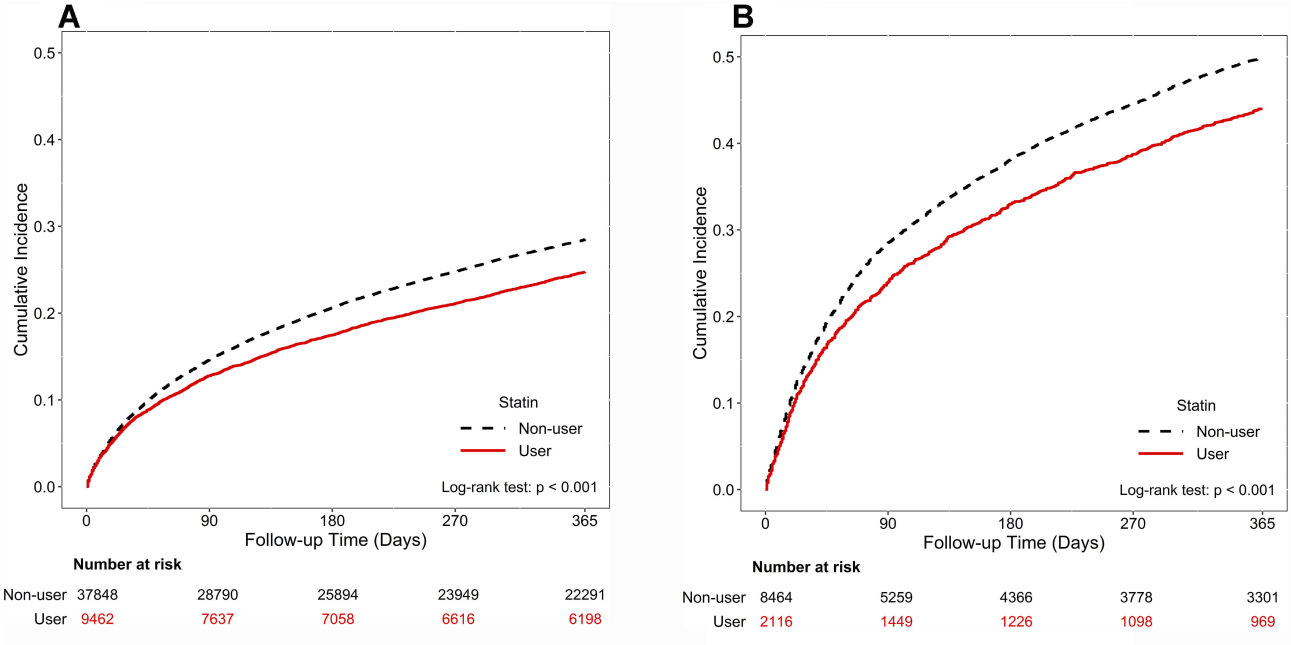

Figure 2 Cumulative incidence of subsequent exacerbation by statin use during the follow-up period in COPD patients with at least one hospitalized exacerbation (**A**) and in COPD frequent exacerbators (**B**) The Log rank test was performed to examine differences in the risk for subsequent exacerbations requiring hospitalizations in each cohort. The cumulative incidence was estimated by using the Kaplan-Meier method.

Table 3 Adjusted Subdistribution Hazard Ratios (SHRs) for the Subsequent Hospitalized Exacerbations in COPD Patients in Subpopulations Treated with Statins in Propensity Score Matched Cohorts

Variable	COPD Patients with a First Hospitalized Exacerbation (Cohort 1)				COPD Frequent Exacerbators (Cohort 2)			
	Statin User (Ref: Non-User)				Statin User (Ref: Non-User)			
	SHR*	95% CI		p-value	SHR*	95% CI		p-value
Gender								
Female	0.92	0.84	1.01	0.088	0.93	0.80	1.08	0.351
Male	0.88	0.83	0.93	<0.001	0.86	0.79	0.93	0.000
Age, years								
40–54	0.75	0.56	1.01	0.055	0.89	0.58	1.35	0.569
55–64	0.82	0.70	0.97	0.017	0.80	0.62	1.03	0.086
65–74	0.85	0.78	0.93	0.001	0.92	0.79	1.06	0.221
≧75	0.92	0.87	0.98	0.009	0.87	0.79	0.96	0.004
Diabetes mellitus								
No	0.88	0.81	0.95	0.001	0.91	0.80	1.03	0.143
Yes	0.89	0.84	0.95	0.000	0.86	0.78	0.94	0.001
Hypertension								
No	0.88	0.71	1.09	0.249	0.93	0.66	1.32	0.686
Yes	0.89	0.85	0.93	<0.001	0.87	0.81	0.94	0.001
Cardiovascular disease								
No	0.87	0.77	1.00	0.041	0.85	0.68	1.06	0.150
Yes	0.89	0.85	0.94	<0.001	0.88	0.81	0.95	0.001
Lung cancer								
No	0.88	0.83	0.92	<0.001	0.88	0.81	0.95	0.001
Yes	1.06	0.89	1.26	0.511	0.86	0.66	1.12	0.261
Osteoporosis								
No	0.86	0.81	0.91	<0.001	0.89	0.81	0.97	0.009
Yes	0.97	0.89	1.05	0.397	0.85	0.74	0.97	0.015
Depression								
No	0.90	0.85	0.95	<0.001	0.87	0.80	0.95	0.001
Yes	0.85	0.76	0.94	0.002	0.90	0.76	1.06	0.194
Tiotropium (LAMA)								
Non-user	0.90	0.86	0.95	<0.001	0.86	0.78	0.93	0.000
User	0.83	0.73	0.94	0.003	0.96	0.82	1.12	0.583
ICS								
Non-user	0.88	0.84	0.93	<0.001	0.87	0.80	0.95	0.001
User	0.91	0.81	1.02	0.097	0.90	0.77	1.05	0.176
ICS/LABA combination								
Non-user	0.87	0.82	0.93	<0.001	0.87	0.78	0.96	0.008
User	0.92	0.85	1.00	0.042	0.88	0.80	0.98	0.024
Acetylcysteine								
Non-user	0.87	0.82	0.92	<0.001	0.87	0.78	0.96	0.008
User	0.94	0.87	1.02	0.133	0.89	0.79	0.99	0.028

(*Continued*)

Table 3 (Continued).

Variable	COPD Patients with a First Hospitalized Exacerbation (Cohort 1)				COPD Frequent Exacerbators (Cohort 2)			
	Statin User (Ref: Non-User)				Statin User (Ref: Non-User)			
	SHR*	95% CI		p-value	SHR*	95% CI		p-value
Oral corticosteroids								
Non-user	0.84	0.77	0.92	0.000	0.71	0.57	0.88	0.002
User	0.91	0.86	0.96	0.001	0.90	0.83	0.98	0.011
Respiratory antibiotics								
Non-user	0.87	0.82	0.92	<0.001	0.83	0.74	0.93	0.001
User	0.92	0.85	0.99	0.032	0.92	0.83	1.02	0.096
Beta-blockers (Cardioselective)								
Non-user	0.90	0.85	0.94	<0.001	0.90	0.83	0.97	0.006
User	0.85	0.75	0.96	0.010	0.74	0.60	0.93	0.008
Beta-blockers (Non-cardioselective)								
Non-user	0.89	0.85	0.93	<0.001	0.88	0.82	0.95	0.002
User	0.89	0.73	1.08	0.232	0.72	0.50	1.04	0.077
ACEI								
Non-user	0.91	0.85	0.97	0.006	0.85	0.77	0.95	0.003
User	0.86	0.81	0.92	<0.001	0.90	0.81	0.99	0.039
Aspirin								
Non-user	0.88	0.83	0.94	0.000	0.87	0.78	0.96	0.007
User	0.89	0.84	0.96	0.001	0.89	0.80	0.99	0.030

Note: *Competing risk regression models were used to compute the subdistribution hazard ratios (SHRs) accompanying 95% CI for subsequent hospitalized exacerbation in each cohort.

Abbreviations: LAMA, Long-acting muscarinic antagonist; ICS, Inhaled corticosteroid; LABA, Long-acting beta agonist; ICS/LABA, Combination of inhaled corticosteroid and long-acting beta agonist; ACEI, angiotensin converting enzyme inhibitor.

Table 4 Adjusted Subdistribution Hazard Ratios (SHRs) for Subsequent Hospitalized Exacerbation According to Dosage and Recency of Statin Use in Propensity Score Matched Cohorts

Statin	COPD Patients with a First Hospitalized Exacerbation (Cohort 1)						COPD Frequent Exacerbators (Cohort 2)					
	N	(%)	SHR*	95% CI		p-value	N	(%)	SHR*	95% CI		p-value
Non-user (reference)	37,848	(80.0%)	1.00				8464	(80.0%)	1.00			
By cDDD												
28–83 cDDD	4126	(8.7%)	0.92	0.87	0.99	0.019	945	(8.9%)	0.84	0.76	0.94	0.002
≥84 cDDD	5336	(11.3%)	0.86	0.81	0.91	<0.0001	1171	(11.1%)	0.90	0.82	0.99	0.032
By recency												
Current	7970	(16.8%)	0.87	0.83	0.92	<0.0001	1714	(16.2%)	0.87	0.80	0.94	0.001
Past	1492	(3.2%)	0.98	0.89	1.09	0.746	402	(3.8%)	0.90	0.77	1.06	0.204

Notes: *Competing risk regression models were used to compute the subdistribution hazard ratios (SHRs) accompanying 95% CI for subsequent hospitalized exacerbation in each cohort. SHRs were estimated by fitting the main model, which was adjusted for gender, age, urbanization, income, diabetes mellitus and cardiovascular disease.
Abbreviation: cDDD, cumulative defined daily dose.

knowledge, this is the first study to observe a reduced risk of hospitalizations for COPD exacerbations with the use of statins in patients with frequent exacerbations.

Wang et al used administrative data from the NHIRD to demonstrate that any use of statins was associated with a 30% decreased risk of COPD exacerbations.[22] However, their

study cohort comprised of only 14,316 patients diagnosed with COPD and 1584 cases with COPD exacerbations. Our study included a larger study population of patients diagnosed with COPD (1,565,248 patients), and 139,223 patients with a first hospitalized exacerbation for COPD were identified. In addition, the impact of statins on clinical outcomes in the frequent exacerbators of COPD had not been previously investigated. Our study was the first to demonstrate a reduced risk of subsequent hospitalized exacerbation with the use of statins in frequent exacerbators of COPD.

Although previous observational studies have reported that statins may reduce the risk of COPD exacerbations, this evidence has been questioned due to the negative results of the STATCOPE trial, which showed no association between the use of statins and COPD exacerbations.[31] However, that prospective study was questioned because the exclusion criteria for the study participants led to decreased generalizability of the results.[33,34] Patients in that study were excluded if they were taking statins previously or had any indications for receiving statins. Excluding these patients may lead to a situation where patients with systemic inflammation and cardiovascular comorbidities were excluded from the trial.[33] In our study, a large proportion of the patients with COPD had cardiovascular comorbidities, and systemic inflammation caused by the cardiovascular comorbidity may act synergistically with pulmonary inflammation, especially in frequent exacerbators of COPD, which could partly explain the findings. To eliminate the impact of cardiovascular comorbidities on the protective effects of statins on COPD exacerbations, propensity score matching was performed for gender, age, urbanization, income level, comorbidities and medications. Adjusted SHRs were calculated by controlling for demographic data and confounding factors, including comorbidities and medications.

The stratified analyses found that in frequent exacerbators, the protective effect of statins was not observed in patients without hypertension or cardiovascular disease. The beneficial effect of statin use on exacerbations may be partly explained by a reduction in systemic inflammation, and the findings of the current study indicate that cardiovascular disease and hypertension seemed to play a more important role in systemic inflammation and pulmonary inflammation in frequent exacerbators of COPD compared with patients with a first exacerbation. Ingebrigtsen et al[30] reported that statin use was associated with a reduced risk of exacerbations in COPD patients, but had no beneficial effects on exacerbations in those with the most severe COPD without cardiovascular comorbidity, which is consistent with the findings of our study. Therefore, our study suggests that statin treatment is important in patients with COPD, especially in frequent exacerbators with cardiovascular comorbidity. Conversely, statins seemed to provide no beneficial effect for exacerbations in COPD patients with lung cancer. This may be partly explained by the worse outcomes and survival in patients with coexisting COPD and lung cancer. Furthermore, the protective effect of statins was not apparent in frequent exacerbators of COPD who had concomitant use of tiotropium and ICS. In frequent exacerbators of COPD, the use of tiotropium or ICS might provide maximal protective and anti-inflammatory effects for these severe COPD patients and thus statins could have no add-on effect to reduce the risk of further exacerbations. Analyses also found that statin use did not provide beneficial effects in frequent exacerbators of COPD with concomitant use of non-cardioselective beta-blockers, and this finding may be due to the fact that non-cardioselective beta-blockers can result in adverse respiratory effects in COPD patients.

Our study had several strengths. The study was conducted using a national database, which is population-based and includes all patients diagnosed with COPD in Taiwan. To ensure that patients who had diagnostic codes for COPD truly had COPD, patients who did not use any medications for COPD in the previous year before the index date were excluded from the study; thus minimizing the possibility of selection bias. Furthermore, data on the use of medications were obtained from the administrative claims database during the study period, which therefore eliminated the possibility of recall bias.

There are several potential limitations to our study. First, histological data on lung function and the severity of symptoms were not obtained, and therefore it was not possible to assess the severity of COPD. However, the patients included in our study have experienced at least one hospitalized exacerbation of COPD. In addition, the patients in cohort 2 were frequent exacerbators of COPD and were considered more severe than most COPD patients. Second, details on several confounders including smoking, body mass index, and radiologic images, which are associated with the extent of emphysema, were not included in the database. Third, it was not possible to confirm the precise dosage of statins that the study participants actually took. The actual dosage they took may have been overestimated if there was poor-compliance. Furthermore, a possible bias in the study was health behavior bias. A person who regularly receives certain healthcare or medications, has specific lifestyle characteristics that may lead to a decreased risk of exacerbations. Previous study found that

patients who adhere to statins are systematically more health seeking than patients who do not remain adherent.[35]

Conclusions

In conclusion, the use of statins was associated with a significant reduction in the risk of hospitalized exacerbations in patients with COPD after a first exacerbation. Current use of statins was associated with a reduced risk of subsequent hospitalized exacerbations. Meanwhile, the use of statins in frequent exacerbators provided a protective effect against subsequent hospitalized exacerbations only in male patients aged 75 years and older coexisting with diabetes mellitus, hypertension, or cardiovascular disease, except for those patients with lung cancer or depression. Therefore, in frequent exacerbators of COPD, statins may be associated with a reduced risk of hospitalized exacerbations in specified patients.

Abbreviations

COPD, chronic obstructive pulmonary disease; SHR, subdistribution hazard ratio; CRP, C-reactive protein; NHIRD, National Health Insurance Research Database; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonists; LAMA, long-acting muscarinic antagonists; cDDD, cumulative defined daily dose; CCI, Charlson comorbidity index; ICS/LABA, Combination of inhaled corticosteroid and long-acting beta agonist, ACEI, angiotensin converting enzyme inhibitor.

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Author Contributions

All authors contributed toward data analysis and interpretation, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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