Original Article

Differential response to roflumilast in patients with chronic obstructive pulmonary disease: real-world evidence

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Background: Roflumilast is effective in reducing acute exacerbation in patients with chronic obstructive pulmonary disease (COPD) at high risk of severe exacerbation. Clinical traits related to the benefits of roflumilast need to be evaluated in patients with COPD.

Methods: A longitudinal observational study in patients newly diagnosed with COPD was conducted using claims data from the Health Insurance Review and Assessment Service in South Korea from 2012–2020 after a 2-year washout period. The primary outcome was to estimate the ratio of hazard ratio (RHR) of roflumilast for moderate-to-severe exacerbation in prespecified subgroups. A time-dependent Cox regression model was used to estimate the hazard ratio (HR) for moderate-to-severe exacerbations.

Results: Among 823,862 patients with COPD, 0.6% used roflumilast. The adjusted HR of roflumilast for moderate-to-severe exacerbations was reduced when treated for ≥3 months (RHR =0.558). Interaction effects of the variables on the HR of roflumilast for moderate-to-severe exacerbation were identified. The adjusted HR of roflumilast for moderate-to-severe exacerbation was significantly reduced in several subgroups: older age (65 years > age ≥50 years, RHR =0.838; age ≥65 years, RHR =0.818), a higher Charlson comorbidity index (1, RHR =0.832; 2, RHR =0.798; ≥3, RHR =0.790), history of exacerbation (RHR =0.886), bronchiectasis (RHR =0.774), chronic bronchitis (RHR =0.793), inhaled therapy [mono-bronchodilator, RHR =0.824; inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA), RHR =0.591; LABA/long-acting muscarinic antagonist (LAMA), RHR =0.822; ICS/LABA/LAMA, RHR =0.570], methylxanthine (RHR =0.853), and statin (RHR =0.888).

Conclusions: The benefit of roflumilast in moderate-to-severe exacerbations was estimated to be greater in specific subgroups of patients with COPD. Personalised approaches to roflumilast based on clinical phenotypes would be effective for COPD.

Keywords: Chronic obstructive pulmonary disease (COPD); exacerbation; roflumilast; population groups; cohort study

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Introduction

Roflumilast is a selective phosphodiesterase 4 inhibitor that exerts anti-inflammatory effects by reducing the hydrolysis of intracellular cyclic adenosine monophosphate (cAMP) (1). cAMP is an intracellular mediator of anti-inflammatory activity in chronic airway diseases (2,3). Although roflumilast was originally developed to treat asthma, growing evidence has supported its clinical benefits for chronic obstructive pulmonary disease (COPD). Several clinical trials have shown that roflumilast reduced moderate-to-severe exacerbations and improved lung function in patients with COPD (4-6). The potential benefit of roflumilast in the prevention of acute exacerbation of COPD (AE-COPD) outweighed the risk in a pooled analysis of randomised controlled trials (7). In particular, the benefit of roflumilast was evident in patients with COPD at a higher risk of severe exacerbation (8). Currently, roflumilast is recommended for only a small proportion of COPD patients.

The benefit of roflumilast in reducing AEs may be extended to a wider range of patients with COPD. Several attempts have been made to identify variables or subgroups related to the benefits of roflumilast. The risk of AE was predominantly reduced by roflumilast in patients with COPD with a history of exacerbation and chronic bronchitis (9-11). A pooled analysis of two clinical trials found that the risk of moderate-to-severe exacerbation was reduced by roflumilast in patients with higher severity or greater frequency of previous exacerbation and higher eosinophil count (12). However, subgroups with a potential benefit of roflumilast have not been sufficiently identified in controlled settings. More potential variables associated with the benefits of roflumilast need to be investigated in real-world large-scale data.

Therefore, we aimed to determine which variable or subgroup was significantly related to the effect of roflumilast on moderate-to-severe AE in patients with COPD. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1129/rc) (13).

Highlight box

Key findings

- An enhanced benefit of roflumilast on moderate-to-severe exacerbations was observed when treatment extended for ≥3 months.

What is known and what is new?

- Roflumilast has been established as effective in reducing acute exacerbations (AEs) in patients with chronic obstructive pulmonary disease (COPD) who are at high risk of severe exacerbations.
- A greater benefit from roflumilast can be expected in patients with multiple comorbidities, a history of previous exacerbation, bronchiectasis, chronic bronchitis, regular inhaled treatment, and methylxanthine treatment. Furthermore, the effectiveness of roflumilast in reducing moderate-to-severe AE was significant higher in patients using inhaled corticosteroid/long-acting beta-agonist (LABA) compared to those using a mono-bronchodilator or LABA/long-acting muscarinic antagonist.

What is the implication, and what should change now?

- Personalized approaches to roflumilast treatment based on clinical phenotypes would be effective for COPD patients.

Methods

Study design and participants

This population-based cohort study was designed using claims data from the Health Insurance Review and Assessment Service (HIRA), which covers the total population in South Korea from 2010 to 2020. Detailed information concerning this data has been published previously (14). No considerable change in nationwide health policies for roflumilast use was found during the study period. The eligibility criteria were: (I) age ≥40 years; (II) newly diagnosed with COPD [International Classification of Diseases 10th revision (ICD-10) codes J43 and J44 as the primary diagnosis or sub-diagnosis] from 2012 to 2020 after a 2-year washout period; and (III) ≥2 visits to the outpatient clinic with the prescription of COPD medications or ≥1 admission for treatment with systemic steroids followed by outpatient visits with the prescription of COPD medications. COPD medications included inhaled therapies [short-acting beta-agonists, long-acting beta-agonists (LABA), short-acting muscarinic antagonists (SAMA), long-acting muscarinic antagonists (LAMA), inhaled corticosteroids (ICS), ICS/LABA, LABA/

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LAMA, and ICS/LABA/LAMA] and oral medications (methylxanthine, phosphodiesterase-4 inhibitor, and oral corticosteroids). COPD was defined based on previous references (15,16).

Variables

We obtained baseline information, including age, sex, Charlson comorbidity index (CCI), previous history of moderate-to-severe exacerbation, history of bronchiectasis, history of chronic bronchitis, regular inhaled treatments, and oral medications. A history of bronchiectasis was identified using the ICD-10 codes (J47 and Q33.4) (17,18). A history of chronic bronchitis was identified using ICD-10 codes (J41 and J42). Regular inhaled treatments included LABA, LAMA, ICS/LABA, LABA/LAMA, and ICS/LABA/LAMA. Anti-inflammatory oral medications included roflumilast, statins, and renin-angiotensin blockers (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers). Anti-inflammatory oral medications were identified using Anatomical Therapeutic Chemical (ATC) codes.

Outcomes

The present study aimed to determine the subgroups that benefit from roflumilast in reducing moderate-to-severe AE-COPD. AE-COPD severity was defined based on a previous study (19). Moderate exacerbation was defined as use of antibiotics or systemic corticosteroids. Severe exacerbation was defined as a visit to the emergency room or hospitalisation. Considering the indication of roflumilast, a considerable bias was expected because it was likely that more patients at high risk of AE-COPD were included in the roflumilast group. The HIRA data do not provide sufficient clinical information for propensity-score matching or adjustment for clinical variables. Therefore, we estimated the ratio of hazard ratio (RHR) of roflumilast for moderate-to-severe AE-COPD in different subgroups. The prespecified subgroups were age (<50, ≥50 and <65, and ≥65 years), sex, CCI (0, 1, 2, and ≥3), previous history of moderate-to-severe exacerbation, history of bronchiectasis, history of chronic bronchitis, regular inhaled treatment (mono-bronchodilator, ICS/LABA, LABA/LAMA, and ICS/LABA/LAMA), and oral medications (methylxanthines, statins, and renin-angiotensin blockers).

Statistical analysis

We compared baseline characteristics based on roflumilast use using Pearson's chi-square test for categorical variables and *t*-test for continuous variables. We performed analyses using a Cox regression model with time-dependent covariates to examine whether roflumilast use was associated with the incidence of moderate-to-severe AE-COPD. To investigate the trends in risks according to the duration of roflumilast exposure, we performed analysis according to split the two-time segments focusing on 90 days since the first roflumilast prescription. For determination of the heterogeneity of the hazard ratio (HR) of roflumilast for moderate-to-severe AE-COPD, subgroup analyses were performed according to age, sex, CCI score, history of moderate to severe exacerbation, history of bronchiectasis, regular inhaled treatment, statin use and renin-angiotension blocker use using Cox regression model. A P value for interaction between roflumilast use and subgroup was calculated. For each subgroup variable, we calculated RHRs and 95% confidence interval (CI) of that as a summary measure of the difference between the HRs of roflumilast for moderate-to-severe AE-COPD in subgroups. An RHR <1.0 indicated that the HR of roflumilast in the subgroup was smaller than that in a reference group. P value <0.05 was considered as statistical significance.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Seoul National University Seoul Metropolitan Government (SNU-SMG) Boramae Medical Center approved the present study (IRB No. 07-2021-22) and waived the need for informed consent for access to HIRA data.

Results

Baseline characteristics

Among the 1,034,697 patients who had ICD-10 code for COPD from 2010 to 2020, 210,835 were excluded who were in washout period from 2010 to 2011. We identified 823,862 patients who were newly diagnosed with COPD from 2012 to 2020 and classified them into roflumilast group (n=5,093, 0.6%) and non-roflumilast

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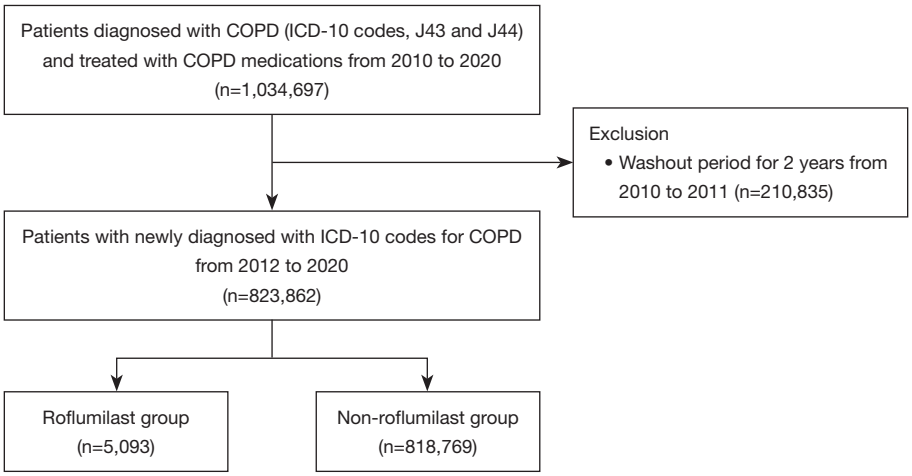

Figure 1 Flow diagram of inclusion and exclusion of patients with COPD. COPD, chronic obstructive pulmonary disease; ICD-10, International Classification of Diseases 10th revision.

group (n=818,769, 99.4%) (*Figure 1*). The duration of observation was median 24.2 [interquartile range (IQR), 7.0–49.4] months. In roflumilast group, the treatment duration of roflumilast was median 2.4 (IQR, 0.8–9.4) months.

The patients in roflumilast group were more likely to be male and had more comorbidities (*Table 1*). History of moderate-to-severe exacerbation in previous year was found 50.7% in roflumilast group and 30.5% in non-roflumilast group. Diagnosis of bronchiectasis was found 32.8% in roflumilast group and 20.3% in non-roflumilast group. Diagnosis of chronic bronchitis was found 71.7% in roflumilast group and 39.7% in non-roflumilast group. Regular inhaled therapy was used in 93.3% of roflumilast group and 70.9% of non-roflumilast group. The most frequently prescribed inhaled therapy was LABA/LAMA (24.7%) and the second most frequently prescribed inhaled therapy was LABA (23.5%). Methylxanthine was more used in roflumilast group compared with non-roflumilast group.

Variables associated with moderate-to-severe exacerbation

In univariable time-dependent Cox regression analyses, age, sex, history of moderate-to-severe exacerbation in previous year, bronchiectasis, chronic bronchitis, regular inhaled treatment, use of statin, use of renin-angiotensin blocker, and use of roflumilast showed an increased HR for moderate-to-severe exacerbation (*Table 2*). In multivariable time-dependent Cox regression analyses, the HR for moderate-to-severe exacerbation was numerically lower in patients with a longer duration of roflumilast use (≥3 months, HR =2.131) compared to those with shorter duration of roflumilast use (<3 months, HR=3.842). The HR of roflumilast for moderate-to-severe exacerbation was significantly reduced when roflumilast was treated for ≥3 months compared to <3 months (RHR =0.555; 95% CI: 0.520–0.592).

Interaction effect of variables

The interaction effects between the variables on HR of roflumilast for moderate-to-severe exacerbation were summarized in *Table 3*. We found significant interaction effects on HR of roflumilast for moderate-to-severe exacerbation according to CCI (P value <0.001), history of moderate-to-severe exacerbation in previous year (P value <0.001), history of bronchiectasis (P value <0.001), history of chronic bronchitis (P value <0.001), regular inhaled treatment (P value <0.001), and use of methylxanthine (P value <0.001).

Demographic and comorbidity factors

Differential efficacy of roflumilast in reducing moderate-to-severe exacerbation according to demographic and comorbidity factors was summarized in *Figure 2*. The adjusted HR of roflumilast in reducing moderate-to-severe exacerbation exhibited a notable decrease in patients aged ≥50 & <65 years (RHR =0.838; 95% CI: 0.706–0.996) and those aged ≥65 years (RHR =0.818; 95% CI: 0.692–0.966) compared to their younger counterparts aged <50 years.

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Table 1 Baseline characteristics of the included patients with COPD according to use of roflumilast

Characteristics	Total (n=823,862)	Roflumilast group (n=5,093)	Non-roflumilast group (n=818,769)	P value
Age (years), mean (SD)	68.3 (11.2)	68.0 (9.6)	68.3 (11.2)	<0.001
<50, n (%)	52,382 (6.4)	198 (3.9)	52,184 (6.4)	<0.001
≥50 & <65, n (%)	239,597 (29.1)	1,532 (30.1)	238,065 (29.1)	<0.001
≥65, n (%)	531,883 (64.6)	3,363 (66.0)	528,520 (64.6)	<0.001
Male, n (%)	483,390 (58.7)	4,339 (85.2)	479,051 (58.5)	<0.001
Charlson comorbidity index, n (%)				
0	114,267 (13.9)	251 (4.9)	114,016 (13.9)	<0.001
1	421,791 (51.2)	2,741 (53.8)	419,050 (51.2)	<0.001
2	137,247 (16.7)	987 (19.4)	136,260 (16.6)	<0.001
≥3	150,557 (18.3)	1,114 (21.9)	149,443 (18.3)	<0.001
History of moderate-to-severe exacerbation in previous year, n (%)	252,364 (30.6)	2,582 (50.7)	249,782 (30.5)	<0.001
Bronchiectasis, n (%)	167,797 (20.4)	1,668 (32.8)	166,129 (20.3)	<0.001
Chronic bronchitis, n (%)	328,912 (39.9)	3,650 (71.7)	325,262 (39.7)	<0.001
Regular inhaled treatment, n (%)				
No treatment	239,170 (29.0)	342 (6.7)	238,828 (29.2)	<0.001
LABA	193,746 (23.5)	503 (9.9)	193,243 (23.6)	<0.001
LAMA	63,863 (7.8)	983 (19.3)	62,880 (7.7)	<0.001
ICS/LABA	122,677 (14.9)	1,889 (37.1)	120,788 (14.8)	<0.001
LABA/LAMA	203,749 (24.7)	1,330 (26.1)	202,419 (24.7)	<0.001
ICS/LABA/LAMA	657 (0.1)	46 (0.9)	611 (0.1)	<0.001
Methylxanthine use, n (%)	539,574 (65.5)	4,156 (81.6)	535,418 (65.4)	<0.001
Statin, n (%)	111,577 (13.5)	694 (13.6)	110,883 (13.5)	0.862
Renin-angiotensin blocker, n (%)	129,338 (15.7)	867 (17.0)	128,471 (15.7)	0.009

COPD, chronic obstructive pulmonary disease; SD, standard deviation; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid.

The adjusted HR of roflumilast for moderate-to-severe exacerbation was statistically reduced in patients with a CCI score of 1 (RHR =0.843; 95% CI: 0.716–0.992), 2 (RHR =0.814; 95% CI: 0.685–0.966), or ≥3 (RHR =0.803; 95% CI: 0.677–0.952) in comparison to those with a CCI score of 0. The effectiveness of roflumilast in reducing moderate-to-severe exacerbations was more pronounced in patients with a documented history of moderate-to-severe exacerbations in the previous year (RHR =0.913; 95% CI: 0.855–0.974). Additionally, patients with bronchiectasis or chronic bronchitis experienced significant benefits from roflumilast therapy, as their adjusted HR for moderate-to-severe exacerbations was markedly reduced (bronchiectasis, RHR =0.791, 95% CI: 0.740–0.846; chronic bronchitis, RHR =0.793, 95% CI: 0.737–0.854).

Treatment factors

Differential efficacy of roflumilast on reducing moderate-to-severe exacerbation according to treatment factors was summarized in *Figure 2*. The adjusted HR of roflumilast for moderate-to-severe exacerbation was significantly

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Table 2 Cox regression analysis for HR of moderate-to-severe exacerbation

Variables	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.008 (1.008–1.008)	<0.001	1.005 (1.005–1.006)	<0.001
Female	0.757 (0.751–0.762)	<0.001	0.833 (0.827–0.839)	<0.001
Charlson comorbidity index	1.116 (1.114–1.118)	<0.001	1.063 (1.061–1.066)	<0.001
History of moderate-to-severe exacerbation in previous year	2.352 (2.336–2.368)	<0.001	2.024 (2.010–2.038)	<0.001
Bronchiectasis	1.474 (1.463–1.486)	<0.001	1.219 (1.210–1.229)	<0.001
Chronic bronchitis	1.641 (1.630–1.652)	<0.001	1.256 (1.247–1.265)	<0.001
Regular inhaled treatment (reference = no treatment)				
Mono-bronchodilator (LABA or LAMA)	1.102 (1.092–1.113)	<0.001	1.342 (1.329–1.355)	<0.001
ICS/LABA	1.906 (1.886–1.926)	<0.001	1.918 (1.897–1.939)	<0.001
LABA/LAMA	1.411 (1.398–1.424)	<0.001	1.528 (1.514–1.543)	<0.001
ICS/LABA/LAMA	3.143 (2.896–3.412)	<0.001	2.156 (1.986–2.341)	<0.001
Methylxanthine use	2.283 (2.263–2.304)	<0.001	2.201 (2.181–2.222)	<0.001
Statin use	1.085 (1.074–1.096)	<0.001	0.958 (0.948–0.969)	<0.001
Renin-angiotensin blocker use	1.125 (1.115–1.135)	<0.001	0.966 (0.956–0.975)	<0.001
Roflumilast use (reference = no roflumilast use)				
<3 months	6.028 (5.738–6.334)	<0.001	3.842 (3.657–4.036)	<0.001
≥3 months	3.740 (3.589–3.897)	<0.001	2.131 (2.044–2.221)	<0.001

HR, hazard ratio; CI, confidence interval; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid.

reduced in the patients who were prescribed with mono-bronchodilator [LABA or LAMA, RHR =0.794 (95% CI: 0.689–0.914); ICS/LABA RHR =0.586 (95% CI: 0.509–0.673); LABA/LAMA, RHR =0.802 (95% CI: 0.696–0.924); and ICS/LABA/LAMA, RHR =0.570 (95% CI: 0.400–0.812)] compared to those without regular inhaled treatment. Notably, the effectiveness of roflumilast for moderate-to-severe exacerbations was even more pronounced among patients receiving ICS/LABA therapy compared to those with mono-bronchodilator (RHR =0.717, 95% CI: 0.662–0.777) or LABA/LAMA (RHR =0.719, 95% CI: 0.663–0.779). The patients treated with methylxanthine (RHR =0.888, 95% CI: 0.807–0.977) and statins (RHR =0.897, 95% CI: 0.818–0.984) experienced a significantly reduced risk of moderate-to-severe exacerbations when administered with roflumilast.

Discussion

In the present study, patients with COPD who used roflumilast had more risk factors for AE-COPD. Contrary to what guidance for COPD management has suggested, roflumilast was pre-emptively prescribed before triple therapy was initiated. In the time-dependent Cox regression analysis, roflumilast was more frequently prescribed in patients with COPD at a higher risk of moderate-to-severe exacerbation. We analyzed significant interaction effects between several variables and roflumilast use on the HR for moderate-to-severe exacerbation. Our results suggest that the effect of roflumilast in reducing moderate-to-severe exacerbation may be better in elderly patients, patients with more comorbidities, patients with a history of moderate-to-severe exacerbation in the previous year, patients with

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Table 3 The interaction effect of variables on HR of roflumilast for moderate-to-severe exacerbation

Subgroup	Unadjusted of roflumilast for moderate-to-severe exacerbation		Adjusted of roflumilast for moderate-to-severe exacerbation		P value for interaction with roflumilast
	HR (95% CI)	P value	HR (95% CI)	P value	
Age (years)					0.613
<50	5.644 (4.808–6.625)	<0.001	3.113 (2.649–3.660)	<0.001	
≥50 & <65	4.723 (4.454–5.008)	<0.001	2.609 (2.460–2.768)	<0.001	
≥65	4.219 (4.059–4.386)	<0.001	2.545 (2.448–2.647)	<0.001	
Sex					0.203
Male	3.968 (3.834–4.106)	<0.001	2.530 (2.444–2.619)	<0.001	
Female	4.509 (4.148–4.901)	<0.001	2.710 (2.493–2.946)	<0.001	
Charlson comorbidity index					<0.001
0	6.049 (5.175–7.070)	<0.001	3.120 (2.667–3.650)	<0.001	
1	4.292 (4.106–4.485)	<0.001	2.629 (2.514–2.748)	<0.001	
2	4.181 (3.901–4.481)	<0.001	2.539 (2.368–2.722)	<0.001	
≥3	3.974 (3.722–4.244)	<0.001	2.506 (2.346–2.678)	<0.001	
History of moderate-to-severe exacerbation in previous year					<0.001
Yes	3.302 (3.168–3.442)	<0.001	2.643 (2.535–2.756)	<0.001	
No	4.529 (4.312–4.758)	<0.001	2.896 (2.756–3.043)	<0.001	
Bronchiectasis					<0.001
Bronchiectasis	3.196 (3.028–3.374)	<0.001	2.227 (2.109–2.352)	<0.001	
No bronchiectasis	4.847 (4.661–5.041)	<0.001	2.814 (2.705–2.927)	<0.001	
Chronic bronchitis					<0.001
Chronic bronchitis	4.629 (4.344–4.934)	<0.001	2.994 (2.808–3.191)	<0.001	
No chronic bronchitis	3.430 (3.306–3.558)	<0.001	2.375 (2.289–2.464)	<0.001	
Regular inhaled treatment					<0.001
No treatment	3.487 (3.066–3.966)	<0.001	3.227 (2.837–3.671)	<0.000	
Mono-bronchodilator (LABA or LAMA)	4.347 (4.100–4.609)	<0.001	2.561 (2.415–2.717)	<0.001	
ICS/LABA	2.303 (2.182–2.430)	<0.001	1.890 (1.791–1.995)	<0.001	
LABA/LAMA	3.949 (3.720–4.193)	<0.001	2.588 (2.436–2.748)	<0.001	
ICS/LABA/LAMA	1.801 (1.301–2.494)	<0.001	1.840 (1.323–2.558)	<0.001	
Methylxanthine use					<0.001
Yes	4.164 (4.025–4.307)	<0.001	2.590 (2.503–2.680)	<0.001	
No	4.610 (4.218–5.038)	<0.001	2.916 (2.667–3.187)	<0.001	
Statin use					0.212
Yes	4.098 (3.764–4.461)	<0.001	2.377 (2.182–2.589)	<0.001	
No	4.484 (4.333–4.639)	<0.001	2.650 (2.560–2.742)	<0.001	
Renin-angiotensin blocker use					0.151
Yes	4.450 (4.132–4.793)	<0.001	2.647 (2.456–2.853)	<0.001	
No	4.419 (4.267–4.577)	<0.001	2.599 (2.509–2.692)	<0.001	

HR, hazard ratio; CI, confidence interval; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid.

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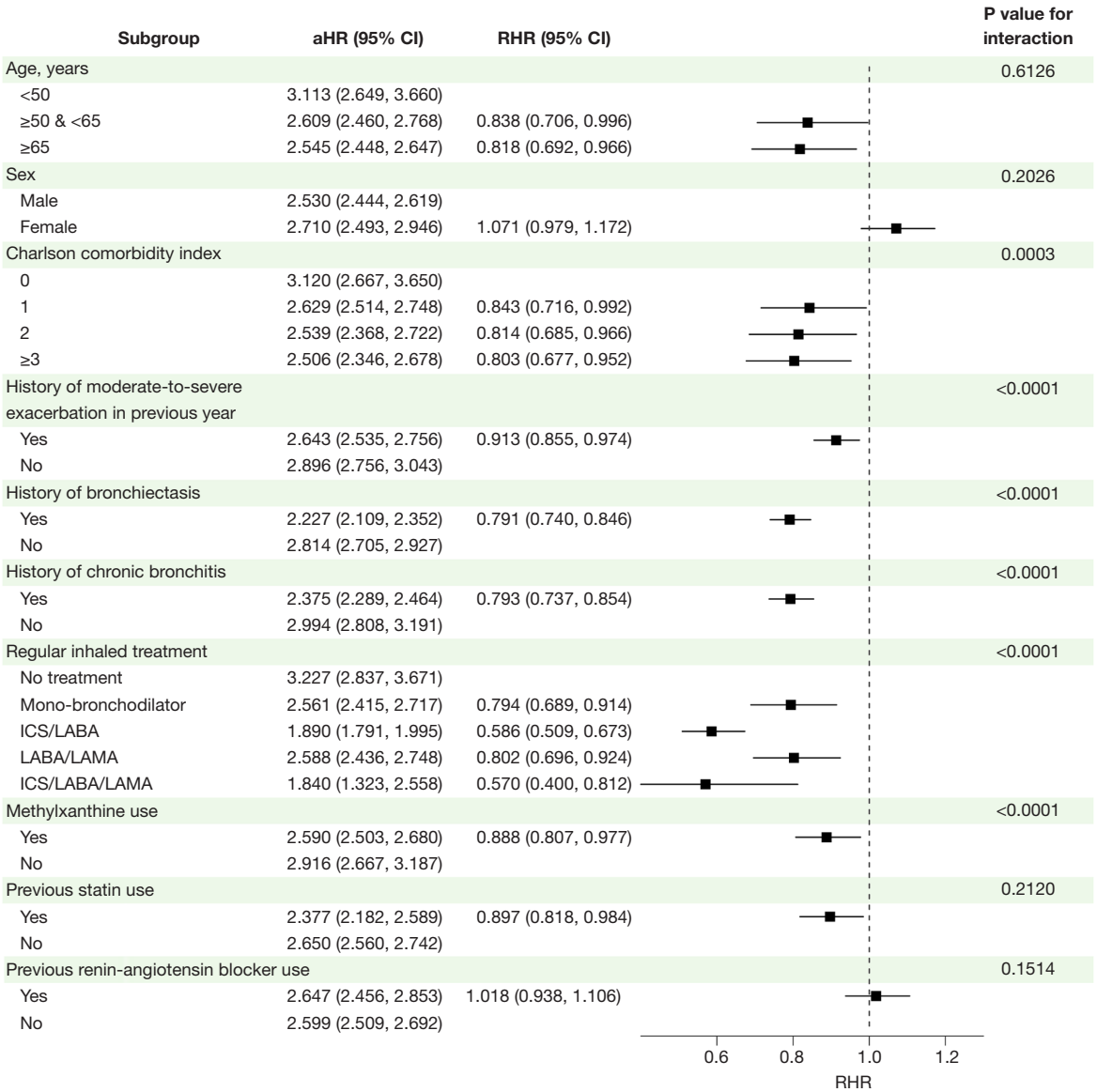

Figure 2 The RHR of roflumilast for moderate-to-severe exacerbation according to different variables. aHR, adjusted hazard ratio; CI, confidence interval; RHR, ratio of hazard ratio; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist.

bronchiectasis or chronic bronchitis, and patients who used inhaled therapy, methylxanthine, or statins. In addition, the HR of roflumilast for moderate-to-severe AE was lower in patients who used ICS/LABA than in those who used a mono-bronchodilator or LABA/LAMA. Considering that the effect of roflumilast on moderate-to-severe exacerbation differed by subgroup, individualised approaches based on clinical phenotypes would improve the clinical outcomes of COPD patients treated with roflumilast.

Our results were consistent with those of previous studies that evaluated subgroups in which roflumilast was effective. In COPD patients who used roflumilast with a post-bronchodilator forced expiratory volume in one second (FEV_1) <50%, the risk of exacerbation was significantly reduced in those >65 years and with previous history of exacerbation and hospitalisation (12). The effect of roflumilast on moderate-to-severe exacerbations did not differ according to sex (11,12). In other studies, roflumilast

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reduced AEs in a subgroup of COPD patients who used ICS or LABA (11,20). These findings suggest that roflumilast provides greater clinical benefits to COPD patients with more severe airway inflammation. Notably, our study included more patients with COPD in the early stages of the disease, while previous clinical trials for roflumilast included patients with more severe or advanced stages of COPD. Therefore, even in patients with milder severity or at earlier stages of COPD with pronounced airway inflammation, roflumilast can be considered to reduce AEs in COPD patients with specific clinical phenotypes.

Our novel finding was that the effect of roflumilast on reducing moderate-to-severe exacerbation was greater in COPD patients with bronchiectasis. Bronchiectasis is a chronic lung disease characterised by neutrophilic airway inflammation and is detected in 4–72% of patients with COPD (21). Bronchiectasis causes cough and sputum production and increases the risk of exacerbation and mortality (22). COPD patients with bronchiectasis experience more exacerbations than those without (23). Therefore, anti-inflammatory therapies have been used to improve the clinical symptoms and prognosis of patients with bronchiectasis. ICS reduces the levels of sputum leukocytes and inflammatory cytokines, improves the quality of life, and reduces mortality in patients with bronchiectasis (24-26). A clinical trial showed that statins reduced serum pro-inflammatory cytokines related to neutrophils and improved St. George's Respiratory Questionnaire (SGRQ) scores in patients with bronchiectasis (27). Roflumilast may improve lung function in patients with bronchiectasis (28). However, it has rarely been studied whether the effect of roflumilast on clinical outcomes differs according to the presence of bronchiectasis in patients with COPD. Our study showed a potential benefit of roflumilast in reducing the HR of moderate-to-severe exacerbation when COPD and bronchiectasis overlap. Further randomised controlled trials are needed to evaluate the effect of roflumilast in reducing AE in COPD patients with bronchiectasis.

Additive effects in combination with roflumilast and inhaled therapies, methylxanthine, or statins were observed in our study. LABA may strengthen the anti-inflammatory effect of roflumilast by increasing intracellular levels of cAMP (29). Combination treatment with roflumilast and a beta-2 adrenergic receptor agonist reduces pro-inflammatory and profibrotic mediators (30). In a clinical trial, a reduced risk of moderate-to-severe exacerbation by roflumilast was evident in COPD patients who used LABA (31). Combination treatment with LAMA and roflumilast has rarely been reported. In one study, the combination of glycopyrrolate and roflumilast did not improve lung function or exercise tolerance compared to glycopyrrolate alone in severe COPD patients (32). Several studies have reported synergistic benefits of ICS and roflumilast. *In vitro* evidence showed that combination treatment with roflumilast and corticosteroids reduced lung inflammation by more than one of them alone (33). The potential mechanism of the synergistic effect was explained by the reduced corticosteroid resistance by roflumilast (34). In clinical studies, further benefits were observed when roflumilast was added to ICS/LABA or ICS/LABA/LAMA (35,36). In a post-hoc analysis of two randomised controlled trials, the benefit of roflumilast in reducing AE-COPD was clearer in the subgroup with concurrent use of ICS (11). Co-administration of roflumilast and methylxanthine can increase the serum levels of roflumilast (37). In our study, the efficacy of roflumilast was potentiated by methylxanthine. In addition, statins may have additive beneficial effects in patients using roflumilast. An experimental study showed that the combination of simvastatin and roflumilast prevented alveolar epithelial-mesenchymal transition induced by cigarette smoke extract (38). In a clinical study, a greater reduction in exacerbation was found in patients who used statin (39).

Our study has several limitations. First, because of the retrospective study design using claim data, adjusting for confounding clinical variables, such as symptoms or lung function, was not sufficiently conducted. Therefore, the future risk of AE was not controlled at the baseline assessment between the roflumilast and non-roflumilast groups. Second, the diagnosis of COPD was operationally defined using ICD-10 codes and COPD medications rather than using spirometric criteria. Therefore, patients without airflow limitations may have been included in our study. However, the prescription of roflumilast is considered a very specific indicator of COPD in South Korea because of the strict health insurance criteria: chronic bronchitis with FEV_1 <50% or a history of ≥2 moderate-to-severe exacerbations. In addition, our results would not change significantly even if COPD patients defined by spirometric criteria were exclusively analysed because the beneficial effect of roflumilast becomes clearer in COPD patients at a higher risk of exacerbation. Third, the duration of treatment with roflumilast varied among patients in the roflumilast group. Therefore, we used a time-dependent Cox regression model to estimate the HR of roflumilast for moderate-to-severe exacerbation. Fourth, it was difficult to

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determine causality, even though the temporal relationship between exposure and outcome was analysed longitudinally. The adjusted HR for moderate-to-severe exacerbation was higher in the roflumilast group. However, it should be interpreted that roflumilast was prescribed more for patients with a higher risk of moderate-to-severe exacerbation.

Conclusions

The benefit of roflumilast on moderate-to-severe exacerbations differed according to subgroups of patients with COPD. A greater benefit of roflumilast can be expected in patients with more comorbidities, a previous history of exacerbation, bronchiectasis, chronic bronchitis, and inhaled therapy. For a more effective treatment of roflumilast in COPD patients, a personalised approach based on clinical phenotypes needs to be considered.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Seoul National University Seoul Metropolitan Government (SNU-SMG) Boramae Medical Center approved the present study (IRB No. 07-2021-22) and waived the need for informed consent for access to HIRA data.

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