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Long-Term Safety of Roflumilast in Patients with Chronic Obstructive Pulmonary Disease, a Multinational Observational Database Cohort Study

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Purpose: This study evaluated the long-term safety of roflumilast in patients with chronic obstructive pulmonary disease or chronic bronchitis using electronic healthcare databases from Germany, Norway, Sweden, and the United States (US).

Patients and Methods: The study population consisted of patients aged ≥40 years who had been exposed to roflumilast and a matched cohort unexposed to roflumilast. The matching was based on sex, age, calendar year of cohort entry date (2010–2011, 2012, or 2013), and a propensity score that included variables such as demographics, markers of chronic obstructive pulmonary disease (COPD) severity and morbidity, and comorbidities. In comparison to the unexposed matched cohort (never use), three exposure definitions were used for the exposed matched cohort: ever use, use status (current, recent, past use), and cumulative duration of use. The main outcome was 5-year all-cause mortality. Cox regression models were used to estimate crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CI).

Results: 112,541 unexposed and 23,239 exposed patients across countries were included. Some variables remained unbalanced after matching, indicating higher COPD disease severity among the exposed patients. Adjusted HRs of 5-year all-cause mortality for "ever use" of roflumilast, compared to "never use", were 1.12 (95% CI, 1.08–1.17) in Germany, 1.00 (95% CI, 0.92–1.08) in Norway, 0.98 (95% CI, 0.92–1.04) in Sweden, and 1.16 (95% CI, 1.12–1.20) in the US. Compared to never users, there was a decrease in 5-year mortality risk observed among "current users" in Germany (HR: 0.93, 95% CI: 0.88–0.98), Norway (HR: 0.77, 95% CI: 0.67–0.87), and Sweden (HR: 0.80, 95% CI: 0.73–0.88).

Conclusion: There was no observed increase in 5-year mortality risk with the use of roflumilast in Sweden or Norway. A small increase in 5-year mortality risk was observed in Germany and the US in the ever versus never comparison, likely due to residual confounding by indication.

Keywords: roflumilast, 5-year all-cause mortality, COPD, electronic healthcare database, propensity score

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide and one of the most prevalent chronic respiratory diseases.[1] In 2019, COPD accounted for an estimated 3.3 million deaths and 74.4 million disability-adjusted life years.[2] COPD patients have a reported 5-year mortality rate of 25.4%.[3] It is projected that by 2030, COPD will become the fourth leading cause of death worldwide, representing about 7.8% of all deaths.[4]

COPD is often complicated by chronic bronchitis (CB), characterized by coughing and the production of sputum for at least 3 months each year over two consecutive years.[5] The complication of COPD with CB is associated with worsening of respiratory symptoms and more frequent exacerbations. This further increases the already high mortality risk associated with the disease.[6]

Pharmacotherapy plays a crucial role in the management of COPD, serving to improve symptoms, ameliorate health status, and decrease the frequency and severity of exacerbations. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) highlights this point by placing a significant emphasis on the role of exacerbations in guiding the choice of COPD treatment. Current pharmacologic agents employed in the treatment of COPD with frequent exacerbations include long-acting β2-agonists, long-acting muscarinic antagonists, and inhaled corticosteroids (ICS).

Roflumilast, a selective phosphodiesterase-4 (PDE-4) inhibitor, was licensed in 2010 as a last-line add-on therapy for the treatment of severe COPD with CB and a history of exacerbations in cases for which the aforementioned standard-therapy is not sufficient to alleviate symptoms.[7] There are currently no other approved treatments for this stage of the disease.[8] The efficacy of roflumilast has been proven through various clinical trials, which showed considerable improvements in lung function and reductions in exacerbations among patients with severe COPD and CB.[9–12] A recent meta-analysis of randomized clinical trials has indicated that, compared to a placebo, roflumilast exhibited marked benefits in the treatment of patients with severe COPD on long-acting β2-agonists and/or ICS. These benefits were observed across various metrics, including an improvement in forced expiratory volume in 1 second (FEV1) both before (mean FEV1 difference between roflumilast group and placebo group, 46.62 mL; 95% confidence interval (CI), (30.69–62.55 mL) and after bronchodilator administration (mean FEV1 difference, 45.62 mL; 95% CI, 34.95–56.28 mL), as well as a reduction in the rate of COPD exacerbations (risk ratio, 0.90; 95% CI, 0.87–0.94).[13] Furthermore, real-world studies have also established the effectiveness of roflumilast,[14] indicating lower COPD exacerbations (2.7 versus 1.16; $p<0.001$) and hospitalizations (0.77 versus 0.32; $p<0.001$) after roflumilast use compared to baseline.[14]

Considering that roflumilast is indicated as a permanent maintenance treatment, the evaluation of its long-term safety is warranted.[15] Although there is sufficient evidence supporting the efficacy of roflumilast in the treatment of severe COPD, data concerning its long-term safety are limited in both clinical trials and real-world studies.[14,16]

Thus, this study is designed to address the existing knowledge gap on the long-term safety of roflumilast in the treatment of COPD and CB in a real-world setting, focusing on 5-year all-cause mortality.

Material and Methods

Study Design

This was an observational, multinational, long-term cohort study using secondary patient-level data from electronic healthcare databases in four countries. Nationwide registries covering the entire population were used in Sweden and Norway. These registries contain extensive historical data for secondary care (inpatient care from 1987 and specialized outpatient care from 2001 for Sweden and inpatient care and specialized outpatient care from 2008 for Norway) and drug dispensations (from 2005 for Sweden and 2004 for Norway).[17] Medical claims databases were used in Germany (German Pharmacoepidemiological Research Database [GePaRD]), a database that collects medical claims from four statutory health insurance providers) and the United States (US) (Military Health System [MHS]), a medical network providing coverage to all US military personnel, their dependents, and retirees) (see Supplementary Material 1 for a detailed description of all data sources used in the study). More limited historical data for patient care and drug dispensations were used for these claims-based databases (from 2009 for Germany and the US). The study period started on roflumilast launch in each country and ended on December 31, 2018. Patients with COPD or CB with a first-time exposure to

roflumilast (exposed cohort) in one of the cohort entry years (2010 [Germany only], 2011, 2012, and 2013) were compared with roflumilast-unexposed patients with COPD or CB (unexposed cohort).

Patient Population

The study population consisted of patients with COPD or CB, aged 40 years and older, who had been first exposed to roflumilast (exposed cohort) in one of the cohort entry years and a matched unexposed cohort (no prior exposure to roflumilast). The cohort entry date (CED) of each patient in the exposed cohort was defined as the date of the first dispensation of roflumilast. In the unexposed cohort, patients were assigned the same CED as their exposed match.

Inclusion criteria for both cohorts were i) presence of a COPD or CB diagnosis or dispensation of a proxy drug (drugs with COPD as indication) at any time before CED (Supplementary Material 2), ii) aged ≥ 40 years at CED, and iii) continuous enrolment in the database for at least 1 year before CED. No exclusion criteria were applied.

Patients could initially enter the study as unexposed and be matched to exposed patients if they did not initiate roflumilast in the same cohort entry year. Such patients would then join the exposed cohort if and when they initiated roflumilast. The matching between exposed and unexposed cohorts was based on sex, age, calendar year of CED (2010–2011, 2012, or 2013), and propensity score (PS) (Supplementary Material 2 Independent variables included in propensity score model with respective coding).

Each yearly cohort was followed up for at least 5 years. Patients were censored at the earliest date of any of these events: end of study period (December 31, 2018), emigration (Sweden and Norway), end of insurance period (US and Germany), interruption of insurance coverage of more than 3 days (Germany), or the day before roflumilast initiation (for unexposed controls who subsequently initiated roflumilast).

Outcome

The primary outcome assessed was 5-year all-cause mortality (ie, death during the 5-year follow-up time). For Germany, the date of death was identified as death being the reason for hospital discharge (inpatient) or the reason for end of insurance (in- and outpatient deaths), with its corresponding date, whichever occurred first. For the US, the date of death provided in the MHS data comes from various sources, including records of death in military and civilian facilities as well as a Social Security Death Index provided by the Social Security Administration. In Sweden and Norway, National Cause of Death Registries were used to ascertain the date of death. In addition to the primary outcome, several other secondary outcomes were evaluated as part of a regulatory commitment to the European Medicines Agency. Results for these secondary outcomes can be found in the European Union Electronic Register of Post-Authorization Studies (EUPAS14852).[18]

Exposure

Exposure to roflumilast (ATC: R03DX07) was ascertained based on the presence of records of dispensed prescriptions in the relevant databases. Episodes of exposure were created to ascertain exposure status using dispensing date, dispensing information on package size, and defined daily doses (DDDs). Three exposure definitions were used for the study comparisons – ever use versus never use, use status (current, recent, past use) versus never use, and cumulative duration of use versus never use (Supplementary Material 2 Exposure variables).

Ever use was time-fixed and defined at CED. Exposed patients all contributed to the ever exposure category. Use status was time-varying and included the following values at any time t after CED: current, if the patient was using roflumilast at time t or had discontinued roflumilast 1 to 5 days before time t; recent, if roflumilast use ended 6 to 60 days before time t; and past, if roflumilast use ended more than 60 days before time t. To determine the periods of continuous exposure, a grace period of 50% of the amount of the previous dispensation was added at the end of the exposure period derived from each dispensation, including the last one before discontinuation. Cumulative duration of use was also time-varying and was defined at time t as the total length of roflumilast use in days (based on the number of DDDs) up to time t, with the following categories: up to 3 months, 3 to 12 months, 12 to 24 months, and more than 24 months. All exposed patients contributed to the "up to 3 months" category. Unexposed patients contributed to the never exposure category for any comparison to roflumilast-exposed patients.

Covariates

The considered covariates included population demographics, markers of COPD severity and morbidity (eg, treatment intensity, exacerbations, emergency room visits, or hospitalizations for COPD), baseline comorbidities, concomitant medications, vaccinations, contraindications for roflumilast, and lifestyle measures. These variables, further detailed in Supplementary Material 2, were collected to describe the study population, for inclusion in the PS model, and for model adjustment.

Main Analysis

PS matching, a method that attempts to control for confounding by accounting for the variables that predict receiving the treatment, was used to select the unexposed cohort. Independent PS were modeled for each month of each cohort entry year using the study covariates (Supplementary Material 2 Independent variables included in propensity score model with respective coding) as predictors. Exposed patients were matched with up to five unexposed patients using a greedy matching algorithm and a caliper (0.2 standard deviations of the logit of the PS). Patients with no prior exposure to roflumilast were eligible for the unexposed cohort if they did not initiate roflumilast in the same cohort entry year. PS matching methods are detailed in Supplementary Material 3.

Patient characteristics after PS matching at CED were assessed. Standardized mean differences were computed to assess covariate balance before and after PS matching. Covariates with a standardized mean difference after matching smaller than 10% were considered balanced.

Considering roflumilast-exposed patients, Kaplan-Meier curves were plotted for the time to the first discontinuation of continuous roflumilast treatment from CED in each country. For each exposure definition, mortality rates, and 95% CIs were estimated. Cox proportional hazards models were fitted to the matched cohorts to estimate crude and adjusted hazard ratios (HRs) for 5-year mortality. All models included quintiles of the PS as strata. Crude HRs were estimated with exposure as the only predictor included in the model. Adjusted HRs were estimated by including in the model preselected covariates (age, sex, markers of COPD severity and morbidity, Supplementary Material 4), and covariates that remained unbalanced after matching (Supplementary Material 5).

Sensitivity Analysis

A first sensitivity analysis aimed to assess whether adjustment for confounding by COPD severity and morbidity could be improved using a high-dimensional propensity score (HD-PS)[19] developed in each study database (Supplementary Material 3). The HD-PS algorithm empirically selects covariates from the pool of all available variables in a database, possibly adjusting for confounding not captured in the pre-specified PS covariates. HD-PS cohorts were matched using the same matching algorithm as in the main analysis.

A second sensitivity analysis investigated the effect of restricting the follow-up to the first exposure period to account for high discontinuation rates in the first year of use. This analysis was carried out in Sweden, Norway, and the US for the "cumulative duration of use" exposure definition by censoring exposed patients at first discontinuation and their matched controls at the same point in time. A grace period of 50% of the last prescription was used to determine the day of first discontinuation.

A third sensitivity analysis explored the degree of consistency in risk as a function of the probability of being prescribed roflumilast (ie, the PS). PS quintiles can be considered as a proxy for disease severity, with larger PS values being associated with higher disease severity. Adjusted HRs were calculated separately within each quintile of the PS for the roflumilast "ever" exposed versus "never" exposed.

A fourth sensitivity analysis investigated the role of disease severity, indicated by FEV1, in the relationship between roflumilast use and 5-year all-cause mortality risk. FEV1 values, derived from the fifth digit of the ICD-10-GM (International Classification of Diseases, Tenth Edition, German Modification) J44 code, were available for about 70% of the German study population, but were not available in any of the other study databases. Crude and adjusted HRs were estimated separately within FEV1 category in Germany only.

Results

Patient attrition is presented in Table 1, with more details in Supplementary Material 6. All countries and years of CED considered, the study population after PS matching consisted of 135,856 patients, including 23,239 patients in the exposed cohort. Specifically, 50,567 patients from Germany were considered in the study, including 8783 roflumilast-exposed patients; 9472 from Norway, including 1624 roflumilast-exposed; 19,025 from Sweden, including 3234 roflumilast-exposed; and 56,792 from the US, including 9598 roflumilast-exposed.

Over 95% of the exposed patients were matched to at least one unexposed patient in all countries. Of these, 21,787 exposed patients (over 93% of all exposed) were matched to five unexposed across all countries. After PS matching, age and sex were balanced at CED. However, not all variables related to COPD severity and morbidity were balanced in the matched cohorts. Standardized mean differences for the PS variables at CED in each country as well as the variables that remained unbalanced after matching are presented in Supplementary Material 5. All countries considered, unbalanced variables indicating higher COPD severity in the exposed cohort included number of hospitalizations due to COPD in the 30 days and in the 12 months before CED, number of emergency room visits due to COPD in the 30 days and in the 12 months before CED and short-acting β2 agonist (SABA)/or short-acting muscarinic antagonist used in the last 4 months before CED.

Characteristics at CED of exposed and unexposed patients after PS matching are presented in Table 2. The proportion of females varied between 44.3% and 57.1% across countries but did not seem to differ between exposed and unexposed patients. Most patients had no previous hospitalization for COPD in the 12 months prior to CED, with seemingly similar proportions between exposed patients and their matched unexposed patients. However, the proportions of patients with three or more hospitalizations for COPD appeared to be higher in the exposed cohort. This is also reflected in the proportions of patients who were hospitalized for COPD during the 30 days preceding CED.

Median follow-up time varied from 4.95–5.53 years across countries and exposure cohorts (Table 2). Around 25% of patients discontinued roflumilast within the first 2 months, over 50% within the first 6 months, and approximately 75% within the first 12 months after initiation (Supplementary Material 7).

Results of the Cox proportional hazards models for 5-year all-cause mortality in "ever use" versus "never use" cohorts, presented in Table 3, revealed an increased risk in Germany (adjusted HR,1.12; 95% CI, 1.08–1.17) and in the US (adjusted HR, 1.16; 95% CI, 1.12–1.20), whereas no difference in risk was observed in Norway (adjusted HR, 1.00; 95% CI, 0.92–1.08) and Sweden (adjusted HR, 0.98; 95% CI, 0.92–1.04). Across all countries, further adjustment after PS matching lowered the risk estimates (adjusted HRs were smaller than crude HRs, presented in Supplementary Material 8).

Adjusted HRs of mortality in "current use", "recent use", and "past use" versus "never use" are presented in Table 4. No elevated mortality risk was seen across the countries for "current use" compared to "never use". For instance, a decrease in the hazard of mortality was observed in "current use" compared to "never use" in Germany (adjusted HR, 0.93; 95% CI, 0.88–0.99), Norway (adjusted HR, 0.77; 95% CI, 0.67–0.87), and Sweden (adjusted HR, 0.80; 95% CI, 0.73–0.88). For "recent use", an increase in mortality risk compared to "never use" was seen in Germany, Norway, and

Table 1 Patient Counts per Country

	Exposed cohort Roflumilast patients with PS matches	Unexposed cohort PS matched control population	Unexposed who become exposed, counted in both cohorts[a]	Roflumilast patients who had no PS matches[b]
Germany	8,783	41,784	1,402	542
Norway	1,624	7,830	260	18
Sweden	3,234	15,776	608	15
US	9,598	47,151	1,637	43
Total (all countries)	23,239	112,541	3,907	618

Notes: [a]The controls included in unexposed annual cohort who become exposed to roflumilast were censored on the date they switched to roflumilast and included in the subsequent annual exposed cohort if eligible. [b] Number of patients exposed to roflumilast who had no PS matches and thus were not included in the analyses.
Abbreviations: PS, propensity score; US, United States.

Table 2 Characteristics of Exposed and Unexposed Patients at Cohort Entry After Propensity Score Matching

	Germany		Norway		Sweden		US	
	Exposed N=8,783	**Unexposed N=41,784**	**Exposed N=1,624**	**Unexposed N=7,830**	**Exposed N=3,234**	**Unexposed N=15,776**	**Exposed N=9,598**	**Unexposed N=47,151**
Median follow-up, years (IQR)	5.50 (2.89, 7.04)	5.53 (2.63, 7.07)	5.06 (2.38, 6.23)	5.05 (1.96, 6.20)	5.22 (2.42, 6.54)	5.19 (2.08, 6.57)	4.95 (2.11, 6.23)	5.14 (2.08, 6.29)
Age at cohort entry (%)								
40–44	75 (0.85)	344 (0.82)	11 (0.68)	45 (0.57)	10 (0.31)	43 (0.27)	19 (0.20)	99 (0.21)
45–49	250 (2.85)	1,193 (2.86)	16 (0.99)	78 (1.00)	26 (0.80)	129 (0.82)	80 (0.83)	475 (1.01)
50–54	530 (6.03)	2,422 (5.80)	57 (3.51)	242 (3.09)	84 (2.60)	373 (2.36)	221 (2.30)	1,147 (2.43)
55–59	972 (11.07)	4,584 (10.97)	108 (6.65)	486 (6.21)	183 (5.66)	899 (5.70)	552 (5.75)	2,818 (5.98)
60–64	1,347 (15.34)	6,481 (15.51)	236 (14.53)	1,052 (13.44)	436 (13.48)	2,082 (13.20)	1,102 (11.48)	5,784 (12.27)
65–69	1,672 (19.04)	7,692 (18.41)	427 (26.29)	1,998 (25.52)	766 (23.69)	3,654 (23.16)	1,784 (18.59)	8,938 (18.96)
70–74	1,846 (21.02)	8,954 (21.43)	293 (18.04)	1,456 (18.60)	712 (22.02)	3,541 (22.45)	2,219 (23.12)	10,999 (23.33)
75–79	1,168 (13.30)	5,635 (13.49)	265 (16.32)	1,298 (16.58)	549 (16.98)	2,750 (17.43)	1,979 (20.62)	9,534 (20.22)
≥80	923 (10.51)	4,479 (10.72)	211 (12.99)	1,175 (15.01)	468 (14.47)	2,305 (14.61)	1,642 (17.11)	7,357 (15.60)
Median age, years (IQR)	68 (61, 74)	68 (61, 74)	69 (65, 76)	70 (65, 77)	71 (66, 77)	71 (66, 77)	72 (66, 77)	72 (65, 77)
Female (%)	3,892 (44.31)	18,606 (44.53)	763 (46.98)	3,702 (47.28)	1,841 (56.93)	9015 (57.14)	4,615 (48.08)	22,647 (48.03)
Number of COPD hospitalizations*,† (%)								
None	6,289 (71.60)	31,652 (75.75)	1,022 (62.93)	5,182 (66.18)	2,183 (67.50)	11,116 (70.46)	7,725 (80.49)	39,214 (83.17)
1–2	2,107 (23.99)	9,122 (21.83)	430 (26.48)	2,060 (26.31)	691 (21.37)	3,356 (21.27)	1,765 (18.39)	7,580 (16.08)
≥3	387 (4.41)	1,010 (2.42)	-	-	-	-	-	-
3–5	–	–	125 (7.70)	452 (5.77)	262 (8.10)	979 (6.21)	99 (1.03)	331 (0.70)
≥6	–	–	47 (2.89)	136 (1.74)	98 (3.03)	325 (2.06)	9 (0.09)	26 (0.06)
COPD hospitalization during the last 30 days before CED (%)								
No	7,881 (89.73)	38,318 (91.70)	1,434 (88.30)	7,291 (93.12)	2,850 (88.13)	14,614 (92.63)	9,142 (95.25)	46,028 (97.62)
Yes	902 (10.27)	3,466 (8.30)	190 (11.70)	539 (6.88)	384 (11.87)	1,162 (7.37)	456 (4.75)	1123 (2.38)
Number of respiratory disease related hospitalizations* (%)								
None	8,189 (93.24)	39,160 (93.72)	1,235 (76.05)	6,146 (78.49)	2,878 (88.99)	14,217 (90.12)	8,694 (90.58)	43,083 (91.37)
1–2	577 (6.57)	2,539 (6.08)	316 (19.46)	1,416 (18.08)	323 (9.99)	1,431 (9.07)	867 (9.03)	3,897 (8.26)
≥3	17 (0.19)	85 (0.20)	73 (4.50)	268 (3.42)	33 (1.02)	128 (0.81)	37 (0.39)	171 (0.36)
ER visits for COPD*,† (%)								
None	6,731 (76.64)	32,539 (77.87)	–	–	–	–	–	–
1–2	1,751 (19.94)	7,982 (19.10)						
≥3	301 (3.43)	1,263 (3.02)						
ER visits for COPD*,† (%)								
No	–	–	1,049 (64.59)	5,284 (67.48)	3,172 (98.08)	15,527 (98.42)	7,552 (78.68)	38,330 (81.29)
Yes			575 (35.41)	2,546 (32.52)	62 (1.92)	249 (1.58)	2,046 (21.32)	8,821 (18.71)
ER visits for COPD in the last 30 days before CED† (%)								
None	8,453 (96.24)	40,239 (96.30)	–	–	–	–	–	–
1–2	276 (3.14)	1,325 (3.17)						
≥3	54 (0.61)	220 (0.53)						
At least one ER visit for COPD in 30 days before CED† (%)								
No	–	–	1,407 (86.64)	7,190 (91.83)	3,219 (99.54)	15,736 (99.75)	9078 (94.58)	45,756 (97.04)
Yes			217 (13.36)	640 (8.17)	15 (0.46)	40 (0.25)	520 (5.42)	1,395 (2.96)
Current use of theophylline (%)	1,734 (19.74)	7,560 (18.09)	178 (10.96)	728 (9.30)	129 (3.99)	442 (2.80)	709 (7.39)	2,615 (5.55)
Current use of acetylcysteine (%)	710 (8.08)	2,860 (6.84)	467 (28.76)	1,888 (24.11)	1,381 (42.70)	6,192 (39.25)	32 (0.33)	122 (0.26)

(*Continued*)

Table 2 (Continued).

	Germany		Norway		Sweden		US	
	Exposed N=8,783	**Unexposed N=41,784**	**Exposed N=1,624**	**Unexposed N=7,830**	**Exposed N=3,234**	**Unexposed N=15,776**	**Exposed N=9,598**	**Unexposed N=47,151**
Emphysema (%)**	3,445 (39.22)	15,578 (37.28)	281 (17.30)	1,124 (14.36)	397 (12.28)	1,676 (10.62)	4,670 (48.66)	21,921 (46.49)
CCI,† (%)**								
None	47 (0.54)	43 (0.10)	–	–	–	–	–	–
1–2	4,738 (53.95)	22,410 (53.63)						
3–5	3,057 (34.81)	14,753 (35.31)						
≥6	941 (10.71)	4,578 (10.96)						
CCI,† (%)**								
0–2	–	–	1,178 (72.54)	5,557 (70.97)	2,097 (64.84)	10,061 (63.77)	3,210 (33.44)	15,636 (33.16)
3–5			384 (23.65)	1,916 (24.47)	990 (30.61)	4,942 (31.33)	3,928 (40.93)	19,233 (40.79)
≥5			62 (3.82)	357 (4.56)	147 (4.55)	773 (4.90)	2,460 (25.63)	12,282 (26.05)
Number of COPD moderate exacerbations* (%)								
None	761 (20.05)	10,692 (25.59)	198 (12.19)	953 (12.17)	469 (14.50)	2,369 (15.02)	931 (9.70)	4,472 (9.48)
1–2	2,583 (29.41)	12,506 (29.93)	363 (22.35)	1,843 (23.54)	688 (21.27)	3,669 (23.26)	1,865 (19.43)	9,470 (20.08)
≥3	4,439 (50.54)	18,586 (44.48)	–	–	–	–	–	–
3–5	–	–	511 (31.47)	2,661 (33.98)	920 (28.45)	4,738 (30.03)	2,490 (25.94)	13,074 (27.73)
≥6	–	–	552 (33.99)	2,373 (30.31)	1,157 (35.78)	5,000 (31.69)	4,312 (44.93)	20,135 (42.70)
Intensity of COPD treatment†, †† (%)								
0	424 (4.83)	1,788 (4.28)	55 (3.39)	319 (4.07)	128 (3.96)	725 (4.60)	1,087 (11.33)	5,270 (11.18)
1	244 (2.78)	783 (1.87)	–	–	–	–	–	–
1–2	–	–	280 (17.24)	1,366 (17.45)	420 (12.99)	2,109 (13.37)	2,339 (24.37)	11,995 (25.44)
2	948 (10.79)	4,519 (10.82)	–	–	–	–	–	–
3	2,415 (27.50)	12,732 (30.47)	444 (27.34)	2,108 (26.92)	645 (19.94)	3,227 (20.46)	2,203 (22.95)	11,524 (24.44)
4	4,752 (54.10)	21,962 (52.56)	845 (52.03)	4,037 (51.56)	2,041 (63.11)	9,715 (61.58)	3,969 (41.35)	18,362 (38.94)
Chronic use of systemic corticosteroids††† (%)	811 (9.23)	2,993 (7.16)	473 (29.13)	1,914 (24.44)	341 (10.54)	1,310 (8.30)	781 (8.14)	3,188 (6.76)

Notes: *During the 12 months prior to cohort entry date. **Any time before cohort entry date. †Different categories were defined in Germany versus in other countries. ††The variable "intensity of COPD treatment" was computed based on COPD treatments used in the last 4 months before CED (Supplementary material 2). †††Defined as patients with more than 8- month supply (based on DDDs) of prednisone, prednisolone or betamethasone in the 12 months before CED.

Abbreviations: CCI, Charlson Comorbidity Index; CED, cohort entry date; COPD, chronic obstructive pulmonary disease; ER, emergency room; IQR, interquartile range; US, United States.

Table 3 Five-Year All-Cause Mortality in "Ever" versus "Never" Users of Roflumilast: Number of Events and Adjusted HRs

Country	Number of ever exposed (PY)	Number of never exposed (PY)	Number of deaths (ever exposed)	Number of deaths (never exposed)	Adjusted HR* (95% CI)
Germany	8,775 (34,453)	41,718 (160,716)	3,230	12,071	1.12 (1.08, 1.17)
Norway	1,624 (6036)	7,830 (28,036)	779	3,251	1.00 (0.92, 1.08)
Sweden	3,214 (12,139)	15,776 (57,594)	1,475	6,104	0.98 (0.92, 1.04)
US	9,598 (34,779)	47,151 (171,688)	4,590	17,539	1.16 (1.12, 1.20)

Notes: *Adjusted for age + sex +country-specific variables imbalanced after PS-matching + markers of COPD severity and morbidity. The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country. "Ever" users are patients with any exposure to roflumilast in a cohort entry year."Never" users are patients in the matched unexposed cohort, with no prior exposure to roflumilast.

Abbreviations: CI, confidence interval; PY, person-years; MR, mortality rate; HR, hazard ratio; US, United States.

Table 4 Five-Year All-Cause Mortality for "Current", "Recent", and "Past Use" of Roflumilast versus "Never Use": Number of Events and Adjusted HRs

Country	Deaths (PY)	N at risk	Adjusted HR* (95% CI)
Germany			
Never	12,071 (160,716)	41,718	1
Current	1,242 (15,183)	8,775	0.93 (0.88, 0.99)
Recent	201 (1481)	7,255	1.57 (1.37, 1.81)
Past	1,787 (17,790)	6,305	1.26 (1.19, 1.32)
Norway			
Never	3,251 (28,036)	7,830	1
Current	258 (2623)	1,624	0.77 (0.67, 0.87)
Recent	43 (221)	1,262	1.42 (1.04, 1.93)
Past	478 (3191)	1,140	1.15 (1.04, 1.27)
Sweden			
Never	6,104 (57,594)	15,776	1
Current	506 (5078)	3,234	0.80 (0.73, 0.88)
Recent	62 (484)	2,520	0.93 (0.72, 1.20)
Past	907 (6575)	2,305	1.12 (1.04, 1.21)
US			
Never	17,539 (171,688)	47,151	1
Current	1,944 (16,576)	9,598	1.00 (0.95, 1.04)
Recent	315 (1525)	7,685	1.79 (1.60, 2.00)
Past	2,331 (16,677)	6,575	1.28 (1.23, 1.34)

Notes: *Adjusted for age + sex +country-specific variables imbalanced after PS-matching + markers of COPD severity and morbidity. The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country. "Current", "recent", and "past use" of roflumilast is defined using a time-varying variable dependent on the timing of roflumilast discontinuation."Never use" concern patients in the matched unexposed cohort, with no prior exposure to roflumilast.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; MR, mortality rates; N, number of patients; PS, propensity score; PY, person-years; US, United States.

the US, but not in Sweden. For "past use", an increase in mortality compared to "never use" was seen in all countries. Crude HRs are presented in Supplementary Material 8. Across all countries and use status categories, further adjustment after PS matching lowered the risk estimates.

Adjusted HRs of mortality for categories of "cumulative duration of use" versus "never use" are presented in Table 5. No association between any category of cumulative use including > 24 months of use and 5-year all-cause mortality was observed in the adjusted models in Norway and in Sweden. Similarly, in Germany, no increased risk was observed for > 24 months of use. However, for lower cumulative exposure durations (3–12 months, 12–24 months), an increased mortality risk was observed. In the US, a significant increase in mortality risk was observed for all categories of

Table 5 Five-Year All-Cause Mortality for "Cumulative Use" (<3 Months, 3 to 12 Months, 12 to 24 Months, >24 Months) of Roflumilast versus "Never Use": Number of Events and Adjusted HRs

	Deaths (PY)	N at risk	Adjusted HR*(95% CI)
Germany			
Never	12,071 (160,716)	41,718	1
<3 months	1053 (11,916)	8775	1.06 (0.99, 1.13)
3 to 12 months	1129 (11,457)	6154	1.18 (1.11, 1.26)
12 to 24 months	489 (4,823)	3642	1.24 (1.13, 1.35)
>24 months	559 (6,258)	2754	1.05 (0.96, 1.15)
Norway			
Never	3,251 (28,036)	7,830	1
<3 months	197 (1,398)	1624	0.92 (0.79, 1.07)
3 to 12 months	373 (2,746)	1297	1.10 (0.98, 1.23)
12 to 24 months	92 (797)	606	0.97 (0.79, 1.20)
>24 months	117 (1,094)	456	0.87 (0.72, 1.05)
Sweden			
Never	6,104 (57,594)	15,776	1
<3 months	503 (3,827)	3234	0.99 (0.90, 1.08)
3 to 12 months	586 (4,686)	2310	0.99 (0.91, 1.08)
12 to 24 months	169 (1,544)	1171	0.96 (0.82, 1.12)
>24 months	217 (2,079)	880	0.94 (0.81, 1.08)
US			
Never	17,539 (171,688)	47,151	1
<3 months	1458 (10,764)	9598	1.17 (1.10, 1.23)
3 to 12 months	1546 (11,802)	6969	1.17 (1.11, 1.24)
12 to 24 months	683 (5427)	4171	1.12 (1.04, 1.21)
>24 months	903 (6785)	3062	1.17 (1.10, 1.26)

Notes: *Adjusted for age + sex +country-specific variables imbalanced after PS-matching + markers of COPD severity and morbidity. The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; N, number of patients; MR, mortality rates; HR, hazard ratio; PY, person-years; US, United States.

cumulative use (Table 5). Further adjustment after PS matching lowered the risk estimates in nearly all categories of cumulative duration of use (Crude HRs are presented in Supplementary Material 8).

The results of the sensitivity analysis utilizing HD-PS matching (Supplementary Material 9), were in line with those of the main analysis (Table 3), with slightly lower adjusted HRs of mortality in the HD-PS-matched analysis than in the main analysis. In the sensitivity analysis censoring patients on the first discontinuation of roflumilast (Supplementary Material 9), no increase in mortality risk compared to "never use" was observed for any of the cumulative use of roflumilast categories in any of the analyzed countries. Instead, a protective effect against mortality was seen with

Table 6 Sensitivity Analysis: Adjusted Hazard Ratios of 5-Year All-Cause Mortality for "Ever Use" versus "Never Use" of Roflumilast Stratified by PS Quintile

Country	Germany	Norway	Sweden	US
Propensity Score Quintiles	**Adjusted* HR (95% CI)**	**Adjusted* HR (95% CI)**	**Adjusted* HR (95% CI)**	**Adjusted* HR (95% CI)**
1st quintile	1.56 (1.40; 1.73)	1.29 (1.05, 1.58)	1.12 (0.96, 1.30)	1.29 (1.18, 1.41)
2nd quintile	1.26 (1.15; 1.39)	1.02 (0.84, 1.24)	1.13 (0.98, 1.31)	1.25 (1.15, 1.36)
3rd quintile	1.09 (1.00; 1.20)	1.19 (0.99, 1.43)	0.95 (0.83, 1.09)	1.23 (1.14, 1.33)
4th quintile	1.12 (1.03; 1.22)	0.97 (0.80, 1.16)	0.91 (0.80, 1.04)	1.14 (1.06, 1.22)
5th quintile	0.90 (0.83, 0.97)	0.79 (0.67, 0.93)	0.87 (0.77, 0.99)	1.01 (0.94, 1.08)

Notes: *Adjusted for age + sex + country-specific variables imbalanced after PS-matching + markers of COPD severity and morbidity.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PS, propensity score; US, United States.

cumulative durations of roflumilast use up to 24 months in Sweden and in the US and with any cumulative duration of roflumilast use in Norway.

In the sensitivity analysis stratifying the study population by PS quintiles (results displayed in Table 6), the adjusted HRs for 5-year all-cause mortality in "ever use" versus "never use" tended to decrease with increasing PS quintile. More specifically, the lowest adjusted HRs were observed in the fifth PS quintile (patients with the highest disease severity), with a protective effect of roflumilast use against 5-year all-cause mortality risk in Germany, Norway, and Sweden.

Finally, in the sensitivity analysis examining the risk of mortality within strata of FEV1 in Germany, the estimated adjusted HRs decreased with decreasing FEV1 values (Supplementary Material 9). No statistically significant difference in mortality risk was observed for "ever use" versus "never use" in any of the strata, except a significant increase in mortality associated with roflumilast use in the stratum where FEV1 values were missing.

Discussion

This is the first real-world study to evaluate the long-term safety of roflumilast in COPD and CB treatment. The study cohorts included 112,541 unexposed and 23,239 exposed patients in electronic healthcare databases from Germany, Norway, Sweden, and the US. PS matching was used to minimize the differences between exposed and non-exposed patients. However, some variables related to COPD severity and morbidity remained unbalanced in the matched cohorts, with slightly higher severity and morbidity in roflumilast cohorts at baseline. After adjusting for unbalanced covariates, no increase in 5-year mortality risk in "ever use" of roflumilast compared to "never use" was observed in Sweden or in Norway, whereas a small[20] increase in 5-year mortality risk remained in Germany and in the US. Similar results were found in duration categories of "cumulative use". "Recent use" and "past use" of roflumilast were also associated with an increased 5-year mortality risk, but not "current use", when compared with "never use". Contrarily, a decrease in 5-year mortality risk was observed in "current use" patients in Germany, Norway, and Sweden, compared to "never use". This decrease in 5-year mortality risk was also identified in the sensitivity analyses in patients in high PS quintiles, low FEV1 value, or with continuous use of roflumilast (sensitivity analysis censoring patients on first roflumilast discontinuation).

This study was primarily designed to evaluate the mortality risk over a 5-year period related to the long-term use of roflumilast. This was intended to complement the randomized clinical trial (RCT) data, which only provide insights into a treatment duration up to 12 months.[21] Although there was no existing evidence for an association between roflumilast and mortality risk in the RCTs, as per the results of a Cochrane meta-analysis of 42 RCTs of roflumilast and other PDE4 drugs in patients with COPD,[21] this study fills the knowledge gap for long-term use in clinical practices, reflective of real-world use.

Evidence from RCTs align with our study findings showing no increase in mortality risk related to roflumilast exposure in "current use" versus "never use" and in the analysis censoring patients on first discontinuation. A possible reason for these results to differ from those related to "ever use" versus "never use" in Germany and the US is that in the "ever use" category, the timing between the exposure and the event is unclear. This is specifically important given the relatively short half-life compared to the follow-up time of roflumilast and its N-oxide metabolite (17 and 30 hours, respectively).[22] Given that 75% of the patients discontinued roflumilast during the first 12 months after CED in the current study, a discontinuation rate that was much higher than those in RCTs (16.5% and 8.9%),[9] limitations on the possibility of drawing firm conclusions from the "ever use" versus "never use" analyses become apparent. Other real-world studies have also reported high discontinuation rates of roflumilast (up to 84% within the first 12 months).[14,23]

The study estimates of an increase in 5-year mortality in relation to "ever use", "recent use", and some durations of 'cumulative use' in Germany and the US, compared to 'never use', are likely biased by inadequate adjustment for the severity of COPD. Notably, important variables indicating disease severity remained unbalanced after PS matching. Furthermore, as roflumilast is used as a last-line treatment in severe COPD cases,[7] where no approved alternative treatment currently exists,[8] it was not possible to optimally match the roflumilast users' group with a comparator group of nonusers with a similar level of disease severity. In Sweden and Norway, no increase in mortality associated with roflumilast use was observed for the abovementioned comparisons. The Nordic registries provide an extended timeframe for retrospective data allowing for better insights on clinical progression of COPD and proxies of disease severity. This enables better possibilities to match patients based on their disease severity. In contrast, the claims nature of the data from Germany and the US does not allow for a comprehensive coverage of key variables, indicating COPD severity, meaning that patients taking roflumilast with an apparent low disease severity are matched with patients with less severe disease due to the limitations of the data. This hypothesis is in line with the results in Germany stratified by FEV1, a marker of COPD severity. Here the 5-year mortality risk in 'ever use' versus 'never use' decreased with decreasing FEV1 values. Additionally, a nominally elevated mortality risk for roflumilast was seen in the less severe FEV1 stratum (FEV1 between 50% and 70%) and a significant increase in mortality associated with roflumilast use in the stratum where FEV1 values were missing. Patients with missing FEV1 measurements were presumed to have a lower disease severity as they are likely to include mostly non-hospitalized patients, given that FEV1 measurements are only registered in inpatient care (as a 5-digit ICD-10-GM code only used in hospitals). A similar observation was made in the analysis stratified by PS quintiles, in which no increased risk was observed for the patients with the highest COPD severity (ie, those with the highest PS quintile). While information on COPD severity could be adjusted for in patients with high COPD severity, by means of hospitalizations or emergency room visits for COPD, such comparable clinical information was not available for patients with less severe disease who did not attend emergency rooms or stay in the hospital due to COPD. Furthermore, the tendency of risk estimates to decline toward the null from crude analyses to adjusted analyses and from PS-matched analysis to HD-PS–matched analysis is suggestive of uncontrolled residual confounding. Taken together, both analyses that stratify the patient cohorts based on disease severity and analyses with comprehensive coverage of proxies of disease severity and progression in Sweden and Norway indicate that residual confounding by indication is a likely explanation of the increase in hazard of 5-year mortality seen in different measures of roflumilast use compared to 'never use' in Germany and the US.

A further indication of residual confounding are the results for Germany and the US showing an increased mortality risk associated with roflumilast use for durations less than 12 months, such as "< 3 months" in the US or "3 to 12 months". These time periods were covered by the RCTs in which no increased risk was observed.[21] Moreover, the analysis censoring patients on first discontinuation of roflumilast suggested that a decrease in 5-year mortality risk in "current users" compared to "never users" could be observed in multiple levels of cumulative exposure, including both exposures of less than 12 months and more than 12 months, as opposed to the results in the main analysis of cumulative exposure. However, as patients who continued roflumilast treatment might differ from those who discontinued it in terms of morbidity, disease severity, and other characteristics, interpretation of these results should be seen in light of this limitation.

The strengths of this large multinational study include its long follow-up and generalizability. Although the length of follow-up ranged between 12 and 52 weeks in RCTs evaluating the safety of roflumilast in COPD patients,[21] our study included 5 years of follow-up, allowing for the assessment of long-term effects of roflumilast as well as the impact of long-term exposure to the treatment. The generalizability of the study results is supported by its real-world setting and by the representativeness of its data from the Norwegian[24] and Swedish[25,26] national registries and large population samples from Germany and the US. These data

sources also constitute a strength in the study considering their internal validity. The Nordic national registries have a proven track record in terms of the quality of their data and their appropriateness for real-world research in pharmacoepidemiology.[27] In addition, analyses of the GePaRD database have shown the database to be representative of the broader German population in terms of age, sex, number of hospital admissions, and patterns of medication use,[28] and its data on all-cause mortality to be of acceptable data quality.[29,30] The strengths of the study are additionally underlined by its methodological approach. PS matching is a well-established method of balancing the probability of treatment selection between the groups compared in the analysis, thereby minimizing treatment selection bias, as well as controlling for confounding.[31]

Nevertheless, our study was restricted by a limited capture of COPD severity and morbidity variables in the study databases. For example, the variable "time since COPD diagnosis", an important proxy of disease stage, could not be derived in the German and US data. Moreover, information on lifestyle variables, notably smoking, a key determinant of COPD exacerbations[32] and a risk factor for mortality, was incomplete in all of the studied countries. In addition, information on clinical characteristics of patients with COPD (eg, magnitude of dyspnea, lung function tests) was not available (apart from categorical information on FEV1 for part of the German study population). Finally, oxygen use was poorly or not captured in most databases. Consequently, the study does not include sufficient data to ensure adequate control for potential confounding by indication. In addition to the limitation related to the data sources, this residual confounding, evidenced by unbalanced variables despite PS matching, is hindered by the absence of an active comparator drug with the same therapeutic indication as roflumilast. However, our study comprised a series of sensitivity analyses that have addressed the bias and shown its likely direction.

Conclusion

No increase in 5-year mortality risk with the use of roflumilast was observed in Sweden or in Norway. However, a small increase in 5-year mortality risk was suggested in Germany and in the US. This increase in mortality risk, not present when considering only current exposure or patients with more severe COPD, is likely due to residual confounding by indication.

Ethics Approval

In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the German Federal Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias results, which was the case in this study. According to the Ethics Committee of the University of Bremen studies based on GePaRD are exempt from institutional review board review. In Norway the study was approved by the Norwegian Regional Committee for Research Ethics (2019/145/REK nord). In Sweden the study was approved by the Swedish Ethical Review Authority (2013/1412-31). In the US the study protocol was approved by the Naval Medical Center – Portsmouth, Institutional Review Board (IRB protocol NMCP.2014.0037).

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Participating investigators

Bob Brody, Bo Ding, Peter McMahon, and Annalisa Rubino contributed to critical review of the study protocol; development/amendment of the statistical plan and scientific oversight during early phases of the project.

Jeremy A. Rassen contributed to the development and implementation of the high dimensional propensity score methodology.

Rosa Lamarca provided statistical supervision and significant contribution to study methodology.

Fredrik Nyberg, Mark Ouwens, Jonas Román, Beatriz Seoane Nuñez provided scientific oversight and technical guidance to the biostatistics component of the study in earlier phases of the project.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Edeltraut Garbe has been chairwoman of the Department of Clinical Epidemiology at the Leibniz Institute for Prevention Research and Epidemiology – BIPS and in this function occasionally performed studies for pharmaceutical industries. The pharmaceutical companies included Byk-Gulden, Nycomed, Bayer, Celgene, GlaxoSmithKline, Mundipharma, Novartis, Sanofi-Aventis, Sanofi Pasteur MSD, and STADA. She has been a consultant to Bayer-Schering, Nycomed, GlaxoSmithKline, Schwabe, Teva, and Novartis, as well as to AstraZeneca (including this study). Per Arkhammar, Marie Carlholm, Eileen O Dareng, Harald Fjällbrant, and Stefan Franzén are employees and shareholders of AstraZeneca. Atul Kumar is an employee of AstraZeneca. Tore Persson is an AstraZeneca contractor and shareholder. Cecilia Hedlund is an AstraZeneca contractor. Gunnar Johansson has served on advisory boards arranged by AstraZeneca, Novartis, and Teva. Bianca Kollhorst, Wiebke Schäfer, and Tania Schink are working at an independent, non-profit research institute, the Leibniz Institute for Prevention Research and Epidemiology – BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry. These are post-authorization safety studies (PASS) requested by health authorities and performed in line with the ENCePP Code of Conduct. Fabian Hoti, Muriel Lobier, Aaro Salosensaari, Xu Qiao, and Vasili Mushnikov are employed by IQVIA, a contract research organization that conducts studies financed by the pharmaceutical industry. Nicholas Sicignano and Kristian Svendsen confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. The authors report no other conflicts of interest in this work.

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