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ORIGINAL RESEARCH

Clinical and Economic Burden of COPD in Patients on Inhaled Triple Therapy in Germany – A Retrospective Claims Data Analysis

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Purpose: This study describes the pharmacological treatment as well as the clinical and economic burden of disease in chronic obstructive pulmonary disease (COPD) patients initiating triple therapy (TT) defined as a combination of a long-acting muscarinic antagonist (LAMA), a long-acting beta2-agonist (LABA) and an inhaled corticosteroid (ICS) in Germany.

Patients and Methods: All COPD patients aged 40 years and older in an anonymized claims database who initiated TT in 2017 were included. Adherence to TT and the use of the guideline-recommended escalation therapies were measured during two years of follow-up. We also describe the number of exacerbations, healthcare resource utilization, and direct healthcare costs observed during the follow-up. Results are reported for the total study population and a subgroup adherent to TT.

Results: Of the 3,458,989 insured individuals in 2017, 6,532 initiated TT. Cardiovascular, respiratory, metabolic, and psychiatric comorbidities were common. Only one in six patients was adherent to TT over two years and one third experienced exacerbations; 18% had one exacerbation, 7% had two, 3% had three and 5% had four or more exacerbations during the follow-up. Both COPD-related and all-cause healthcare costs increased with the number of exacerbations during follow-up, as did the proportion of COPD-related costs among all healthcare costs. Mean all-cause costs per person-year of follow-up were €8,110 for patients without and €20,832 for patients with four or more exacerbations, respectively. Escalation therapy with roflumilast, which is recommended in German guidelines, was prescribed to 3.1% of patients, of whom two-thirds discontinued the drug during the two-year follow-up.

Conclusion: A substantial proportion of COPD patients initiating TT experience exacerbations resulting in high resource utilization and costs for the healthcare system. With poor treatment adherence and rare use of guideline-recommended escalation therapies, effective new treatments are needed to address the unmet medical need in this patient population.

Keywords: exacerbation, roflumilast, costs, healthcare resource utilization, treatment

Introduction

Chronic obstructive pulmonary disease (COPD) is associated with high mortality rates and is currently the third leading cause of death worldwide.[1,2] Its severity is heavily influenced by exacerbations—episodes of worsening symptoms, severe and persistent airflow limitation as well as systemic, in particular cardiovascular, consequences.[3] Frequent exacerbations significantly drive disease progression, accelerating the decline in lung function, reducing quality of life, and contributing to the high risk of death in COPD patients.[4–6] Minimizing the impact of exacerbations and reducing the risk of future exacerbations are therefore critical goals in the management of COPD.[3]

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The recommended initial maintenance therapy for moderate to severe COPD includes a long-acting muscarinic antagonist (LAMA), a long-acting beta$_2$-agonist (LABA), or a combination of both (LAMA+LABA).[3,7] Accordingly, a combination of these was the most common first-line therapy for newly diagnosed COPD patients in Germany.[8,9] For patients who continue to experience exacerbations on LAMA+LABA dual therapy, escalation to triple therapy (TT) by adding inhaled corticosteroids (ICS) is recommended.[3,7,8] In Germany, both multiple-inhaler triple therapy (MITT) and single-inhaler triple therapies such as fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) and beclomethasone dipropionate/glycopyrronium/formoterol (BDP/GLY/FOR) are frequently used, although MITT remains most common among both incident and prevalent TT users.[10] Several studies have shown that TT with combined bronchodilation (LABA + LAMA) and an anti-inflammatory treatment (ICS) can reduce the risk of exacerbations compared to LABA and/or LAMA therapy alone.[11,12] However, the evidence on the superiority of TT over dual therapy remains unclear.[8,12] Patients with low blood eosinophil (EOS) counts are less likely to benefit from ICS treatment, and several studies have highlighted an increased risk of side effects associated with long-term ICS use, including pneumonia.[13,14] Therefore, triple therapy is not recommended for certain patient groups, such as those at high risk of infections or with low blood EOS counts.[3]

International studies suggest that most patients initiating TT continue to experience exacerbations within 12 months.[15–17] For instance, a subgroup analysis of a 52-week Phase 3 trial demonstrated that up to 50% of patients on TT continue to experience moderate and severe exacerbations.[17] Exacerbations in turn are associated with progressive and potentially irreversible lung damage.[18] The occurrence of every new severe exacerbation has been shown to worsen the disease course, to increase the risk of subsequent exacerbations, and to elevate the risk of death.[19] Furthermore, exacerbations are associated with a sustained risk of severe cardiopulmonary events, highlighting the urgency for comprehensive clinical management.[20]

The economic burden of patients receiving TT who experience exacerbations is likely substantial. To our knowledge, specific estimates for this patient group have not been reported for Germany, but data from the COSYCONET registry yielded estimates of direct healthcare costs amounting to €8924 per year among patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 4 COPD.[21] Moreover, a history of moderate or severe exacerbations has been identified as one of the strongest predictors for future healthcare costs in COPD patients.[22]

However, there are limited therapy escalation options for patients who continue to experience exacerbations despite being on TT. The 2025 GOLD report suggests either roflumilast, the antibiotic azithromycin or dupilumab,[3] while the latest German guideline, published in 2017, only recommends roflumilast.[7] Azithromycin offers immunomodulatory effects beyond its antimicrobial activity. Roflumilast, a PDE-4 inhibitor, reduces airway inflammation and has been associated with improvements in lung function and exacerbation outcomes in a phase 3 trial.[23] Dupilumab, a fully human monoclonal antibody targeting the underlying type 2 inflammatory cascade by specifically inhibiting interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling pathways, key drivers of inflammatory response, was recently approved for a subset of COPD patients with elevated eosinophils.[24,25] The extent to which established last-line therapies are utilized in Germany remains unknown. Since dupilumab was not available for the treatment of COPD until recently, studies investigating its use in real-world clinical practice are not yet available. A population-based German study reported that 7% of newly diagnosed COPD patients received TT 36 months after diagnosis,[9] but did not examine the use of roflumilast or azithromycin. However, understanding current treatment practices is crucial for guiding clinical decisions and for improving outcomes for COPD patients.

This study therefore explored the clinical and economic burden of COPD patients treated with TT in Germany. Specifically, we sought to identify the proportion of patients who continue to experience exacerbations on TT and to estimate their healthcare resource utilization (HCRU) as well as direct healthcare costs. Additionally, we examined the implementation of the – until recently – only available last-line therapies azithromycin and roflumilast among patients who continue to experience exacerbations while receiving TT.

Materials and Methods

Study Design and Population

This retrospective cohort study is based on anonymized healthcare claims data from the WIG2 benchmark database, a claims database held by the Scientific Institute for Health Economics and Health System Research (Wissenschaftliches

Institut für Gesundheitsökonomie und Gesundheitssystemforschung, WIG2). The database contains longitudinal data from approximately 4.5 million German residents with statutory health insurance and is representative of the German population in terms of age, sex, and morbidity.[26] In order to obtain results that are not affected by changes in healthcare utilization during the COVID-19 pandemic, data up to the end of 2019 were used.

The study base included all individuals with prevalent COPD aged 40 years and older who initiated TT in 2017 followed over up to two years. In German claims data, information on diagnoses and treatments in the outpatient sector are available on a quarterly basis (four times annually). Therefore, we defined the lookback period as four consecutive quarters before the index date and the follow-up as eight successive quarters following the index date (Figure 1). Individuals who were not continuously insured during a 1-year lookback period, who already received TT during the lookback period, or who could not be continuously observed during the lookback or during a two-year follow-up (unless deceased) were excluded.

All patients who newly initiated TT were included. Individual treatment history or criteria leading to the initiation of TT in individual patients were not considered. Additionally, a subgroup of patients adherent with TT throughout the follow-up was defined based on the proportion of days covered approach. Patients were considered adherent if they received a sufficient amount of dispensed medication to cover at least 70% of days during their follow-up. Included individuals were followed until the end of the two-year-follow-up or until their death, whichever came first.

Variables and Definitions

Diseases and smoking status were identified through ICD-10-GM codes (International Statistical Classification of Diseases and Related Health Problems, 10th edition, German modification) documented in in- or outpatient care.[27] All ICD-codes used in this study are listed in Supplementary Table 1. COPD prevalence in 2017 was defined as (i) at least one primary inpatient COPD diagnosis; (ii) at least two outpatient diagnoses of COPD in different quarters; or (iii) a secondary inpatient diagnosis as well as at least one outpatient diagnosis of COPD during 2017. In Germany, outpatient physicians must assign a level of certainty to each recorded diagnosis; in this study, only COPD-diagnoses categorized as "confirmed" were considered while "tentative" diagnoses or diagnoses referring to a "post-disease state" were excluded. Comorbidities and smoking status were assessed during the lookback period.

Medication use was measured through Anatomical Therapeutic Chemical (ATC) codes on prescriptions filled by pharmacies.[28] All ATC-codes used to identify COPD treatments are listed in Supplementary Table 2. Drugs administered during hospitalizations cannot be identified in the claims data as they are not recorded individually; however, their costs are included in the recorded hospitalization costs.

The claims data set only contains information on the total dose prescribed (by package) and not the duration for which the treatment was intended. Therefore, we used the prescribed doses together with the defined daily dose (DDD) to calculate the assumed number of days during which the patient was treated. DDDs are a statistical measure defined as the assumed average maintenance dose for a drug's main indication and set by a research institute.[28] For example, in Germany the DDD for roflumilast is 0.5mg orally.[28] As an assumed average, the DDD does not reflect the individual maintenance dose prescribed to each patient (which are not recorded in the data).

The duration of treatment was estimated using the dispensation date and the dispensed number of DDD (days of supply). Days of supply were added in case of overlapping dispensations. For example, two consecutive fills with 30 days of supply of the same medication totaled 60 days, regardless of whether the second prescription was filled after 20 or 30 days. A grace

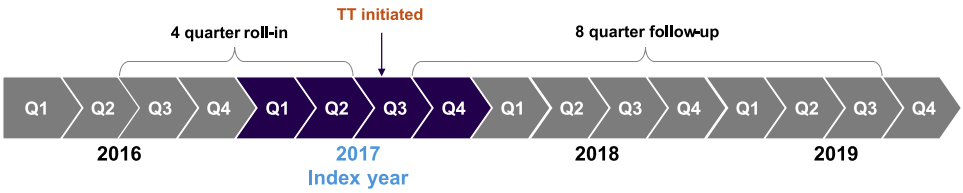

Figure 1 Study timeline.
Notes: Each quarter spans three consecutive months (for example, the first quarter is January to March).
Abbreviations: Q, Quarter; TT, Triple therapy.

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period of 25% of supply days was used to cover potential gaps in prescription coverage. For instance, treatment was considered continuous if a new prescription was filled 35 days after a previous 30-day prescription, despite the gap of 5 days.

Triple therapy was defined as an overlap of LABA, LAMA, and ICS treatment in free-dose or fixed-dose combinations for at least 30 days. The prescription of the third TT component was considered the initiation of TT, ie, the index date. Patients were considered adherent if they received prescriptions covering at least 70% of days during the follow-up. Previous studies commonly used a cut-off of 80% to indicate good treatment adherence.[17,29–32] In this study, we chose a cut-off of 70% in order to reach a sufficient size of the adherent subpopulation after conducting feasibility analyses. A comparatively low cut-off also allowed us to obtain conservative estimates of non-adherence.

Exacerbations were defined as any moderate or severe COPD exacerbations identified in the claims data. The 2025 GOLD report classifies exacerbations requiring treatment with systemic corticosteroids and/or antibiotics as moderate, while exacerbations requiring hospital or emergency care are classified as severe.[3] Considering the inability to unequivocally attribute drug treatments to specific diseases in German claims data, we did not consider antibiotic treatment as an indicator for exacerbations and considered oral corticosteroids only when prescribed in certain doses for short-term therapy or when prescribed in the same quarter as a COPD diagnosis. Specifically, we used the following algorithm to measure moderate or severe exacerbations: (i) at least one prescription of oral or intravenous corticosteroids for at least 5 days and with a dose equivalent to 10–40mg prednisolone (excluding packages for permanent therapy); (ii) at least one hospitalization coded with a main COPD diagnosis; or (iii) a prescription of oral corticosteroids in the same quarter as a COPD diagnosis. The frequency of exacerbations during the follow-up was categorized into 0, 1, 2, 3, and 4 or more (4+) moderate or severe exacerbations.

Healthcare resource utilization examined included the total number of outpatient visits, the number of outpatient pulmonologist visits, the number of all-cause hospitalizations, and participation in a pulmonary rehabilitation program. Due to the nature of the claims data set, it was only possible to measure whether a patient visited a physician during one quarter while the number of visits during the quarter could not be ascertained. The measured number of visits at a specific physician was thus limited to one per quarter or four per year. As a result, two or more reported outpatient visits within one quarter reflect visits to at least two different physicians.

We examined healthcare costs from the payer perspective including costs due to outpatient care (both primary care and specialist care), inpatient care, and prescription medication. Costs paid entirely out of pocket, such as for transportation or over-the-counter medication, or societal costs such as productivity loss due to absence from work, were not considered. We distinguished between all-cause healthcare costs and costs directly attributable to COPD. The definition of COPD-attributable costs is available in Supplementary Table 3.

Analyses

Incidence rates were calculated as incident cases in 2017 divided by the number of insured in the database. An extrapolation of the number of incident cases to the total population with statutory health insurance (SHI) in Germany was conducted accounting for the relative distribution of age and gender (see Supplementary Materials for details). The German population stratified by gender, age, and type of health insurance fund was retrieved from national statistics.[33] Healthcare resource utilization and direct healthcare costs were calculated for the total study population and the adherent subpopulation, stratified by number of exacerbations during the follow-up. Mean values were reported together with standard deviations. Direct healthcare costs during the follow-up were aggregated and divided by the total number of person-years observed.

Results

Study Population

We identified 119,517 patients with COPD in 2017 among approximately 1.8 million insured individuals aged 40 years and older. Triple therapy was used by 21,325 patients (17.8%); of these, 6,532 newly initiated TT in 2017 and were observable throughout the entire study period, comprising the study population (Supplementary Figure 1). Among 6,532 individuals in the study population, 1,044 (16,0%) received TT covering at least 70% of their follow-up (adherent subpopulation). Non-compliance with TT was high regardless of the number of exacerbations, ranging from 76.6% to 85.5% (Supplementary Figure 2). Characteristics of the study population are shown in Table 1.

Table 1 Characteristics of the Study Population

	Total Study Population N=6,532	Adherent Subpopulation N=1,044
Female, n (%)	2,659 (40.7)	413 (39.6)
Mean age	66.8	67.2
Age, n (%)		
40-49	387 (5.9)	60 (5.7)
50-59	1,478 (22.6)	233 (22.3)
60-69	2,010 (30.8)	335 (32.1)
70-79	1,778 (27.2)	273 (26.1)
80+	879 (13.5)	143 (13.7)
Recorded smoking at baseline, n (%)	2,272 (34.8)	371 (35.5)
Enrolled in DMP COPD, n (%)	1,699 (26.0)	249 (23.9)
Baseline comorbidities, n (%)		
Asthma	2,131 (32.6)	426 (40.8)
Cardiovascular disease	4,651 (71.2)	727 (69.6)
Hypertension	4,500 (68.9)	698 (66.9)
Heart failure	1,404 (21.4)	238 (22.8)
Chronic ischemic heart disease	1,855 (28.4)	294 (28.2)
Dyslipidemia	2,964 (45.4)	476 (45.6)
Type-2-Diabetes mellitus	1,809 (27.7)	277 (26.5)
Obesity	1,709 (26.2)	264 (25.3)
Osteoporosis	814 (12.4)	137 (13.1)
Anxiety	613 (9.4)	92 (8.8)
Depression	1,486 (22.7)	232 (22.2)
Exacerbations during follow-up, n (%)		
0	4,333 (66.3)	627 (60.1)
1	1,184 (18.1)	183 (17.5)
2	484 (7.4)	113 (10.8)
3	128 (2.0)	51 (4.9)
4+	313 (4.8)	70 (6.7)
Mean number (SD)	0.7 (1.5)	0.9 (1.6)
Mean days to first exacerbation (SD)	123 (163)	122 (165)

Abbreviations: COPD, Chronic obstructive pulmonary disease; DMP, Disease Management Program; SD, Standard deviation.

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Men comprised 59.3% of the study population and the majority was aged 60 years or older (71.4%). Approximately one third had medical records indicating tobacco use (smoking) at baseline. Cardiovascular diseases (CVD) were the most common comorbidities and recorded among 71.2% of the study population. Among these, hypertension, chronic ischemic heart disease, and heart failure were most commonly recorded. An asthma diagnosis was recorded in 32.6% of the study population, while depression and anxiety were present in 22.7% and 9.4%, respectively. One in four patients was enrolled in the structured disease management plan for COPD-treatment.

During the follow-up, one third of the study population experienced exacerbations; 18.1% had one, 7.4% had two, 2.0% had three, and 4.8% had 4+ exacerbations. It took a mean of 123 days (SD: 163) for a patient to experience an exacerbation during follow-up. On average, individuals in the study population experienced a mean of 0.7 exacerbations across 8 quarters of follow-up.

These numbers correspond to an incidence of 366.7 COPD-cases with incident TT per 100,000 individuals aged 40 years and older in the database. Extrapolated to the total German population, this corresponds to 178,216 cases with incident TT in this age group annually.

Utilization of Recommended Therapy Escalations

Overall, 914 patients (14.0%) with newly initiated TT in the database were treated with azithromycin and 201 (3.1%) with roflumilast during the two-year follow-up (Figure 2). The proportion of patients prescribed azithromycin and roflumilast increased with increasing follow-up exacerbations; 12.9% and 1.3% of patients with no exacerbations, and 18.5% and 15.7% of patients with 4+ exacerbations were prescribed azithromycin and roflumilast, respectively. Azithromycin treatment was overall more common in the total study population than among adherent patients, while only minor differences between the total study population and adherent subpopulation were found in roflumilast treatment.

In patients with at least one prescription, the mean number of DDD dispensed per patient-year were 5.3 and 181.0 for azithromycin and roflumilast, respectively. The mean number of DDD of azithromycin dispensed were highest among patients with 4+ exacerbations, reaching 10 DDD in the study population (Supplementary Table 4). The association between number of follow-up exacerbations and roflumilast treatment was less clear, but an overall fewer number of DDD per patient-year were observed among individuals with 2 or more exacerbations during follow-up than among those with 0–1 exacerbations (Table 2). Generally, we observed a large variation in the number of DDD of roflumilast dispensed. Considering this large variation, differences between the total study population and adherent subpopulation were small.

In total, 69% of patients in the total study population with one or more roflumilast prescriptions discontinued treatment during follow-up. In the adherent subpopulation, 72% of patients discontinued roflumilast. There was no clear association between number of exacerbations during follow-up and roflumilast discontinuation in the total study population or in the adherent subpopulation. Due to the low average number of DDD of azithromycin prescribed, it was concluded that the vast majority of patients are treated during short episodes only and data on treatment discontinuation was thus not reported.

Healthcare Resource Utilization: In- and Outpatient Care

All COPD-patients had at least one outpatient visit and on average, patients accumulated 30 outpatient contacts during two years of follow-up (Table 3). Among these, we observed an average of 5 pulmonologist consultations. While we did not observe a correlation between all-cause outpatient contacts and follow-up exacerbations, the number of hospitalizations increased substantially with an increasing number of follow-up exacerbations. While only 60% of the study population without exacerbations were hospitalized, over 90% of those with 3 or more exacerbations were hospitalized at least once. On average, we observed 6.4 hospitalizations per person with 4+ exacerbations, and 1.7 hospitalizations per person without exacerbations in the study population during the 2-year follow-up period. COPD and CVD were the most common main diagnoses and recorded for 18.5% and 17.0% of all hospitalizations in the total study population, respectively. In the adherent subpopulation, 27.0% and 15.0% of hospitalizations had main diagnoses of COPD and CVD, respectively. There were only minor differences in the number of in- and outpatient contacts between the total study population and the adherent subpopulation (Table 3).

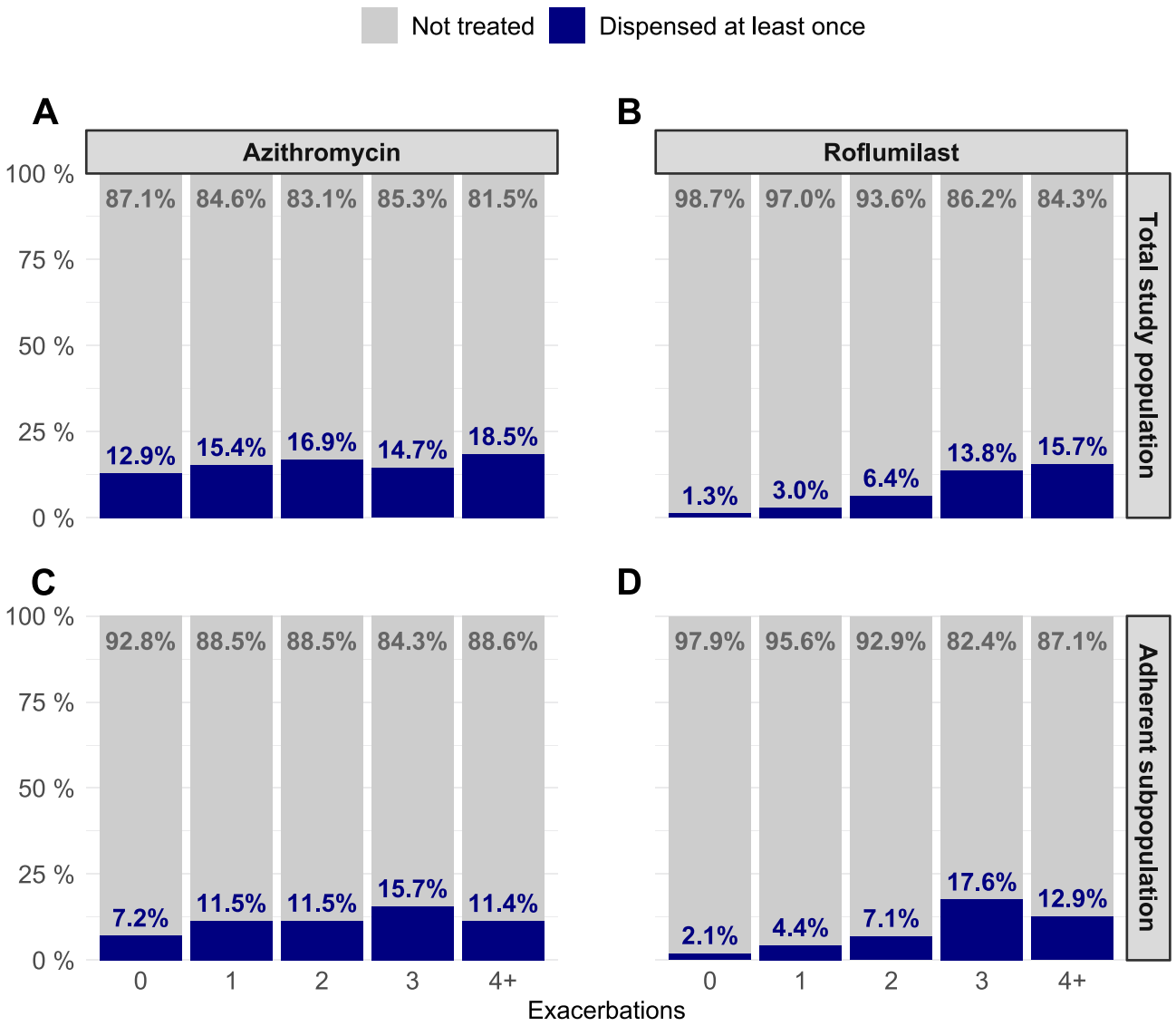

Figure 2 Proportion of patients with dispensed last-line therapies by number of exacerbations during the follow-up. (**A** and **B**) depict the proportion of patients with azithromycin (**A**) and roflumilast (**B**) dispensations in the total study population, (**C** and **D**) depict the proportion of patients with azithromycin (**C**) and roflumilast (**D**) dispensations in the adherent subpopulation.

Costs

The economic burden measured through all-cause and COPD-attributable costs is shown in Figure 3. Mean outpatient costs ranged between €1,272 and €1,615 per person-year of follow-up, of which up to €909 were attributable to COPD. There was no clear association between the number of exacerbations during the follow-up and average outpatient costs. Mean medication costs per person-year ranged from €2,494 among COPD patients with no exacerbations during the follow-up in the total study population to €4,038 among those with three exacerbations during the follow up in the adherent subpopulation. Overall, increasing numbers of exacerbations during the follow-up were associated with higher medication costs. COPD accounted for approximately 40% and 50% of medication costs in the total study population and adherent subpopulation, respectively.

In the total study population, the highest amount of costs was generated by inpatient care, with increasing average inpatient costs among patients with higher numbers of follow-up exacerbations. In the total study population, mean costs increased from €4,232 per person-year among patients without exacerbations to €15,521 among those with 4+ exacerbations. A similar trend was observed in the adherent subpopulation. The proportion of inpatient costs directly attributable to COPD increased with increasing numbers of exacerbations during the follow-up from 2.7% to 51.2% in the total study population and 5.3% to 56.7% in the adherent population.

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Table 2 Escalation of Therapy with Roflumilast Among Patients with Newly Initiated Triple Therapy

Exacerbations during Follow-up	Patients (total) N=6,532	≥ 1 Roflumilast-Prescription n (%)	Discontinued Treatment n (%)	Number of DDD Per Patient-Year[a] Mean (SD)
Total study population				
0	4,333	56 (1.3)	40 (71.4)	198.4 (304.9)
1	1,184	35 (3.0)	23 (65.7)	222.9 (317.0)
2	484	31 (6.4)	22 (71.0)	193.5 (244.9)
3	218	30 (13.8)	20 (66.7)	157.7 (222.5)
4+	313	49 (15.7)	34 (69.4)	137.6 (221.1)
Adherent subpopulation				
0	627	13 (2.1)	10 (76.9)	213.1 (283.3)
1	183	8 (4.4)	6 (75.0)	232.8 (318.9)
2	113	8 (7.1)	5 (62.5)	149.9 (252.6)
3	51	9 (17.6)	8 (88.9)	114.3 (197.9)
4+	70	9 (12.9)	5 (55.6)	131.6 (202.2)

Notes: [a]among patients with ≥ 1 prescription; 1 DDD=0.5 mg when administered orally. Number of patients treated during the follow-up, proportion discontinuing roflumilast treatment and average number of DDD per person-year by number of exacerbations during the follow-up.
Abbreviations: DDD, defined daily dose; SD, standard deviation.

Table 3 Healthcare Resource Utilization Among Patients with Newly Initiated TT by Number of Exacerbations During the Two-year Follow-up

Number of Exacerbations during Follow-up	All Outpatient Contacts during Follow-up Mean (SD)	Pulmonologist Contacts Mean (SD)	Individuals with at least 1 Hospitalization n (%)	Number of Hospitalizations per COPD-Patient Mean (SD)	Pulmonary Rehabilitation n (%)	Died during Follow-up n (%)
Total study population						
0	29.4 (15.7)	4.2 (2.6)	2599 (60.0)	1.7 (2.5)	87 (2.0)	611 (14.1)
1	29.9 (15.1)	4.6 (2.7)	907 (76.6)	2.5 (3.1)	29 (2.4)	220 (18.6)
2	30.0 (15.9)	4.8 (2.7)	424 (87.6)	3.3 (3.2)	<5	484 (24.6)
3	29.6 (16.4)	4.9 (2.6)	200 (91.7)	4.2 (3.7)	<5	218 (26.6)
4+	30.6 (15.8)	4.7 (2.8)	303 (96.8)	6.4 (4.5)	5 (1.6)	106 (33.9)
Adherent subpopulation						
0	26.9 (16.7)	5.3 (2.7)	377 (60.1)	1.6 (2.1)	14 (2.2)	154 (24.6)
1	28.5 (15.4)	5.0 (2.7)	147 (80.3)	2.2 (2.0)	5 (2.7)	41 (22.4)
2	28.9 (18.1)	5.5 (2.8)	102 (90.3)	3.5 (2.8)	<5	40 (35.4)
3	30.1 (18.6)	5.1 (2.6)	49 (96.1)	4.4 (3.0)	0 (0)	12 (23.5)
4+	29.0 (14.0)	5.0 (3.0)	68 (97.1)	5.8 (3.8)	<5	17 (24.3)

Abbreviation: SD, standard deviation.

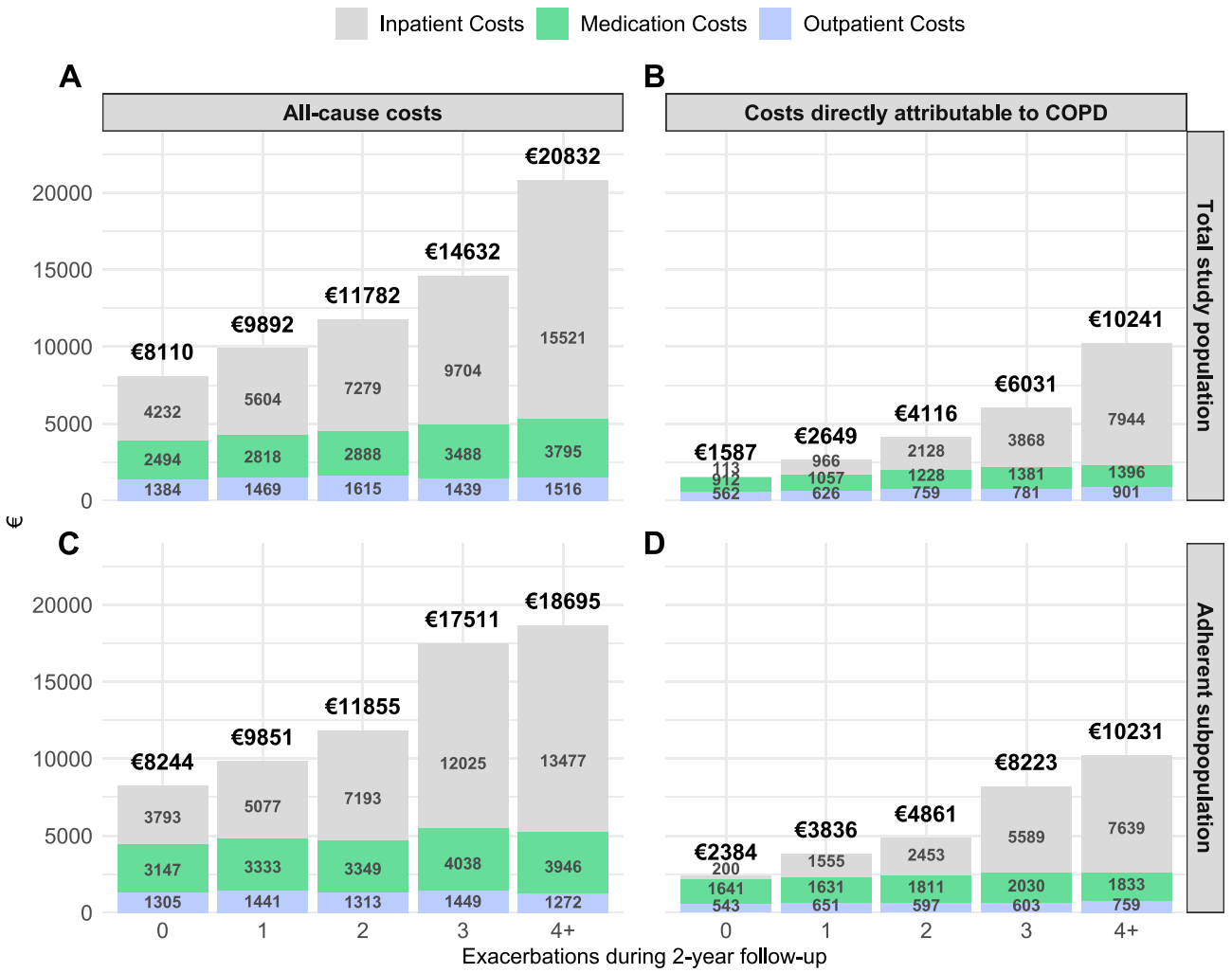

Figure 3 Mean all-cause and COPD-attributable costs by sector (inpatient, outpatient, and medications) in (€) per personyear and by number of exacerbations during follow-up. (**A** and **B**) depict all-cause costs (**A**) and costs directly attributable to COPD (**B**) in the total study population, (**C** and **D**) depict all-cause costs (**C**) and costs directly attributable to COPD (**D**) in the adherent subpopulation.

Discussion

Patients who receive TT comprise a group of patients in an advanced stage of COPD with a high exacerbation frequency. This study underscores the substantial clinical and economic burden of this patient population and reveals a critical gap in feasible and effective therapy escalation. This is even more relevant given the elevated cardiopulmonary and mortality risk of COPD patients following exacerbations.

In the present study, only one in six patients newly initiating TT was adherent over two years. In line with these results, a German study conducted by Vogelmeier et al recently found that only a minority of COPD patients initiating TT were persistent with their treatment for six months or longer.[34] Vogelmeier et al also showed that less than one in five patients on single-inhaler TT were persistent users after 18 months of treatment although the use of a single inhaler has been associated with a higher patient adherence and persistence compared to the treatment with multiple inhalers.[34] Similar findings of poor treatment adherence and persistence have been reported in international studies, all of which showed that most patients initiating TT discontinued treatment within one year.[30–32,35]

The poor treatment adherence in this patient group is associated with a considerable exacerbation risk. Our study showed that approximately one in three patients experienced exacerbations during a two-year follow-up. Other observational studies reported even higher numbers of exacerbations among COPD patients.[15,16,35–38] Two studies from the United States, for instance, found that two thirds of patients with TT exacerbate within one year of initiating

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treatment.[15,16] In a multinational study including data from Germany, Benson et al reported that approximately one third of German TT patients exacerbated during a 12-month period, but no data on patients initiating TT was reported.[38] Differences in the reported frequency of exacerbations may be attributable to challenges in accurately identifying exacerbations within claims data. Our study employed an algorithm with lower sensitivity – but a presumably higher positive predictive value – likely resulting in a conservative estimate of exacerbation numbers.

The high comorbidity level constitutes an additional burden of disease for patients with COPD. Our study population had a high prevalence of cardiovascular, respiratory, metabolic, and psychiatric comorbidities which is overall in line with previous studies on COPD patients in Germany, including patients initiating TT.[9,10,39,40] The complexity of comorbidities not only complicates disease management but can negatively impact quality of life and exacerbation risk in COPD patients.[41,42] This underscores the importance of integrated care approaches that address the treatment of COPD not only as a single disease, but as a multimorbid state comprising both respiratory and comorbid conditions.[43]

Asthma is one comorbid condition that could potentially affect treatment adherence among COPD patients. In our study, one third of patients had concurrent asthma diagnoses and we therefore explored the association between asthma prevalence and treatment adherence in sensitivity analyses. In these, we found no apparent association between asthma prevalence and adherence with TT. Nevertheless, it is possible that the high comorbidity level and associated challenges for patients and clinicians may be one mechanism behind the poor adherence with TT observed in our and in previous studies.

In accordance with the considerable comorbidity level and exacerbation risk, we observed high healthcare resource utilization and costs among patients initiating TT. Our estimates of COPD-related costs are largely consistent with those previously reported in Germany, especially when comparing our study cohort to patients with moderate-to-severe COPD.[42,44] In addition to the healthcare costs estimated in this study, direct costs not covered by insurance as well as indirect costs contribute to the total economic burden of COPD patients.[21,42] These may include societal costs due to sick leave, early retirement, and productivity losses of COPD patients or their family members, costs for rehabilitation or medical aids (such as non-invasive home ventilation or physiotherapy), and healthcare costs paid entirely out-of-pocket.

The outpatient costs estimated in this study may appear low in comparison with medication and with hospitalization costs. However, the burden of frequent physician visits on the German outpatient care system is presumably high. We observed an average of 30 outpatient visits per patient during a two-year follow-up which corresponds well with previous German studies reporting 12–16 annual outpatient visits among COPD patients.[42,44–46] However, these numbers may still underestimate the true number of outpatient contacts taking place since physician contacts are not billed individually in German healthcare claims.

It is essential to address the clinical and economic burden of COPD patients insufficiently controlled on TT. Although roflumilast is one medication recommended as escalation therapy for patients with suboptimal response to TT,[3,7] our results show that roflumilast is only used in a minority of patients in clinical practice. Furthermore, we found that a substantial proportion (69%) of patients who initiated roflumilast discontinued their treatment during the two-year follow-up. This aligns with a previous study from Denmark which reported 72% of patients using roflumilast to discontinue treatment within one year[47] and underlines the limitation of this therapy as effective and save treatment escalation. The limited uptake and poor persistence with roflumilast likely reflect multiple barriers in clinical practice. This may be attributable to the elevated risk of adverse effects and scepticism about potential benefits of roflumilast in patients without an obvious risk of severe exacerbations.[48] Physicians may also hesitate to prescribe roflumilast due to lack of awareness of its indication, a low efficacy regarding prevention of exacerbations, or concerns about a particularly high incidence of adverse events observed in real-world populations.[47,49,50]

In addition to roflumilast, the 2025 GOLD report further suggests escalation treatment using the antibiotic azithromycin or the monoclonal antibody dupilumab.[3] Since it had not yet been approved for COPD treatment in Germany during the study period, we did not examine the use of dupilumab in this study. However, our results show that azithromycin was not commonly prescribed in this patient population in Germany. This corresponds with a previous study from the United States, which found an even lower proportion of patients using azithromycin.[51] The minimal use of azithromycin as maintenance therapy despite guideline recommendations reflects several potential clinical concerns including antimicrobial resistance and potential hearing impairment with long-term use as shown in a meta-analysis in patients with chronic lung diseases.[52] Altogether, these results point towards a critical gap between guideline recommendations and real-world clinical practice

and to an unmet treatment need in this group of COPD patients with advanced disease progression and frequent exacerbations. These barriers highlight the need for more nuanced guideline recommendations that address not only when to escalate therapy but also how to manage potential adverse effects and select appropriate patients. Clinical practice may benefit from implementation strategies that address physician education on these mechanistically distinct escalation options and provide clear algorithms for identifying suitable candidates based on biomarkers, phenotypes, and comorbidity profiles. Since dupilumab has been approved for COPD treatment in Germany during 2024 and shown good efficacy in preventing exacerbations and improving lung function in some groups of COPD patients treated with TT in clinical trials,[24,25] future research should explore how treatment patterns and outcomes continue to evolve.

This study has several strengths including a large study population and low attrition rates. Administrative claims data allowed us to measure all direct healthcare costs from a payer perspective and the WIG2 benchmark database has been shown to be representative of the total German population with respect to age, sex, and morbidity indicating that our results are generalizable to the total German population.[53]

Nevertheless, our results must be considered in light of some limitations. Since claims data are not collected for research purposes, data on some clinical characteristics including lung function and blood EOS count is not conclusively available and diagnoses are not validated through gold standard methods. Considering that COPD is a common disease and that TT recipients are usually severely affected, it is likely that COPD diagnoses among TT recipients are in most cases present and correct. By contrast, the prevalence of some diseases or risk factors, such as depression or smoking, is likely underestimated in claims-based studies.[54] Secondly, while exact dates of drug prescriptions and hospitalizations are known, dates of outpatient physician visits are only recorded in three-month intervals. This may have led to some inaccuracy in the identification of exacerbations. Since we identified exacerbations through either inpatient diagnoses or through a combination of outpatient diagnoses and prescriptions or oral corticosteroids, milder exacerbations solely treated in outpatient care and without oral corticosteroids or exacerbations treated with antibiotics could not be identified. As a result, the number of exacerbations is likely underestimated in our study. Finally, the choice of a 70% of days covered cut-off for treatment adherence may have led to an overestimation of TT adherence in our study in comparison to studies using a higher threshold and to a dilution of differences between the total study population and adherent subpopulation. Moreover, we could not identify drugs supplied by physicians or hospitals and could not assure that dispensed drugs were indeed taken as prescribed. If some patients did not comply with prescribed therapies, treatment adherence may have been overestimated. These limitations point towards an overestimation of treatment adherence; the true share of patients adherent with TT may thus be even lower than reported in our study.

Conclusion

This retrospective claims data analysis underlines significant care gaps in COPD management. Only a minority of COPD patients who initiate TT remain adherent to treatment over a two-year follow-up period and a significant proportion of this patient group continues to experience exacerbations. Guideline-recommended last-line therapies are rarely prescribed, and when they are, most patients discontinue them. Overall, our findings highlight the substantial disease burden faced by COPD patients on TT and emphasize an unmet medical need for an effective therapy escalation.

Data Sharing Statement

The data used in this study are anonymized health insurance claims data provided by statutory health insurance funds in Germany. Due to data protection regulations and contractual agreements with the data provider, these data are not publicly available.

Ethics Approval

No primary patient data was collected for the conduct of this research. According to the 10th chapter of book V of social code in Germany (SGB V, Sozialgesetzbuch), anonymised healthcare claims data can be used for research purposes, therefore ethics approval was not required. Only WIG2 employees were granted access to the data for the research, and only aggregated results were generated and presented.

Author Contributions

All authors significantly contributed to the work reported, either in conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors were involved in drafting, revising or critically reviewing the article for important intellectual content and gave final approval of the version to be published. They have agreed on the journal to which the article has been submitted and to be 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.

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References

1. Vos T, Lim SS, Abbasi N, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1204–1222.
2. Safiri S, Carson-Chahhoud K, Noori M, et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. *BMJ*. 2022;378:e069679. doi:10.1136/bmj-2021-069679
3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2025 Report); 2025. Available from: https://goldcopd.org/2025-gold-report/. Accessed November 17, 2025.
4. Stöber A, Lutter JI, Schwarzkopf L, et al. Impact of lung function and exacerbations on health-related quality of life in COPD patients within one year: real-world analysis based on claims data. *Int J Chronic Obstr Pulm Dis*. 2021;16:2637–2651. doi:10.2147/COPD.S313711
5. Søgaard M, Madsen M, Løkke A, et al. Incidence and outcomes of patients hospitalized with COPD exacerbation with and without pneumonia. *Int J Chronic Obstr Pulm Dis*. 2016;11:455–465. doi:10.2147/COPD.S96179
6. Guo J, Chen Y, Zhang W, Tong S, Dong J. Moderate and severe exacerbations have a significant impact on health-related quality of life, utility, and lung function in patients with chronic obstructive pulmonary disease: a meta-analysis. *Int J Surg*. 2020;78:28–35. doi:10.1016/j.ijsu.2020.04.010
7. Vogelmeier C, Buhl R, Burghuber O, et al. Leitlinie zur Diagnostik und Therapie von Patienten mit chronisch obstruktiver Bronchitis und Lungenemphysem (COPD)*. *Pneumologie*. 2018;72:253–308. doi:10.1055/s-0043-125031
8. Buhl R, Criée C-P, Kardos P, et al. Dual bronchodilation vs triple therapy in the "real-life" COPD DACCORD study. *Int J Chronic Obstr Pulm Dis*. 2018;13:2557–2568. doi:10.2147/COPD.S169958
9. Buhl R, Wilke T, Picker N, et al. Real-world treatment of patients newly diagnosed with chronic obstructive pulmonary disease: a retrospective German claims data analysis. *Int J Chron Obstruct Pulmon Dis*. 2022;17:2355–2367. doi:10.2147/COPD.S375190
10. Beeh K-M, Rothnie KJ, Claussen J, et al. Characteristics of users and new initiators of single- and multiple-inhaler triple therapy for chronic obstructive pulmonary disease in Germany. *Int J Chronic Obstr Pulm Dis*. 2024;19:945–956. doi:10.2147/COPD.S431291
11. Cazzola M, Rogliani P, Calzetta L, Matera MG. Triple therapy versus single and dual long-acting bronchodilator therapy in COPD: a systematic review and meta-analysis. *Eur Respir J*. 2018;52:1801586. doi:10.1183/13993003.01586-2018
12. Zhang S, Wang J, Li X, Zhang H. Comparative effectiveness and safety of triple therapy and non-triple therapy interventions for COPD: an overview of systematic reviews. *Ther Adv Respir Dis*. 2024;18:17534666241259634. doi:10.1177/17534666241259634
13. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2016;CD002991.
14. Singh D, Agusti A, Martinez FJ, et al. Blood eosinophils and chronic obstructive pulmonary disease: a Global Initiative for Chronic Obstructive Lung Disease Science Committee 2022 Review. *Am J Respir Crit Care Med*. 2022;206:17–24. doi:10.1164/rccm.202201-0209PP
15. Tkacz J, Evans KA, Touchette DR, et al. PRIMUS – prompt initiation of maintenance therapy in the US: a real-world analysis of clinical and economic outcomes among patients initiating triple therapy following a COPD exacerbation. *Int J Chronic Obstr Pulm Dis*. 2022;17:329–342. doi:10.2147/COPD.S347735

16. Evans KA, Pollack M, Portillo E, et al. Prompt initiation of triple therapy following hospitalization for a chronic obstructive pulmonary disease exacerbation in the United States: an analysis of the PRIMUS study. *J Manag Care Spéc Pharm*. 2022;28. doi:10.18553/jmcp.2022.28.12.1366
17. Halpin DMG, Dransfield MT, Han MK, et al. The effect of exacerbation history on outcomes in the IMPACT trial. *Eur Respir J*. 2020;55:1901921. doi:10.1183/13993003.01921-2019
18. Hansel TT, Barnes PJ. New drugs for exacerbations of chronic obstructive pulmonary disease. *Lancet*. 2009;374:744–755. doi:10.1016/S0140-6736(09)61342-8
19. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax*. 2012;67:957. doi:10.1136/thoraxjnl-2011-201518
20. Nordon C, Simons SO, Marshall J, et al. The sustained increase of cardiovascular risk following COPD exacerbations: meta-analyses of the EXACOS-CV studies. *ERJ Open Res*. 2025;11:01091–02024. doi:10.1183/23120541.01091-2024
21. Wacker ME, Jörres RA, Schulz H, et al. Direct and indirect costs of COPD and its comorbidities: results from the German COSYCONET study. *Respir Med*. 2016;111:39–46. doi:10.1016/j.rmed.2015.12.001
22. Byng D, Lutter JI, Wacker ME, et al. Determinants of healthcare utilization and costs in COPD patients: first longitudinal results from the German COPD cohort COSYCONET. *Int J Chronic Obstr Pulm Dis*. 2019;14:1423–1439. doi:10.2147/COPD.S201899
23. Rabe KF, Bateman ED, O'Donnell D, et al. Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet*. 2005;366:563–571. doi:10.1016/S0140-6736(05)67100-0
24. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with blood eosinophil evidence of type 2 inflammation. *N Engl J Med*. 2024;390:2274–2283. doi:10.1056/NEJMoa2401304
25. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. *N Engl J Med*. 2023;389:205–214. doi:10.1056/NEJMoa2303951
26. Ständer S, Ketz M, Kossack N, et al. Epidemiology of Prurigo Nodularis compared with Psoriasis in Germany: a claims database analysis. *Acta Derm -Venereol*. 2020;100:5903. doi:10.2340/00015555-3655
27. Deutsches Institut für Medizinische Dokumentation und Information (DIMDI). ICD-10-GM Version 2019, Systematisches Verzeichnis, Internationale Statistische Klassifikation Der Krankheiten Und Verwandter Gesundheitsprobleme, 10. Revision, Stand: 05; 2018. Available from: https://www.bfarm.de/SharedDocs/Downloads/DE/Kodiersysteme/klassifikationen/icd-10-gm/vorgaenger-bis-2020/icd10gm2019_zip.html?nn=841246&cms_dlConfirm=true&cms_calledFromDoc=841246. Accessed November 17, 2025.
28. GKV-Arzneimittelindex im Wissenschaftlichen Institut der AOK (WIdO). Anatomisch-Therapeutisch-Chemische Klassifikation Mit Tagesdosen. Amtliche Fassung Des ATC-Index Mit DDD-Angaben Für Deutschland Im Jahre 2019; 2019. Available from: https://www.wido.de/publikationen-produkte/analytik/arzneimittel-klassifikation/amtliche-atc-klassifikation/. Accessed November 17, 2025.
29. Baumgartner PC, Haynes RB, Hersberger KE, Arnet I. A systematic review of medication adherence thresholds dependent of clinical outcomes. *Front Pharmacol*. 2018;9:1290. doi:10.3389/fphar.2018.01290
30. Bogart M, Stanford RH, Laliberté F, et al. Medication adherence and persistence in chronic obstructive pulmonary disease patients receiving triple therapy in a USA commercially insured population. *Int J Chronic Obstr Pulm Dis*. 2019;14:343–352. doi:10.2147/COPD.S184653
31. Yu AP, Guérin A, Ponce de Leon D, et al. Therapy persistence and adherence in patients with chronic obstructive pulmonary disease: multiple versus single long-acting maintenance inhalers. *J Méd Econ*. 2011;14:486–496. doi:10.3111/13696998.2011.594123
32. Deslee G, Fabry-Vendrand C, Poccardi N, et al. Use and persistence of single and multiple inhaler triple therapy prescribed for patients with COPD in France: a retrospective study on THIN database (OPTI study). *BMJ Open Respir Res*. 2023;10:e001585. doi:10.1136/bmjresp-2022-001585
33. Bundesministerium für Gesundheit. KM-6-Statistik 2022. Available from: https://www.bundesgesundheitsministerium.de/themen/krankenversicherung/zahlen-und-fakten-zur-krankenversicherung/kennzahlen-daten-bekanntmachungen.html. Accessed November 17, 2025.
34. Vogelmeier CF, Beeh K-M, Schultze M, et al. Evaluation of adherence and persistence to triple therapy in patients with COPD: a German Claims Data Study. *Int J Chronic Obstr Pulm Dis*. 2024;19:1835–1848. doi:10.2147/COPD.S460903
35. Halpin DMG, Rothnie KJ, Banks V, et al. Comparative adherence and persistence of single- and multiple-inhaler triple therapies among patients with chronic obstructive pulmonary disease in an English Real-World Primary Care setting. *Int J Chronic Obstr Pulm Dis*. 2022;17:2417–2429. doi:10.2147/COPD.S370540
36. Alcázar-Navarrete B, Garcia-Rio F, Sanchez G, et al. Burden of disease among exacerbating patients with COPD treated with Triple Therapy in Spain. *Int J Chronic Obstr Pulm Dis*. 2021;16:2149–2161. doi:10.2147/COPD.S310319
37. Dalon F, Roche N, Belhassen M, et al. Dual versus triple therapy in patients hospitalized for COPD in France: a claims data study. *Int J Chronic Obstr Pulm Dis*. 2019;14:1839–1854. doi:10.2147/COPD.S214061
38. Benson VS, Pascoe KC, Siddall J, Small M, Müllerová H. Exacerbation frequency and eosinophil counts among patients with COPD currently prescribed triple therapy. *Int J Chronic Obstr Pulm Dis*. 2019;14:2711–2723. doi:10.2147/COPD.S217503
39. Greulich T, Weist BJD, Koczulla AR, et al. Prevalence of comorbidities in COPD patients by disease severity in a German population. *Respir Med*. 2017;132:132–138. doi:10.1016/j.rmed.2017.10.007
40. Quint JK, O'Leary C, Venerus A, et al. Prescribing pathways to triple therapy: a multi-country, retrospective observational study of adult patients with chronic obstructive pulmonary disease. *Pulm Ther*. 2020;6:333–350. doi:10.1007/s41030-020-00132-7
41. Negewo NA, Gibson PG, McDonald VM. COPD and its comorbidities: impact, measurement and mechanisms. *Respirology*. 2015;20:1160–1171. doi:10.1111/resp.12642
42. Kirsch F, Schramm A, Schwarzkopf L, et al. Direct and indirect costs of COPD progression and its comorbidities in a structured disease management program: results from the LQ-DMP study. *Respir Res*. 2019;20:215. doi:10.1186/s12931-019-1179-7
43. Fabbri LM, Celli BR, Agustí A, et al. COPD and multimorbidity: recognising and addressing a syndemic occurrence. *Lancet Respir Med*. 2023;11:1020–1034. doi:10.1016/S2213-2600(23)00261-8
44. Achelrod D, Welte T, Schreyögg J, Stargardt T. Costs and outcomes of the German disease management programme (DMP) for chronic obstructive pulmonary disease (COPD)—A large population-based cohort study. *Heal Polic*. 2016;120:1029–1039. doi:10.1016/j.healthpol.2016.08.002
45. Nowak D, Dietrich E, Oberender P, et al. Krankheitskosten von COPD in Deutschland. *Pneumologie*. 2004;58:837–844. doi:10.1055/s-2004-830143
46. Menn P, Heinrich J, Huber RM, et al. Direct medical costs of COPD – an excess cost approach based on two population-based studies. *Respir Med*. 2012;106:540–548. doi:10.1016/j.rmed.2011.10.013

47. Salvesen ØNU, Davidsen JR, Pottegård A, Henriksen DP. Roflumilast usage from 2010 to 2016: a Danish Nationwide Drug Utilization Study. *Basic Clin Pharmacol Toxicol*. 2018;123:314–319. doi:10.1111/bcpt.13014
48. Yu T, Fain K, Boyd CM, et al. Benefits and harms of roflumilast in moderate to severe COPD. *Thorax*. 2014;69:616. doi:10.1136/thoraxjnl-2013-204155
49. Cilli A, Bal H, Gunen H. Efficacy and safety profile of roflumilast in a real-world experience. *J Thorac Dis*. 2019;11:1100–1105. doi:10.21037/jtd.2019.04.49
50. Holm CP, Holm J, Nørgaard A, Godtfredsen N. COPD, stage and treatment in a large outpatient clinic. *Eur Clin Respir J*. 2017;4:1267470. doi:10.1080/20018525.2017.1267470
51. Lam J, Tonnu-Mihara I, Kenyon NJ, Kuhn BT. Comparative effectiveness of roflumilast and azithromycin for the treatment of chronic obstructive pulmonary disease. *Chronic Obstr Pulm Dis*. 2021;8:450–463.
52. Li H, Liu D-H, Chen -L-L, et al. Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. *Antimicrob Agents Chemother*. 2013;58:511–517. doi:10.1128/AAC.02067-13
53. Ständer S, Kasperkiewicz M, Thaçi D, et al. Prevalence and presumptive triggers of localized bullous pemphigoid. *J Dermatol*. 2021;48:1257–1261. doi:10.1111/1346-8138.15912
54. Langner I, Riedel O, Czwikla J, et al. Linkage of routine data to other data sources in Germany: a practical example illustrating challenges and solutions. *Das Gesundheitswesen*. 2019;82:S117–S121. doi:10.1055/a-0999-5509