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Roflumilast Usage from 2010 to 2016: A Danish Nationwide Drug Utilization Study

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Running head: Roflumilast utilization

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ØNUS, JRD and DPH, declare no conflicts of interest

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Abstract: Roflumilast, a phosphodiesterase-4-inhibitor, is marketed as add-on treatment to inhaled bronchodilators and corticosteroids in COPD patients with frequent exacerbations. Although marketed since 2010, usage pattern of roflumilast for an entire nation has not previously been explored. This study aimed to estimate the total utilization of roflumilast in Denmark during 2010 to 2016, using the Danish nationwide health registers.

We identified 1,573 individuals (47% males) who used roflumilast during the study period, of whom 705 (45%) redeemed only one prescription. Of all patients initiating roflumilast, 67% discontinued treatment within the first year. The rate of treatment initiation decreased 73% from 2011 (7.5/100,000 person-years) to 2016 (2.0/100,000 person-years) concurrent with a stable prevalence of 3.0-4.0/100,000 persons throughout the study period. The median duration of roflumilast use was 76 days. Patients with severe co-morbidity tended to exhibit a lower degree of early discontinuation (Charlson Co-morbidity Index 3+: Odds Ratio [OR]: 0.59; 95% confidence interval [CI] 0.33-1.04), as well as patients with a COPD-related admission within a year prior to roflumilast initiation (OR 0.62; 95% CI 0.49-0.80).

The decreasing incidence and high level of early roflumilast discontinuation could be due to lack of benefit, a low awareness of roflumilast’s indication among physicians, secondary to a challenging prescribing procedure, or to adverse effects.

Chronic obstructive pulmonary disease (COPD) is estimated to affect more than 430,000 individuals in Denmark, and the prevalence of moderate and severe to very severe COPD has been estimated to 9% and 2%, respectively. The disease is estimated to be the third leading cause of death worldwide in 2020 with more than 3 million deaths per year (2). Roflumilast is a phosphodiesterase-4-inhibitor (PDE4), which was introduced to the European market in July 2010 (3). The drug was approved as a prophylactic treatment for COPD patients with frequent exacerbations (4) and has been included in the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines (5). In such, COPD patients must experience chronic cough and sputum production, as well as having a history of exacerbations before roflumilast is indicated (4). The European Medicines Agency (EMA)
summary has approved roflumilast as an “add-on” treatment to bronchodilators, and according to the GOLD guidelines, there is also an effect when treating patients who are not “controlled on fixed-dose long-acting beta-2-agonists (LABA)/inhaled corticosteroid (ICS) combinations” (5).

Studies from 2009 concluded that roflumilast reduced the number of exacerbations in patients with more than two exacerbations a year by 17% (6), consistent with observations in the REACT study from 2015 in which roflumilast reduced the number of severe exacerbations by 24% among well-selected COPD patients (7). Only sparse data on roflumilast utilization are available from Northern European COPD populations. However, a new Danish clinical cross-sectional study of 547 patients found that only one in four (22.6%) COPD patients eligible for treatment were prescribed roflumilast (8). A recent Cochrane review found roflumilast to be beneficial over placebo in improving lung function and reducing the likelihood of exacerbations. However, only a limited impact on quality of life and symptoms was found (9). The numbers needed to treat for a beneficial outcome was estimated to 20, whereas the numbers needed to harm was estimated to 15.

Due to the questionable benefit and the increased risk of adverse effects, The Danish National Board of Health recommended that initiation with roflumilast is reserved for specialist use in respiratory medicine only.

As clinical trial populations often are highly selected, it is important to assess “real-world” patterns of usage. This has not previously been done for roflumilast.

Our study aimed to assess the utilization pattern of roflumilast in Denmark since its market release in 2010 in relation to incidence, prevalence and duration of roflumilast usage.
Methods

We performed an observational register-based study, aiming to assess roflumilast usage in Denmark from 1 January 2010 to 31 December 2016 with use of information from nationwide Danish registers.

Data sources

Due to the unique civil registration number and the Danish National Health Service providing tax-supported health care for the entire Danish population, it is possible to conduct true population-based register-linkage studies covering the entire population (10).

The following registers were used:

The National Prescription Registry (NPR) contains data on all redeemed drugs prescribed to all Danish citizens (11) from 1995 to present and includes information regarding the type of drug, date of dispensing and the number of defined daily doses redeemed. Drugs are categorized according to the Anatomical Therapeutic Chemical (ATC) code, developed by the World Health Organization (12). The quantity in each prescription is expressed by the defined daily dose (DDD) measure (12). Data about dosing information and indication for prescription are not available; nor with information regarding drugs dispensed at hospital level. However, only 2.4% of the total amount of roflumilast is sold to hospitals (13).

The Danish National Patient Registry contains data on all contacts to Danish hospitals since 1977 (14). Discharge diagnoses are coded according to International Classification of Diseases, tenth revision (ICD-10) since 1994.

The Danish Civil Person Register contains data on date of birth, death and migration to and from Denmark (10).

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Study drugs

Roflumilast (ATC R03DX07) is the only PDE4 inhibitor marketed in Denmark. The DDD for roflumilast is 500 µg daily according to the WHO Collaborating Centre for Drug Statistics Methodology ATC/DDD index (12). Each individual was defined as a ‘current user’ on a given day if he/she had redeemed a prescription for roflumilast with sufficient doses to cover that specific day. The duration of each roflumilast prescription was defined as the number of tablets dispensed (i.e., assuming a consumption of one tablet per day), while adding 25% to the duration to account for irregular prescription refills and/or primary non-compliance (i.e. a patient redeeming 30 DDDs was calculated as being treated for 37.5 days). The addition of 25% to the duration is based on an assumption of 80% compliance, which is often seen in traditional compliance research (15,16).

Ethics

According to Danish law, studies based solely on register data do not require approval from an ethics review board (17). The study was approved by the Danish Data Protection Agency (Application no. 2008-58-0035).

Analysis

Baseline characteristics of individuals initiating roflumilast in the period of 2010 to 2017 were presented as absolute numbers and percentages for categorical values and medians with interquartile ranges (IQR) for continuous values. For our analyses of redeemed medication excluding roflumilast, we assumed that if a prescription was redeemed within the last 12 months before initiating roflumilast, the patient was a user of the given medication.

For each calendar year (2010 to 2016), we calculated the total amount of DDD of roflumilast redeemed per individual. Comparisons of continuous variables were performed using the Wilcoxon rank-sum test.
Annual prevalence proportions, i.e., the number of current users per 100,000 in the population from 2010 to 2017 were calculated using the entire population living in Denmark as of 1 January each relevant year as the denominator.

The duration of treatment was described using the proportion of patients covered (PPC) method (18). All individuals were followed from their first prescription corresponding to incident users. The proportion of patients being alive and still using roflumilast was estimated over time. If a patient stopped the treatment with a following re-initiation, the patient was again considered a current user when redeeming a new prescription. The overall PPC was calculated as well as stratified by sex and co-morbidity.

We calculated the median duration of treatment stratified by sex and year of roflumilast initiation.

We used logistic regression analysis to assess the association of demographic risk factors and early roflumilast discontinuation in two models: a crude model and an adjusted model where we adjusted for the pre-defined clinically relevant confounders sex, age and co-morbidity. Roflumilast discontinuation was defined as users redeeming only one prescription for roflumilast with at least one-year observation period.

To define the co-morbidity burden of the patients, we used the Charlson Co-morbidity Index (CCI) (19). In brief, a selected number of diseases are given a weighted number, and a higher CCI score is an indicator of severe co-morbidity due to a high number of co-morbidities.

Stata version 14.1 (StataCorp, College Station, TX, USA) was used for all data analyses.
Results

Demographic characteristics
In total, 1,573 individuals (47% males) redeemed at least one prescription for roflumilast during the study period. The median age of the females initiating roflumilast were 69 years (interquartile range (IQR) 63-76) and for males 71 (IQR 65-77). The majority of patients (n=730) initiating roflumilast had a CCI of 1 (46%), whereas 25% (n=391) were defined as having severe co-morbidity (CCI 3+).

During the study period, 10,500 prescriptions for roflumilast were filled, totalling 463,740 DDDs (Fig. 1).

We found that 77.4 % (n=1,218) of the patients received oral corticosteroids 12 months days preceding roflumilast initiation, while 53.8% had prescriptions of LABA, long-acting muscarinic antagonists (LAMA) and ICS (Table 1).

During a total follow-up of 4710 years, 705 patients (45%) redeemed one prescription for roflumilast, while 22% and 38% redeemed 2-4 and 5+ prescriptions, respectively. Patients redeemed a median of 60 DDDs (IQR 30-360), regardless whether patients were male or female (p=0.68).

The point prevalence was generally stable, increasing slightly from January 2011 (3.1 per 100,000 persons) to January 2014 (4.3 per 100,000 persons) and decreasing slightly thereafter. In December 2016, the point prevalence was 3.8 per 100,000 persons (Fig. 2).

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The incidence rate was at its highest in 2011 (7.5 per 100,000 person-years) for both males (6.6 per 100,000 person-years) and females (8.4 per 100,000 person-years) and decreased thereafter by 73% to 2.0 per 100,000 person-years. The decrease in incidence rates from 2011 to 2016 was more pronounced among females (decrease of 75% from 8.4 to 2.1 per 100,000 person-years) compared to males (decrease of 71% from 6.6 to 1.9 per 100,000 person-years) (Fig. 3).

**Duration of use**

Overall, 30% were still users one year after initiating roflumilast (Fig. 4). Patients with low co-morbidity burden showed a comparable proportion of patients still in roflumilast treatment compared with patients with high co-morbidity burden (PPC 365 days: CCI 0: 22% versus CCI 3+: 29%). We found no difference in the sex-specific duration of use.

Early discontinuation was associated with age 65+ years (adjusted OR 1.71 [95%CI 1.33-2.21]). A COPD-related admission up to one year prior to roflumilast initiation was associated with a continuous treatment with roflumilast (adjusted OR 0.62 [95%CI 0.49-0.80]) (Table 2).

During the years 2011 to 2015, the median treatment duration was 109 days (IQR 38-468). An increase was observed each year from 2011 to 2015, from 66 days (IQR 38-423) in 2011 to 114 (IQR 38-438) in 2015 (p= 0.004).

**Discussion**

This is the first study to report the usage of roflumilast in a nationwide setting. We found a 73% decrease of new users initiating roflumilast from 2011 to 2016, and nearly half of all patients initiating roflumilast only redeemed one prescription. Further, only 28% were still in treatment after 12 months. However, the number of users in treatment was consistent throughout the study period, and consistent with regard to different patient characteristics.

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Our study showed that only 55% of the patients redeemed more than one prescription, and that about 28% were users for 12 months or more. The low compliance has previously been demonstrated in similar settings, as a real-life study of 55 patients in Spain from 2014 found that 50.9% of roflumilast-treated patients remained on the treatment for more than one year (20).

There are several possible explanations for the relatively low compliance. Firstly, clinical trials describe a number of adverse effects that are associated with poor compliance, especially affecting the gastrointestinal system (nausea, diarrhoea and weight loss) (21).

As the adverse effects manifest before the benefits of the anti-inflammatory action, the likelihood of high compliance is decreased. This could be a plausible explanation of why a Danish study from 2017 concluded that only 22.6% of patients who met the criteria for roflumilast treatment were actually prescribed the drug (8). Secondly, the drug is relatively expensive (2.28 Euro per DDD) (22), and thirdly, the Danish subsidy system requires the patients to have at least two exacerbations per year and to receive optimal treatment in order to be reimbursed (23). Furthermore, the subsidy lasts for 12 months, and the effect of the treatment must be described in detail in order to obtain a prolonged subsidy. The time-consuming process of writing prescriptions with subsidies combined with the high price and adverse effects may have an influence on the treatment persistence.

We assessed the association between demographic characteristics and early discontinuation of roflumilast and found that patients with severe comorbidity, a COPD-related admission, and patients prescribed oral corticosteroids within one year prior to roflumilast initiation were more likely to redeem more than one prescription for roflumilast.

Two separate meta-analyses (4,24) found that roflumilast is effective in reducing the number of exacerbations, and a full incremental analysis from the UK in 2012 concluded that roflumilast treatment is both clinical- and cost-effective in the treatment of patients “continuing to exacerbate despite existing bronchodilator therapy” (25). Identifying means to specifically select well-responders to the treatment may consequently reduce the number of hospital admissions and lower the costs associated with COPD exacerbations.

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The Danish Ministry of Health requires treatment with ICS as a prerequisite for roflumilast subsidy (23). In 2011, during the study period, a revised version of the GOLD guidelines was published, which recommended roflumilast treatment to patients with moderate and severe exacerbations treated with ICS (group D). However, we have not been able to derive the number of patients meeting these recommended indications for roflumilast prescription, as patients in GOLD group C can be treated with roflumilast as an “alternative choice to standard first-line therapy with ICS and LABA or LAMA” (26). Knowledge of the GOLD COPD stage of all patients treated with roflumilast could help further analyse the utilization pattern and better identify patients who may benefit from roflumilast treatment.

**Strengths**

This study included all roflumilast redeemed to the Danish population outside hospitals during seven years regardless of socioeconomic or insurance status. The completeness of Danish Register of Medicinal Products Statistics allowed the analyses to be conducted without risk of recall bias or dropout (11).

**Limitations**

The study's main limitation was the lack of information regarding the exact duration of use. Therefore, we had to use the number of redeemed DDDs adding 25% to the duration of therapy is based on a definition of 80% compliance. Patients redeeming only one package with 90 DDDs are likely to consume a lower percentage of the prescribed doses, compared with patients redeeming only one package with 30 DDDs. As 48.1% of the total DDDs sold came in packages with 90 DDDs, our calculations of treatment duration could be over-estimated.

We only had information of outpatient pharmacy prescriptions, but only a negligible 2.4% of the total amount of roflumilast is sold to the hospitals (13). Further, the relatively short period of study, the recent introduction of the drug and the limited number of patients receiving prescriptions makes it difficult to analyse and predict any trend.
The COPD severity was not possible to assess, because we lacked information regarding the extent of airway obstruction (FEV1 and FVC) as well as clinical information (MRC). Instead, we reported the different combinations of LABA, LAMA and ICS, as well as COPD admissions up to roflumilast initiation.

In conclusion almost half of the patients who initiated roflumilast in the period of 2010 to 2017 did not redeem a second prescription. The incidence rates decreased by 73% from 2011 to 2016 while a stable point prevalence was observed. The decreasing incidence and high level of early roflumilast discontinuation could be due to lack of benefit, a low awareness among physicians, secondary to a challenging prescribing procedure or adverse effects.

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Figures

Figure 1: Total consumption of roflumilast, 2010-2016

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Figure 2: Point prevalence of roflumilast usage, with data sampled each day from 2010 to 2017.
Figure 3: The overall and sex specific incidence rate of redeemed roflumilast per 100,000 from 2010 to 2016
Figure 4: Proportion of patients covered, showing the distribution among patients scoring different on the Charlson Co-morbidity Index.
## Tables

**Table 1: Characteristics of patients initiating roflumilast treatment in the period of 2010 to 2016.**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Age 18 to 64 years</th>
<th>Age 65+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>(n=1,573)</td>
<td>(n=433)</td>
<td>(n=1,140)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>835 (53.1%)</td>
<td>250 (57.7%)</td>
<td>585 (51.3%)</td>
</tr>
<tr>
<td>Male</td>
<td>738 (46.9%)</td>
<td>183 (42.3%)</td>
<td>555 (48.7%)</td>
</tr>
<tr>
<td><strong>Age groups</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-64 years</td>
<td>433 (27.5%)</td>
<td>433 (100.0%)</td>
<td>n&lt;10</td>
</tr>
<tr>
<td>65+ years</td>
<td>1,140 (72.5%)</td>
<td>n&lt;10</td>
<td>1,140 (100.0%)</td>
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<tr>
<td><strong>Charlson Co-morbidity Index (CCI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>69 (4.4%)</td>
<td>23 (5.3%)</td>
<td>46 (4.0%)</td>
</tr>
<tr>
<td>1</td>
<td>730 (46.4%)</td>
<td>236 (54.5%)</td>
<td>494 (43.3%)</td>
</tr>
<tr>
<td>2</td>
<td>383 (24.3%)</td>
<td>86 (19.9%)</td>
<td>297 (26.1%)</td>
</tr>
<tr>
<td>3+</td>
<td>391 (24.9%)</td>
<td>88 (20.3%)</td>
<td>303 (26.6%)</td>
</tr>
<tr>
<td><strong>Admissions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma-related</td>
<td>10 (0.6%)</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
</tr>
<tr>
<td>COPD-related</td>
<td>582 (37.0%)</td>
<td>159 (36.7%)</td>
<td>423 (37.1%)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Medicine based on active ingredient</th>
<th>Only ICS</th>
<th>Only LABA+ICS</th>
<th>Only LABA</th>
<th>Only LAMA</th>
<th>Only LAMA+ICS</th>
<th>Only LABA+LAMA</th>
<th>Only LABA+LAMA+ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS (either ICS or LABA+ICS)</td>
<td>16 (1.0%)</td>
<td>152 (9.7%)</td>
<td>n&lt;10</td>
<td>19 (1.2%)</td>
<td>11 (0.7%)</td>
<td>26 (1.7%)</td>
<td>1,315 (83.6%)</td>
</tr>
<tr>
<td>LABA (either LABA or LABA+ICS or LABA+LAMA)</td>
<td>152 (9.7%)</td>
<td>56 (12.9%)</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>56 (12.9%)</td>
<td>96 (8.4%)</td>
</tr>
<tr>
<td>LAMA (either LAMA or LAMA+LABA)</td>
<td>19 (1.2%)</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>12 (1.1%)</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
</tr>
<tr>
<td>LABA+ICS</td>
<td>11 (0.7%)</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>341 (78.8%)</td>
</tr>
<tr>
<td>LABA+LAMA</td>
<td>26 (1.7%)</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>974 (85.4%)</td>
</tr>
<tr>
<td>LABA+LAMA+ICS</td>
<td>1,315 (83.6%)</td>
<td>341 (78.8%)</td>
<td>974 (85.4%)</td>
<td>1,089 (95.5%)</td>
<td>1,092 (95.8%)</td>
<td>1,014 (88.9%)</td>
<td></td>
</tr>
</tbody>
</table>

*within one year prior to roflumilast initiation*

LABA Long Acting Beta Agonists; LAMA Long Acting Muscarinic Antagonists; ICS Inhaled Corticosteroids
Table 2: Crude and adjusted odds ratios for early discontinuation of roflumilast among users with at least one-year observation period (n=1264)

<table>
<thead>
<tr>
<th></th>
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<th>More than one prescription redeemed</th>
<th>Crude OR *</th>
<th>Adjusted OR *</th>
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<tr>
<td>Total</td>
<td>(n=537)</td>
<td>(n=727)</td>
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<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>286 (53.3%)</td>
<td>386 (53.1%)</td>
<td>REF</td>
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<tr>
<td>Male</td>
<td>251 (46.7%)</td>
<td>341 (46.9%)</td>
<td>0.99 (0.79-1.24)</td>
<td>0.97 (0.78-1.22)</td>
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<tr>
<td>Age groups</td>
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<tr>
<td>18-64 years</td>
<td>125 (23.3%)</td>
<td>246 (33.8%)</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>65+ years</td>
<td>412 (76.7%)</td>
<td>481 (66.2%)</td>
<td>1.69 (1.31-1.21)</td>
<td>1.71 (1.33-2.21)</td>
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<td>Charlson Co-morbidity Index (CCI)</td>
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<tr>
<td>0</td>
<td>31 (5.8%)</td>
<td>28 (3.9%)</td>
<td>REF</td>
<td>REF</td>
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<tr>
<td>1</td>
<td>261 (48.6%)</td>
<td>355 (48.8%)</td>
<td>0.66 (0.39-1.13)</td>
<td>0.65 (0.38-1.12)</td>
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<td>2</td>
<td>128 (23.8%)</td>
<td>175 (24.1%)</td>
<td>0.66 (0.38-1.16)</td>
<td>0.62 (0.35-1.09)</td>
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<tr>
<td>3+</td>
<td>117 (21.8%)</td>
<td>169 (23.2%)</td>
<td>0.66 (0.38-1.16)</td>
<td>0.62 (0.35-1.09)</td>
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<tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Asthma-related</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
</tr>
<tr>
<td>COPD-related</td>
<td>151 (28.1%)</td>
<td>282 (38.8%)</td>
<td>0.62 (0.49-0.78)</td>
<td>0.62 (0.49-0.80)</td>
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<tr>
<td>Medicine$</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only ICS</td>
<td>10 (1.9%)</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
</tr>
<tr>
<td>Only LABA+ICS</td>
<td>56 (10.4%)</td>
<td>68 (9.4%)</td>
<td>1.13 (0.78-1.64)</td>
<td>1.21 (0.83-1.77)</td>
</tr>
<tr>
<td>Only LABA</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
</tr>
<tr>
<td>Only LAMA</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
</tr>
<tr>
<td>Only LAMA+ICS</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
</tr>
<tr>
<td>Only LABA+LAMA</td>
<td>13 (2.4%)</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
<td>n&lt;10</td>
</tr>
<tr>
<td>Only LABA+LAMA+ICS</td>
<td>431 (80.3%)</td>
<td>624 (85.8%)</td>
<td>0.67 (0.50-0.90)</td>
<td>0.63 (0.47-0.86)</td>
</tr>
<tr>
<td>Medicine based on active ingredient$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICS (either ICS or LABA+ICS)</td>
<td>505 (94.0%)</td>
<td>698 (96.0%)</td>
<td>0.66 (0.39-1.10)</td>
<td>0.63 (0.38-1.07)</td>
</tr>
<tr>
<td>LABA (either LABA or LABA+ICS or LABA+LAMA)</td>
<td>501 (93.3%)</td>
<td>703 (96.7%)</td>
<td>0.48 (0.28-0.81)</td>
<td>0.46 (0.27-0.79)</td>
</tr>
<tr>
<td>LAMA (either LAMA or LAMA+LABA)</td>
<td>459 (85.5%)</td>
<td>644 (88.6%)</td>
<td>0.76 (0.54-1.06)</td>
<td>0.71 (0.51-0.99)</td>
</tr>
</tbody>
</table>

* adjusted for age, sex and co-morbidity

OR odds ratio; CI confidence ratio; LABA Long Acting Beta Agonists; LAMA Long Acting Muscarinic Antagonists; ICS Inhaled Corticosteroids

$ Within one year prior to roflumilast initiation