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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Discontinuation of therapy among COPD patients who experience an improvement in exacerbation status

Mette Reilev[1,2] · Kasper Bruun Kristensen[1] · Jens Søndergaard[2] · Daniel Pilsgaard Henriksen[3] · Wade Thompson[2] · Anton Pottegård[1]

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Abstract

Purpose A subset of patients with chronic obstructive pulmonary disease (COPD) experience a decrease in exacerbation frequency, leading to a diminished need for treatment with inhaled corticosteroids (ICS). We investigated prescribing and discontinuation patterns of long-acting bronchodilators and ICS in COPD patients according to exacerbation frequency.

Methods Using the nationwide Danish health registries, we conducted a drug utilization study among patients who had at least two exacerbations or one hospitalization due to an exacerbation during 2011–2012. This study population was stratified according to consistency of exacerbation occurrence after 12, 24, 36, and 48 months of follow-up and the groups were described according to use of ICS, long-acting β_2-agonists (LABA), and long-acting anticholinergics (LAMA), and combinations thereof.

Results We identified 29,010 COPD exacerbators during 2011–2012. Upon inclusion, 70% received ICS-containing regimens, in combination with LABA (23%) or both LABA and LAMA (41%). The proportion of prevalent users of ICS-containing regimens decreased to 56% during follow-up among exacerbation-free individuals, while it increased to 86% in individuals who experienced at least one exacerbation annually. Persistence to ICS-containing regimens was 58% after 4 years in individuals without exacerbations compared to 74% among those with annual exacerbations. Similar patterns were observed for triple therapy which was the most extensively used drug combination regardless of consistency of exacerbation occurrence.

Conclusions The extensive use of ICS and the relatively high persistence to ICS-containing regimens in individuals who had a decrease in exacerbation occurrence highlight a need for the development and implementation of de-escalation strategies in clinical practice.

Keywords Utilization patterns · COPD · Long-acting bronchodilators · Inhaled corticosteroids · Pharmacoepidemiology

Introduction

Traditionally, chronic obstructive pulmonary disease (COPD) has been considered a progressive disease with an overall worsening of daily symptoms and lung function impairment over time [1]. However, the vast majority of COPD patients have a varying exacerbation occurrence over time and for some individuals the proneness to exacerbate might even be mitigated [2–4].

Long-acting bronchodilators and inhaled corticosteroids (ICS) are the cornerstones of COPD treatment, aiming to reduce respiratory symptoms and prevent acute exacerbations [5]. The effect sizes of therapy are generally considered to be modest [6–9]. As an example, a Cochrane review found that when adding ICS to use of long-acting β_2-agonists (LABA), the annual rate of exacerbations dropped only slightly from 1.21 to 1.05 (RR 87, CI 0.80–0.94) while the reduction in severe exacerbations was insignificant [10]. Though withdrawal of ICS even in patients with severe COPD appears feasible [11, 12], physicians seem to have an inclination to add more drugs and a reluctance toward discontinuing therapy [13]. This increases both financial costs related to the

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✉ Mette Reilev
mreilev@health.sdu.dk

[1] Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense C, Denmark

[2] Research Unit of General Practice, Department of Public Health, University of Southern Denmark, JB Winsløwsvej 19, 2, 5000 Odense C, Denmark

[3] Department of Clinical Biochemistry & Pharmacology, Odense University Hospital, Odense C, Denmark

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treatment of COPD and the risk of adverse effects, with ICS therapy having been linked to an increased risk of pneumonia and osteoporotic fractures [14, 15], and long-acting bronchodilators to an increased risk of cardiac events [16, 17].

Acknowledging that patients with improved symptoms over time may be at risk of inappropriate overuse of inhaled therapy, GOLD guidelines recently introduced de-escalation strategies, including withdrawal of ICS [5]. However, it is unknown to what extent de-escalation and discontinuation of therapy are already occurring in clinical practice in individuals with diminished needs. We therefore aimed to describe drug utilization patterns according to consistency of COPD exacerbation frequency over time with emphasis on investigating prescription and discontinuation patterns of long-acting bronchodilators and ICS in COPD patients experiencing a decrease in exacerbation frequency.

Methods

Using Danish nationwide healthcare registry data (outlined in Appendix S1), we evaluated trends in the use of long-acting bronchodilators and ICS in Danish COPD patients with different trajectories of exacerbation status during a 4-year follow-up period (2012–2016).

Study population

We constructed a closed cohort comprised of all users of medication targeting obstructive pulmonary disease (ATC: R03) who were 55 years or older and had either (i) two or more COPD exacerbations within a period of 12 months from January 1, 2011, to December 31, 2012, or (ii) at least one exacerbation requiring hospitalization within the same period. These criteria were introduced to reduce the risk of misclassifying asthma patients as having COPD. The date of the second exacerbation or the date of the first hospitalization due to an exacerbation was considered the index date. Individuals were followed for 4 years from the index date or until the date of death or emigration (Fig. 1). The cohort inclusion period of 2011–2012 was selected to ensure that the GOLD 2011 guideline had been implemented in a Danish setting, thus ensuring uniform treatment recommendations during the study period.

Definition of exacerbations

Acute COPD exacerbations were defined as short-term use of oral corticosteroids (OCS) or hospitalizations due to COPD. This definition is considered valid and robust in epidemiological studies based on a positive predictive value of 92% for discharge diagnosis codes to predict COPD exacerbations, as well as a strong correlation between medically treated exacerbations and characteristics of COPD such as FEV_1, previous exacerbations, and breathlessness [18, 19]. The definition has previously been used in other registry-based studies [2, 20, 21]. A detailed description of the definition of exacerbations is provided in Appendix S2.

Categorization according to stability of exacerbation status

Each individual's exacerbation status, i.e., exacerbation rate in the previous 12 months, was established at the index date, and at four assessment dates after 12, 24, 36, and 48 months, respectively. At each of these assessment dates, the study population was categorized into three groups according to stability of exacerbation status since the index date:

- Individuals who had one or more exacerbations annually after 12, 24, 36, and 48 months, respectively.
- Individuals who (besides the index year) had zero exacerbations after 12, 24, 36, and 48 months, respectively.
- Individuals who experienced varying exacerbation rates, i.e., had either one or more exacerbations followed by year(s) with zero exacerbations or the opposite.

Study drugs

We subcategorized long-acting bronchodilators and ICS according to pharmacological drug classes into LABA, long-acting anticholinergics (LAMA), and ICS, and combinations thereof. ATC codes used to define drug use are provided in Appendix S3.

Analyses

Intending to assess utilization patterns over time with respect to consistency of exacerbation status, we investigated the proportion of prevalent users, i.e., those who had filled at least one prescription for the corresponding drug within the previous 6 months of ICS, LABA, and LAMA, and combinations thereof, as well as any ICS-containing regimens at the index date and after 12, 24, 36, and 48 months. Further, we investigated the proportion of individuals persistent to therapy, i.e., those who used a specific drug regimen at baseline and continuously redeemed prescriptions of the same drug regimen every 6 months during follow-up. Of note, when individuals had initiated triple therapy, no further escalation of therapy would be possible and non-persistence to this regimen was considered equivalent to a de-escalation of therapy.

In supplementary analyses, we (i) stratified the cohort by sex and (ii) restricted the study population to severe exacerbators, i.e., patients with a hospital admission due to COPD at baseline. Further, acknowledging the uncertainty

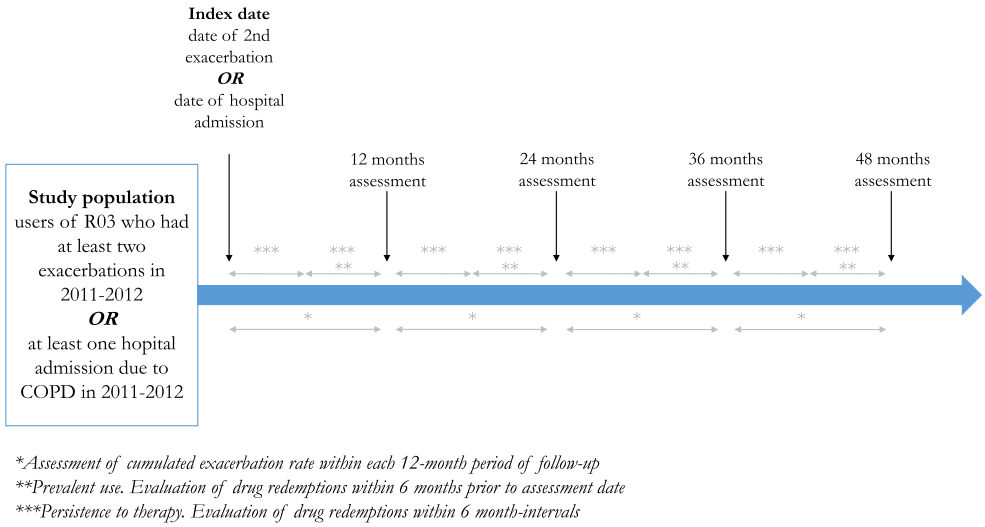

Fig. 1 An outline of the study illustrating time intervals for assessing exacerbation rates, prevalent use, and persistence to therapy in the main analysis

surrounding the duration of single prescriptions, we (iii) redid all analyses defining use as having filled at least one prescription within the preceding 4 months (instead of 6 months in the main analysis). Lastly, we performed post hoc analyses in which we expanded the definition of exacerbations to include (iv) the recommended first-line antibiotic for treatment of exacerbations, i.e., amoxicillin combined with clavulanic acid, and (v) all antibiotics used in the treatment of respiratory infections (see Appendix A).

Other

According to Danish law, studies based entirely on registry data do not require approval from an ethics review board [22].

Data availability statement Data for this study cannot be shared due to Danish legislation but can be applied for at the Danish Health Data Authority, provided relevant permissions are obtained. Analytical programs (Stata) can be obtained from the corresponding author upon request.

Results

We identified 29,010 COPD patients who experienced two or more exacerbations, or at least one hospitalization due to COPD, from 2011 to 2012. The majority were women (56%) and the median age was 74 years (interquartile range (IQR) 67–81). After 48 months of follow-up, 51% had died (Table 1). During follow-up, the proportion of the cohort who experienced at least one exacerbation decreased slightly from 49% within the first year of follow-up to 42% in the fourth year (Table 1). Of individuals eligible for the full 4 years of follow-up, 12% ($n = 1780$) experienced at least one exacerbation annually, whereas 25% ($n = 3614$) were consistently exacerbation free (Table 2).

Proportion of prevalent users

At the index date, 70% of treatment regimens included ICS, primarily in combination with LABA or LABA and LAMA (22.5% and 40.6% of the study population, respectively). ICS as a single therapy or in combination with LAMA was uncommon (4.7% and 2.0%, respectively) (Table 2). When stratifying the population according to consistency of exacerbation occurrence, the use of ICS-containing regimens remained extensive throughout the study period. It was, however, lower among those who experienced a consistent improvement in exacerbation occurrence over time (56% after 48 months), compared to individuals with varying exacerbation rates (77% after 48 months) or consistently at least one exacerbation annually (86% after 48 months) (Table 2). Similarly, the use of triple therapy decreased (29% after 48 months) among those who experienced a consistent improvement in exacerbation occurrence whereas it increased among consistent exacerbators (70% after 48 months) (Table 2).

Persistence to therapy

Persistence to any ICS therapy (i.e., the proportion of individuals who received any ICS-containing regimens at baseline and remained persistent to therapy until each of the assessment dates) was lower among individuals who experienced a consistent improvement in exacerbation rate over time (58% after 48 months) compared to those who experienced at least one exacerbation annually (74% after 48 months) (Table 3). The same pattern was observed for triple therapy. In all subgroups, persistence to triple therapy was higher than for any other drug combinations. Persistent use of LABA, LAMA, and dual therapy was less common among individuals who consistently experienced at least one exacerbation annually, most likely reflecting escalation of therapy (Table 3).

Table 1 Population characteristics at assessment dates, i.e., upon cohort inclusion (index date) and after 12, 24, 36, and 48 months of follow-up

	Index date ($n = 29,010$)	After 12 months ($n = 22,325$)	After 24 months ($n = 19,025$)	After 36 months ($n = 16,474$)	After 48 months ($n = 14,280$)
Age (IQR)	74 (67–81)	74 (67–81)	74 (67–81)	74 (67–81)	74 (68–81)
Male	12,689 (43.7%)	9454 (42.3%)	7936 (41.7%)	6754 (41.0%)	5760 (40.3%)
Cumulated mortality		6685 (23.0%)	9983 (34.4%)	12,532 (43.2%)	14,726 (50.8%)
Exacerbation status previous 12 months					
Zero exacerbations		11,345 (50.8%)	10,627 (55.9%)	9587 (58.2%)	8355 (58.5%)
One or more exacerbations	29,010 (100%)	10,980 (49.2%)	8398 (44.1%)	6887 (41.8%)	5925 (41.5%)
Severe exacerbators*	21,313 (73%)	6166 (27.6%)	4759 (25.0%)	3842 (23.3%)	3332 (23.3%)

*Defined as exacerbators who experienced at least one hospitalization due to COPD in the given 12-month period

Supplementary analysis

The observed patterns in prevalent use and persistence to therapy were similar when restricting to severe exacerbators at baseline (Tables S1 and S2) and when stratifying by sex (data not shown). Likewise, including antibiotics in the definition of exacerbations revealed similar results (data not shown). Introducing a more restrictive definition of prevalent and persistent use by requiring at least one prescription within a 4-month interval instead of a 6-month interval did not change the overall patterns in prevalent and persistent use of ICS-containing regimens and triple therapy. However, as expected because of the more restrictive definition, the proportions of both prevalent and persistent use were lower for all drug regimens (Tables S3 and S5).

Discussion

In this nationwide drug utilization study, we investigated prescribing and discontinuation patterns of long-acting bronchodilators and ICS in COPD patients from 2012 to 2016 according to exacerbation status. We found that the majority of exacerbators received ICS-containing regimens at baseline, primarily triple therapy. After 48 months of follow-up, use of ICS-containing regimens was still extensive among individuals who experienced a consistent reduction in exacerbation frequency during follow-up. Persistent use of ICS-containing regimens, particularly triple therapy, was generally high regardless of consistency of exacerbation occurrence, though discontinuation was slightly more common among individuals who experienced a consistent improvement in exacerbation rate over time.

The main strength of this study is the nationwide approach. Since the Danish health registries cover the entire Danish population, they provide a unique opportunity to investigate nationwide drug use patterns without the risk of selection bias. Further, individual-level identification of all users of long-acting bronchodilators and ICS is possible in the registries. Since these drugs are not available over the counter, the recording of prescriptions for home use is complete [23]. Finally, bias from primary non-adherence is eliminated, since our data represent medicines that have actually been purchased at the pharmacy [24].

An important limitation of this study is the absence of information about the underlying indication for treatment. This entails a risk of misclassifying exacerbations in case of use of short-term OCS for other indications than exacerbations. However, short-term OCS is rarely used for other indication than COPD exacerbations and defining exacerbations by prescriptions of short-term OCS is considered a valid and robust approach in epidemiological studies [18]. Similarly, the positive predictive value of hospital discharge diagnoses used to define exacerbations is high [19]. Conversely, as only prescription and hospital data were available, less severe exacerbations that are handled without OCS or a hospitalization were not included. This will lead to a slight underestimation of the observed exacerbation rate. However, the sensitivity analysis in which we included antibiotics in the definition of exacerbations revealed similar prevalence and persistence patterns. Another limitation is the lack of spirometry data to confirm the diagnosis of COPD, as this is not available in the registries. The risk of misclassifying users of long-acting bronchodilators and ICS for other indications than COPD is, however, considered minor when only including individuals above 55 years who had an exacerbation. Spirometry data and information on daily symptoms would similarly allow us to investigate whether individuals received long-acting bronchodilators for other indications, e.g., impaired lung function or respiratory symptoms. This is, however, reported to have only minimal influence on the prescribing of triple therapy [13] and the impact of such misclassification is expected to be minor. Finally, information about the prescribed daily dose and duration of therapy was not available. Thus, reduced use rather than discontinuation of therapy would not be evident from our data. Defining use by at least one prescription within 6-month intervals may overestimate both the proportion of prevalent and persistent users. It is, however, of note that the supplementary analysis using 4-month intervals did not affect the observed patterns.

The extensive use of ICS among persons with decreasing exacerbation frequency in our study suggests potentially

Table 2 Prevalent use of medication. The proportion of individuals who were prevalent users of ICS, LABA, or LAMA or combinations of these within each subgroup of COPD patients who had consistently one or more exacerbations, varying exacerbation rates, or consistently zero exacerbations after 12, 24, 36, and 48 months of follow-up. Visualized in supplementary figure 1

	Index date (n = 29,010)	After 12 months (n = 22,325)	After 24 months (n = 19,027)	After 36 months (n = 16,478)	After 48 months (n = 14,284)
Consistently one or more exacerbations					
All		(n = 10,980)	(n = 5413)	(n = 3010)	(n = 1780)
ICS	1351 (4.7%)	314 (2.9%)	124 (2.3%)	58 (1.9%)	27 (1.5%)
LABA	602 (2.1%)	129 (1.2%)	60 (1.1%)	27 (0.9%)	15 (0.8%)
LAMA	1991 (6.9%)	520 (4.7%)	221 (4.1%)	94 (3.1%)	52 (2.9%)
ICS+LABA	6519 (22.5%)	2179 (19.8%)	865 (16.0%)	461 (15.3%)	236 (13.3%)
LABA+LAMA	601 (2.1%)	264 (2.4%)	162 (3.0%)	119 (4.0%)	99 (5.6%)
ICS+LAMA	586 (2.0%)	180 (1.6%)	75 (1.4%)	41 (1.4%)	22 (1.2%)
ICS+LABA+LAMA	11,789 (40.6%)	6586 (60.0%)	3595 (66.4%)	2051 (68.1%)	1240 (69.7%)
No use	5571 (19.2%)	808 (7.4%)	311 (5.7%)	159 (5.3%)	89 (5.0%)
Any ICS-containing regimens	20,245 (69.8%)	9259 (84.3%)	4659 (86.1%)	2611 (86.7%)	1525 (85.7%)
Varying exacerbation rates					
All			(n = 6576)	(n = 8515)	(n = 8886)
ICS			175 (2.7%)	228 (2.7%)	210 (2.4%)
LABA			125 (1.9%)	130 (1.5%)	136 (1.5%)
LAMA			377 (5.7%)	428 (5.0%)	412 (4.6%)
ICS+LABA			1358 (20.7%)	1691 (19.9%)	1672 (18.8%)
LABA+LAMA			200 (3.0%)	357 (4.2%)	511 (5.8%)
ICS+LAMA			93 (1.4%)	107 (1.3%)	111 (1.2%)
ICS+LABA+LAMA			3561 (54.2%)	4685 (55.0%)	4850 (54.6%)
No use			687 (10.4%)	889 (10.4%)	984 (11.1%)
Any ICS-containing regimens			5187 (78.9%)	6711 (78.8%)	6843 (77.0%)
Consistently zero exacerbations					
All		(n = 11,345)	(n = 7036)	(n = 4949)	(n = 3614)
ICS		417 (3.7%)	256 (3.6%)	180 (3.6%)	131 (3.6%)
LABA		297 (2.6%)	189 (2.7%)	143 (2.9%)	93 (2.6%)
LAMA		935 (8.2%)	643 (9.1%)	464 (9.4%)	308 (8.5%)
ICS+LABA		2500 (22.0%)	1540 (21.9%)	1097 (22.2%)	814 (22.5%)
LABA+LAMA		318 (2.8%)	239 (3.4%)	225 (4.5%)	214 (5.9%)
ICS+LAMA		192 (1.7%)	103 (1.5%)	65 (1.3%)	39 (1.1%)
ICS+LABA+LAMA		4718 (41.6%)	2576 (36.6%)	1591 (32.1%)	1052 (29.1%)
No use		1968 (17.3%)	1490 (21.2%)	1184 (23.9%)	963 (26.6%)
Any ICS-containing regimens		7827 (69.0%)	4475 (63.6%)	2933 (59.3%)	2036 (56.3%)

inappropriate use of ICS and likely reflects a reluctance toward discontinuing therapy. In our study, this seemed particularly evident among users of triple therapy, where the largely similar persistence to treatment across subgroups suggests that discontinuation of therapy is even more difficult to implement when extensive treatment has previously been deemed necessary. Overuse of ICS has been reported in previous studies. For example, White et al. [25] described that 25–38% of COPD patients in a primary care setting were inappropriately treated with ICS, while Jones et al. [26] found that only 23% of ICS users were treated according to guidelines. Similarly, Miravitlles et al. [27] found that more than half of COPD patients with stage II lung function impairment received ICS although this is not recommended by contemporary guidelines. Such inappropriate use of ICS is of concern, due to the risk of side effects, particularly pneumonia [9, 28], as well as excessive economical expenses related to inappropriate treatment. In agreement with this, the GOLD guidelines have recently been revised, now recommending a more restrictive use of ICS and emphasizing that ICS should only be added in case of further exacerbations [5].

This study adds to previous knowledge by specifically describing use patterns in a subgroup of COPD patients at risk of overuse, i.e., those who experience an improvement in

Table 3 Persistence to drug use. The proportion of individuals who were persistent to ICS, LABA, or LAMA or combinations of these within each subgroup of COPD patients who had consistently one or more exacerbations, varying exacerbation rates, or consistently zero exacerbations after 12, 24, 36, and 48 months of follow-up

	Index date ($n = 29,010$)	After 12 months ($n = 22,325$)	After 24 months ($n = 19,025$)	After 36 months ($n = 16,474$)	After 48 months ($n = 14,280$)
Consistently one or more exacerbations					
All	($n = 29,010$)	($n = 10,980$)	($n = 5413$)	($n = 3010$)	($n = 1780$)
ICS	1351	144 (30.4%)	46 (21.5%)	17 (13.9%)	7 (9.6%)
LABA	602	36 (17.6%)	9 (9.2%)	($n < 5$)	(n < 5)
LAMA	1991	110 (19.3%)	11 (4.4%)	(n < 5)	(n < 5)
ICS+LABA	6519	1186 (47.4%)	359 (30.0%)	117 (18.2%)	51 (14.1%)
LABA+LAMA	601	59 (25.7%)	21 (21.2%)	7 (11.1%)	(n < 5)
ICS+LAMA	586	64 (26.2%)	18 (14.1%)	6 (8.1%)	(n < 5)
ICS+LABA+LAMA	11,789	4486 (84.1%)	2230 (77.0%)	1200 (70.6%)	672 (65.1%)
No use	5571	296 (20.8%)	59 (11.1%)	18 (7.5%)	6 (4.8%)
Any ICS-containing regimens	20,245	7638 (89.3%)	3700 (83.4%)	1990 (78.4%)	1122 (74.0%)
Varying exacerbation rates					
All			($n = 6576$)	($n = 8515$)	($n = 8886$)
ICS			49 (14.1%)	54 (11.4%)	45 (8.8%)
LABA			17 (11.7%)	16 (8.3%)	15 (7.3%)
LAMA			70 (17.0%)	52 (10.4%)	36 (7.0%)
ICS+LABA			601 (36.0%)	627 (28.1%)	543 (22.7%)
LABA+LAMA			22 (13.4%)	21 (10.1%)	18 (9.2%)
ICS+LAMA			17 (12.7%)	19 (11.2%)	20 (11.7%)
ICS+LABA+LAMA			1939 (74.6%)	2315 (69.5%)	2167 (64.0%)
No use			155 (14.0%)	160 (11.3%)	145 (9.6%)
Any ICS-containing regimens			3806 (80.1%)	4651 (75.0%)	4507 (69.8%)
Consistently zero exacerbations					
All		($n = 11,345$)	($n = 7036$)	($n = 4949$)	($n = 3614$)
ICS		207 (32.1%)	84 (18.7%)	48 (14.0%)	27 (9.9%)
LABA		82 (29.4%)	35 (18.6%)	19 (14.0%)	12 (11.5%)
LAMA		283 (32.7%)	129 (23.2%)	69 (18.4%)	39 (14.5%)
ICS+LABA		1356 (50.9%)	680 (40.3%)	406 (34.1%)	261 (29.5%)
LABA+LAMA		77 (32.9%)	39 (28.7%)	19 (22.6%)	11 (17.2%)
ICS+LAMA		75 (37.1%)	35 (31.8%)	18 (24.0%)	5 (9.3%)
ICS+LABA+LAMA		2841 (81.5%)	1296 (72.5%)	693 (63.5%)	386 (56.8%)
No use		713 (24.0%)	402 (19.0%)	280 (16.9%)	212 (16.5%)
Any ICS-containing regimens		5905 (84.4%)	2982 (73.9%)	1757 (65.0%)	1094 (57.8%)

exacerbation status over time and therefore may not have the implicit need for the same continued level of treatment. Recent research indicates that discontinuation of ICS is safe in patients at low risk of exacerbations [29–31] and also in those with stable, severe COPD [11]. In line with this evidence, de-escalation and restricted use of ICS are now mentioned in the 2017 GOLD guidelines though recommendations do not contain specific instructions or advice for how to approach de-escalation [5]. Since previous guidelines did not incorporate de-escalation strategies, it was not clear to what extent discontinuation of ICS (based on burden of exacerbations) was already occurring in clinical practice. We found that discontinuation of ICS-containing regimens was only implemented in a minority of patients despite a consistent improvement in exacerbation status over time. Though we cannot rule out that some individuals without exacerbations continued therapy because of respiratory symptoms and/or lung

function impairment, our study signals a need for disseminating knowledge around de-escalation and developing and implementing de-escalation strategies in clinical practice, e.g., how to determine if de-escalation is appropriate, how to discuss with patients, whether to discontinue abruptly or taper, what to monitor, and how frequently. It is also important to be able to distinguish between individuals who experience an improvement in symptoms and exacerbation status because of appropriate treatment and individuals who experience an improvement as a part of the natural trajectory of their COPD. Thus, improved tools to predict and monitor exacerbation rates are crucial for clinicians to promote safe, evidence-based de-escalation of therapy and minimize rates of potentially inappropriate ICS usage in patients with COPD.

In conclusion, we found an extensive use of ICS-containing regimens, particularly triple therapy. Additionally, persistence to ICS-containing therapy was relatively high among individuals who experienced an improvement in exacerbation status. This highlights a need for developing and implementing de-escalation strategies for COPD patients in clinical practice.

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Compliance with ethical standards

Conflict of interest Mette Reilev reports participation in research projects funded by LEO Pharma, all with funds paid to the institution where she was employed (no personal fees) and with no relation to the work reported in this paper.

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Kasper Bruun Kristensen, Wade Thomson, and Daniel Pilsgaard Henriksen report no potential conflicts of interest.

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