International Journal of Chronic Obstructive Pulmonary Disease

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ORIGINAL RESEARCH

# Adherence to Inhaled Medication Guidelines in Patients with COPD: Evaluating the GOLD 2023 Strategy in a Real-World Secondary Care Setting

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**Introduction:** The 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy introduced updates to the prescription of inhaled medication, including withdrawing recommendation of long-acting beta-agonist/inhaled corticosteroids (LABA/ICS) as double therapy, restricting ICS use to patients with exacerbations, and recommending earlier escalation to triple therapy. These changes are expected to have a substantial impact on clinical practice. This study aims to describe how well clinicians adhere to the GOLD strategy in daily practice, and to explore the extent to which the 2023 update has changed prescribing patterns.

**Methods:** Data were collected from a real-world cohort at a teaching hospital in the Netherlands in 2022, and the same cohort was reassessed in 2023. To determine guideline adherence, each patient's treatment was assessed against the applicable GOLD strategy at that time. Subgroups that did not receive treatment according to the GOLD strategy were identified. Finally, a more detailed assessment of ICS prescriptions and their indications was conducted.

**Results:** A total of 1318 patients were included in 2022. In 2022, 51.6% received inhaled medication in line with the applicable GOLD strategy, compared to 57.3% in 2023 in accordance with that year's GOLD strategy. Patients with low eosinophils, those without exacerbations, and those with less severe GOLD classification were less frequently treated in accordance with the 2023 strategy. Overtreatment with ICS was common (25.4%).

**Conclusion/Discussion:** A substantial proportion of patients with COPD are not treated in accordance with GOLD recommendations. While there may be valid reasons for deviating from the recommendations, these findings should prompt physicians to consider whether their patients' current treatment is optimal. Clear criteria exist for initiating ICS treatment. However, there is no data-driven evidence or consensus on how to manage ICS treatment once a patient has stabilised. Identifying and discussing the barriers for implementation of the GOLD strategy is essential.

**Keywords:** COPD, GOLD strategy, guideline adherence, inhaled medication prescription

## Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) releases an annual report outlining recommendations for diagnosis, management, and prevention of Chronic Obstructive Pulmonary Disease (COPD).[1] While the GOLD reports are formally classified as a strategy, they are commonly regarded as guidelines for prescription of inhaled medication. In the Netherlands, COPD care is guided by either the GOLD strategy or the national guideline, which largely reflect the GOLD recommendations regarding pharmacological treatment.[2,3] The 2023 edition of the GOLD strategy introduced significant updates to inhaled medication treatment.[4,5] These revised guidelines should have

Received: 28 June 2025
Accepted: 7 November 2025
Published: 2 December 2025

substantial implications for clinical practice. Some treatment recommendations remained consistent between the 2022 and 2023 strategy. Two treatment algorithms are used to select the appropriate follow-up inhaled therapy: the exacerbation algorithm for patients experiencing exacerbations and the dyspnoea algorithm for those with persistent dyspnoea. Furthermore, asthma as a comorbidity or history requires primary treatment for asthma, including the use of inhaled corticosteroids (ICS).[5,6] The 2023 strategy introduced three key changes compared with the 2022 recommendations: 1) the use of ICS in the absence of exacerbations, regardless of dyspnoea severity, is no longer recommended; 2) earlier escalation to triple therapy is advised for patients with elevated blood eosinophil counts ($\geq$0.3 x$10^9$/L), and 3) the combination of ICS and a long-acting beta-agonist (LABA) as a double therapy is no longer recommended. When ICS is indicated, triple therapy combining a LABA, a long-acting muscarinic antagonist (LAMA), and ICS is advised.[5] This last recommendation was supported by two large trials that showed that triple therapy was more effective compared to LABA +ICS.[7,8] However, this change resulted in debate regarding patients who were clinically stable on LABA+ICS. To address this, the 2025 strategy introduced an important nuance: clinically stable patients already using LABA+ICS may continue this regimen.[1]

There is considerable debate on the appropriate use of ICS in COPD. Although the GOLD strategy provides clear guidance on initiating ICS, it offers no recommendations on how or whether ICS should be withdrawn in (clinically stable) patients, aside from a brief note on discontinuation in case of side effects.[1,5,6] Overuse of ICS could potentially be harmful due to the increased risk for side effects (for example pneumonia). Conversely, there is an undesirable risk for undertreatment when withholding ICS in COPD patients with exacerbations and high eosinophil counts.[9] Therefore, it is important to assess prescribing patterns in daily practice and to investigate clinicians' adherence to the latest evidence-based recommendations. Clinicians may encounter barriers when implementing guideline recommendations in daily practice, for example due to resistance to modifying existing treatment regimens or frequent annual guideline updates.[10] Identifying patients whose treatment more frequently deviates from the GOLD strategy may encourage clinicians to evaluate whether current treatment remains appropriate in these patients. Findings from this Dutch cohort study could provide valuable guidance for other healthcare systems facing similar challenges in implementing the GOLD recommendations.

Therefore, this descriptive study aims to evaluate clinicians' adherence to the recommendations on inhaled medications of the GOLD strategy in daily practice and describe whether, and to what extent, the 2023 update has influenced prescribing patterns. Also, we aimed to identify subgroups of patients at risk for receiving inhaled medication not in line with GOLD recommendations. Furthermore, we explored ICS use and indication, specifically in the context of clinically stable patients. Lastly, barriers to implementation of the GOLD recommendations are discussed.

# Methods

## Study Design

In this retrospective observational cohort study, data of patients with COPD were collected from the Franciscus Gasthuis and Vlietland hospital, a large teaching hospital specializing in COPD and asthma care in Rotterdam, the Netherlands. First, data of patients with a COPD diagnosis in 2022 were automatically extracted from electronic patient records. Data on asthma as a comorbidity and lung function data that could not be automatically extracted were supplemented by the researchers manually. Secondly, to determine adherence to the guidelines, a cross-year comparison between 2022 and 2023 was conducted. Each patient's treatment was assessed against the treatment algorithms in the 2022 GOLD strategy at the time it was last in effect. This assessment was repeated in November 2023, after the 2023 GOLD strategy had been in effect for one year. For adequate interpretation, it is important to note that the update of GOLD for the new year (eg "202x") is routinely presented in the last months of the year before (202x-1). We assessed whether specific patient groups were less likely to receive treatment in accordance with the most recent recommendations. Finally, an in-depth evaluation of ICS use was performed. Ethics approval for this retrospective data study was waived by the Institutional Review Board of the Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands (identification number 2023–037). The study complies with the Declaration of Helsinki. This study was reported in line with the STROBE reporting checklist for observational studies.[11]

## Setting

Data were sourced from a secondary care hospital specializing in COPD and asthma. This hospital serves as a regional centre of expertise due to its coordination of care. Patients were referred to this hospital by their general practitioners or from other medical facilities, implying that initial therapy had likely been initiated elsewhere. Approximately 20 to 25 healthcare professionals, including treating physicians and specialized nurses, are responsible for the outpatient clinic care and therefore prescribe the inhaled medication.

## Patient Selection

Data of all patients with an active COPD diagnosis and at least one inhaled medication prescription in the year before the release of the GOLD 2023 strategy (1–12-2021 until 01–12-2022) were included in the study. Patients were excluded from the study if essential data for objective clinical assessment were missing, such as eosinophil count or Clinical COPD Questionnaire (CCQ) score. Patients younger than 40 years were excluded to avoid including those with primarily asthma. Lastly, patients with a Forced Expiratory Volume in 1 second/Forced Vital Capacity (FEV1/FVC) ratio >0.7 were also excluded, as this criterion does not align with the GOLD definition of COPD.

## Data Collection

Data on age, sex, inhaled medication, eosinophils, Clinical COPD Questionnaire (CCQ) score, exacerbations, hospitalizations, and the use of prednis(ol)one, azithromycin, or roflumilast, were automatically extracted from electronic patient records. An exacerbation was defined as a prescription of 30 or 40 mg prednis(ol)one daily for a duration of 3 to 14 days, which, according to COPD guidelines, is the primary treatment for COPD exacerbations in both primary and secondary care in the Netherlands. Use of other systemic corticosteroids is uncommon. The range of doses and number of days was chosen to capture potential variations in prescribing practices between physicians. Prednisone prescriptions were extracted from pharmacy records of our hospital and of the "Landelijk Schakel Punt (LSP)". LSP is the national pharmacy data-sharing system in the Netherlands and includes the community prescriptions from general practitioners.[12] Antibiotics were excluded from the exacerbation definition as it is very uncommon in the Netherlands to treat COPD exacerbations with antibiotic monotherapy. Hospitalization was classified as any hospital stay linked to the COPD diagnosis, where the primary physician overseeing care was a pulmonologist. Asthma was considered a comorbidity next to COPD if the treating physician documented asthma, asthmatic characteristics, or ACO/ACOS in the medical history or conclusion in the patient record. However, if asthma was not mentioned or if only reversibility or bronchial hyperactivity were described, we considered this variable as negative. Most recent FEV1, FVC, and FEV1/FVC values before the visit to the pulmonologist were collected from the electronic patient record. If there was both a pre- and post-bronchodilator value known, the post value was used. Multiple eosinophil counts were extracted, including the most recent value, the highest count in the past year, the highest count over the past three years, and the highest count recorded ever. The CCQ is the widely used COPD questionnaire in the Netherlands, in contrast to COPD Assessment Test (CAT) or the Medical Research Council (MRC) dyspnoea scale. As the CCQ represents the same domains, these data were collected.[13]

## Assessment of Adherence to Inhaled Medication Recommendations

We evaluated the inhaled medication at two time points: 1) the date of the most recent inhaled medication prescription before December 1, 2022, when the 2022 GOLD strategy applied; and 2) one year after the release of the 2023 strategy (November 14, 2023), Figure 1A. By that time, it could be assumed that patients had attended at least one follow-up visit since the new recommendations applied and, if necessary, had had the opportunity to have their inhaled medication adjusted. Our main outcome was the percentage of COPD patients with inhaled treatment according to the relevant GOLD strategy at each timepoint. The assessment of guideline adherence was based on the treatment algorithms in the GOLD strategies. Six objective parameters were used: (i) presence of asthma as comorbidity or in the past; (ii) number of exacerbations; (iii) number of hospitalizations; (iv) previous medication; (v) eosinophil count; and (vi) CCQ symptom score, Figure 1B-C. Guideline adherence was assessed by comparing the recommended treatment, as determined from

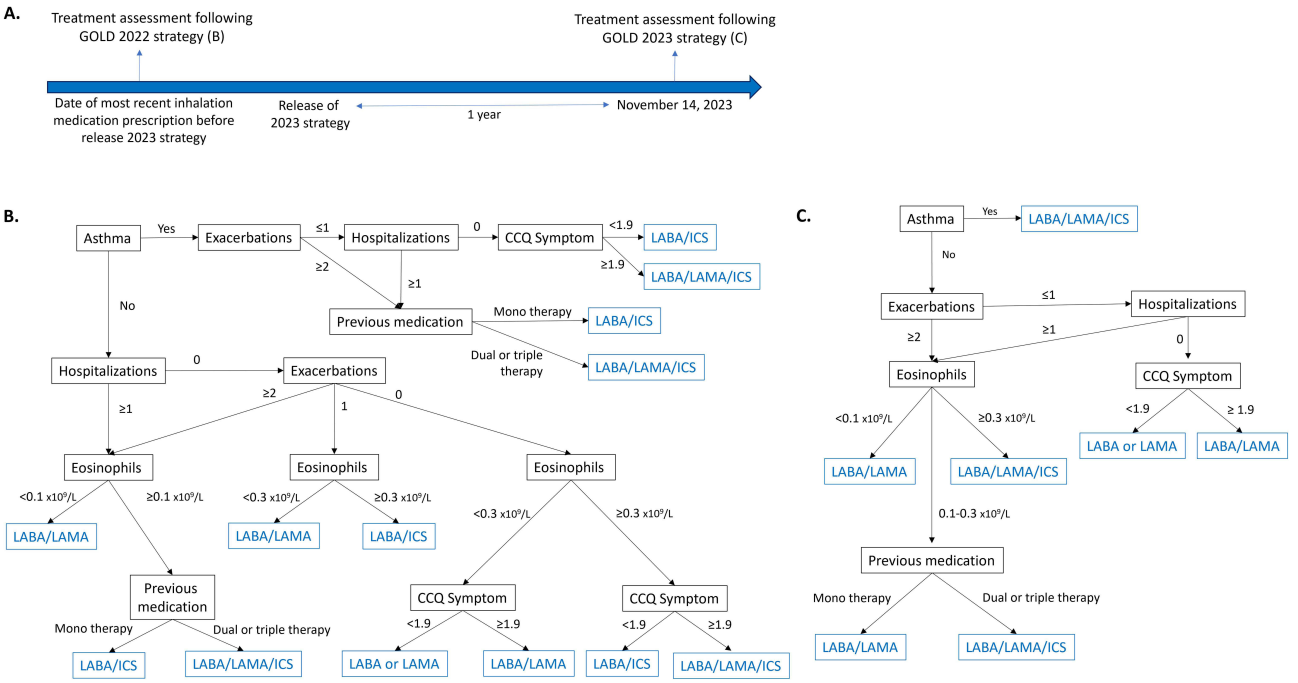


**Figure 1** Overview of the 2022 and 2023 assessment. This figure provides an overview of the two assessments conducted in this study. (**A**) shows the timeline of the two assessments. (**B**) illustrates our assessment based on the follow-up treatment protocols in the 2022 GOLD strategy, while (**C**) illustrated the assessment based on the follow-up treatment protocols in the 2023 GOLD strategy.
**Abbreviations**: LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting Beta-Agonist; ICS, Inhaled corticosteroids.

the assessment shown in Figure 1, with the patient's actual treatment. If these were identical, guideline adherence was scored as "adherent"; if not, it was scored as "nonadherent". For the primary assessment of the treatment, we used the most recent CCQ symptom score, highest-ever eosinophil count, and the number of exacerbations and hospitalizations in the previous three years. The CCQ symptom score (the subdomain determined by the sum of question 1, 2, 5 and 6 dived by 4) was used as an objective parameter for dyspnoea. A threshold of 1.9 points was used for severe symptoms, based on a previous study.[14] Our assessment followed the pharmacological follow-up protocols outlined in the GOLD strategies, rather than the initial treatment protocol.[5,6] Finally, while the follow-up inhaled medication protocol in the 2023 and currently applicable 2025 strategies is similar, the latter provides an additional nuance for stable patients on LABA/ICS. The 2025 strategy states that LABA/ICS could be continued if patients currently have no exacerbations, a low symptom load, and no features of asthma.[1] Therefore, we investigated how many patients in 2023 would have had treatment according to the guideline if the 2025 nuance was already applicable.

## Differences Between Specific Patient Groups

To evaluate specific patient groups at higher risk of inadequate treatment, we used the 2023 strategy exclusively, since its recommendations are identical to those of the 2025 strategy currently in force. Guideline adherence was assessed in various subgroups: patients with low (<0.1 x$10^9$/L), medium (0.1–0.3 x$10^9$/L) and high (>0.3 x$10^9$/L) eosinophil count; patients treated by the dyspnoea algorithm and those treated by the exacerbation algorithm; different GOLD classifications based on severity of airflow obstruction (I, II, III, IV); and patients on single inhaler triple therapy (SITT) or multiple inhaler triple therapy (MITT).

## In-Depth Evaluation of ICS Use

To evaluate ICS use and its indications in greater depth, we first conducted a cross-sectional analysis at the second measurement point of this study (end of 2023), as the 2023 strategy recommendations for ICS are consistent with those of the 2025 strategy currently in effect. We then assessed whether adherence to the 2023 GOLD strategy changed when

different timeframes for exacerbations and hospitalizations were applied (previous one, two, or three years). Additionally, we examined the impact of using either the most recent eosinophil count or the highest count recorded in the last year, last three years, or ever. Next, we compared the 2022 and 2023 strategy at the same historical time point: the end of 2022, which was the final moment the 2022 strategy was applicable. We determined ICS indications among ICS users according to the 2022 strategy and assessed what the indication would have been at that same time according to the 2023 strategy. Patients who had an indication under the 2022 strategy but not under the 2023 strategy represent those whose medication would need to be adjusted to align with the newest recommendations. These patients were then re-evaluated one year later, at the second measurement point of this study.

## Statistical Analysis

Most outcomes are presented descriptively using means and standard deviations, median and interquartile ranges, or numbers and percentages, as appropriate. The primary outcome (guideline adherence at each time point) is presented as a percentage with the 95% confidence interval (CI). The McNemar test is used to test for statistical significant differences in guideline adherence between 2022 and 2023. The chi-square test was used to compare clinicians' adherence to the GOLD strategy across different subgroups.

# Results

## Patient Characteristics

Data of 2434 patients with an active COPD diagnosis in 2022 were automatically extracted from the electronic patient records. After excluding patients under 40 years of age (n=5), those with FEV1/FVC >0.7 (n=85), and those with missing data on eosinophils (n=350) or CCQ score (n=675), a total of 1318 patients were included in the study cohort, Figure 2. Within this cohort, 689 (52.3%) patients were female, and the median age was 70 [interquartile range (IQR) 64–76], Table 1. Median FEV1 post bronchodilator percent predicted was 47 [IQR 36–63]. Asthma was documented as a comorbidity or past diagnosis in 245 patients (18.6%). The majority of patients in the study cohort (n=962, 73.0%) received triple therapy (the combination of a LABA, LAMA and ICS). This proportion of triple therapy users was higher in the study cohort than in the exclusion cohort based on missing eosinophils (54.0%) and the exclusion cohort based on missing CCQ (48.1%), Table S1. Consequently, LABA/LAMA and LABA/ICS use was lower in the study cohort (12.6% and 9.4% respectively) compared to the exclusion sub cohorts with missing eosinophils (21.1% and 11.4% respectively) and the sub cohort with missing CCQ (23.7% and 18.1% respectively). Maintenance use of prednisone and azithromycin was higher in the study cohort (4.7% and 10.9% respectively) than in the exclusion cohorts (2.0–2.1% and 3.0–3.7% respectively).

## Assessment of Adherence to Inhaled Medication Recommendations

During the first measurement point of this study (end of 2022), 680 patients received inhaled medication in line with the recommendations of the 2022 strategy (51.6% with 95% CI interval 48.9–54.3%). During the second measurement point

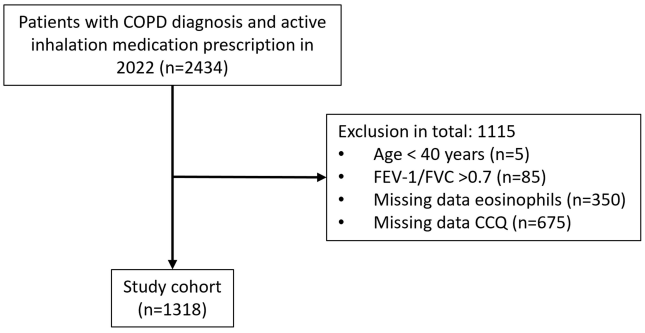


**Figure 2** Patient selection.

 https://doi.org/10.2147/COPD.S543458 

**Table 1** Baseline Characteristics

| Characteristics | Study Cohort (n=1318) |
|---|---|
| **Female sex, n (%)** | 689 (52.3) |
| **Age, median [IQR]** | 70 [64–76] |
| **Smokers, n (%)** | |
| *Active* | 383 (29.1) |
| *Former* | 774 (58.7) |
| *Never* | 39 (3.0) |
| *Unknown* | 122 (9.3) |
| **FEV-1 post % predicted, median [IQR]** | 47 [36–63] |
| **FEV-1/FVC %, median [IQR]** | 45 [36–56] |
| **GOLD classification (severity of airflow obstruction), n (%)** | |
| GOLD I | 108 (8.2) |
| GOLD II | 469 (35.6) |
| GOLD III | 537 (40.7) |
| GOLD IV | 168 (12.7) |
| Missing FEV-1 | 36 (2.7) |
| **Asthma as comorbidity or in the past, n (%)** | 245 (18.6) |
| **Eosinophils, median [IQR]** | 0.19 [0.10–0.32] |
| **Maintenance inhaled medication at entry in cohort, n (%)** | |
| *LAMA* | 44 (3.3) |
| *LABA* | 9 (0.7) |
| *ICS* | 4 (0.3) |
| *LABA+LAMA* | 166 (12.6) |
| *LABA+ICS* | 124 (9.4) |
| *LAMA+ICS* | 9 (0.7) |
| *LABA+LAMA+ICS* | 962 (73.0) |
| **Other maintenance therapy, n (%)** | |
| Prednisolone | 62 (4.7) |
| Azithromycin | 144 (10.9) |
| Roflumilast | 9 (0.7) |

**Abbreviations**: IQR, Interquartile range; FEV-1, Forced Expiratory Volume in 1 second; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting Beta-Agonist; ICS, Inhaled corticosteroids.

of this study (end 2023), one year after the 2022 analysis, 1074 patients of the study cohort were still alive (81.4%). Of those, the inhaled medication regimen of 615 patients was adherent to the 2023 strategy (57.3% with 95% CI interval 54.3–60.2%). There was no difference in guideline adherence to the 2022 strategy between patients who were alive in 2023 and those who had died: 51.8% and 50.8%, respectively (p=0.789).

Among the patients alive at both time points (n=1074), the inhaled medication prescriptions of 454 patients (42.3%) adhered to both GOLD strategies, 102 (9.5%) adhered in 2022 but not in 2023, 161 (15.0%) did not adhere in 2022 but did in 2023, and the prescriptions of 357 patients (33.2%) did not adhere to the guideline at both time points, Table 2. In these patients, the adherence to the 2022 strategy in 2022 was statistically significantly different from the adherence to the 2023 strategy in 2023 ($p < 0.001$).

**Table 2** Adherence to GOLD Strategy in 2022 and 2023

| | Treatment in line with 2023 Strategy | Treatment not in line with 2023 Strategy |
|---|---|---|
| **Treatment in line with 2022 strategy** | 454 (42.3%) | 102 (9.5%) |
| **Treatment not in line with 2022 strategy** | 161 (15.0%) | 357 (33.2%) |

**Note**: Of the 1074 patients alive in 2023.

The vast majority of patients who had prescriptions in line with the GOLD strategy at both time points, as well as those who were deviating from GOLD strategies at both time points, did not have their medication adjusted during the study period: 447 out of 454 (98.5%) and 294 out of 357 (82.4%) respectively, Figure 3A and D.

Of the 102 patients whose treatment went from adherent to the 2022 strategy to non-adherent to the 2023 strategy, approximately half had no change in medication (n=52, 51.0%) and half had a change in medication (n=50, 49.0%), Figure 3B. For patients whose medication remained the same, changes should have been made according to the 2023 strategy due to the use of LABA/ICS (n=22) or the use of triple therapy due to high symptom burden, which is no longer a justification for ICS in the 2023 strategy (n=5). The treatment of the remaining patients (n=25) no longer met the

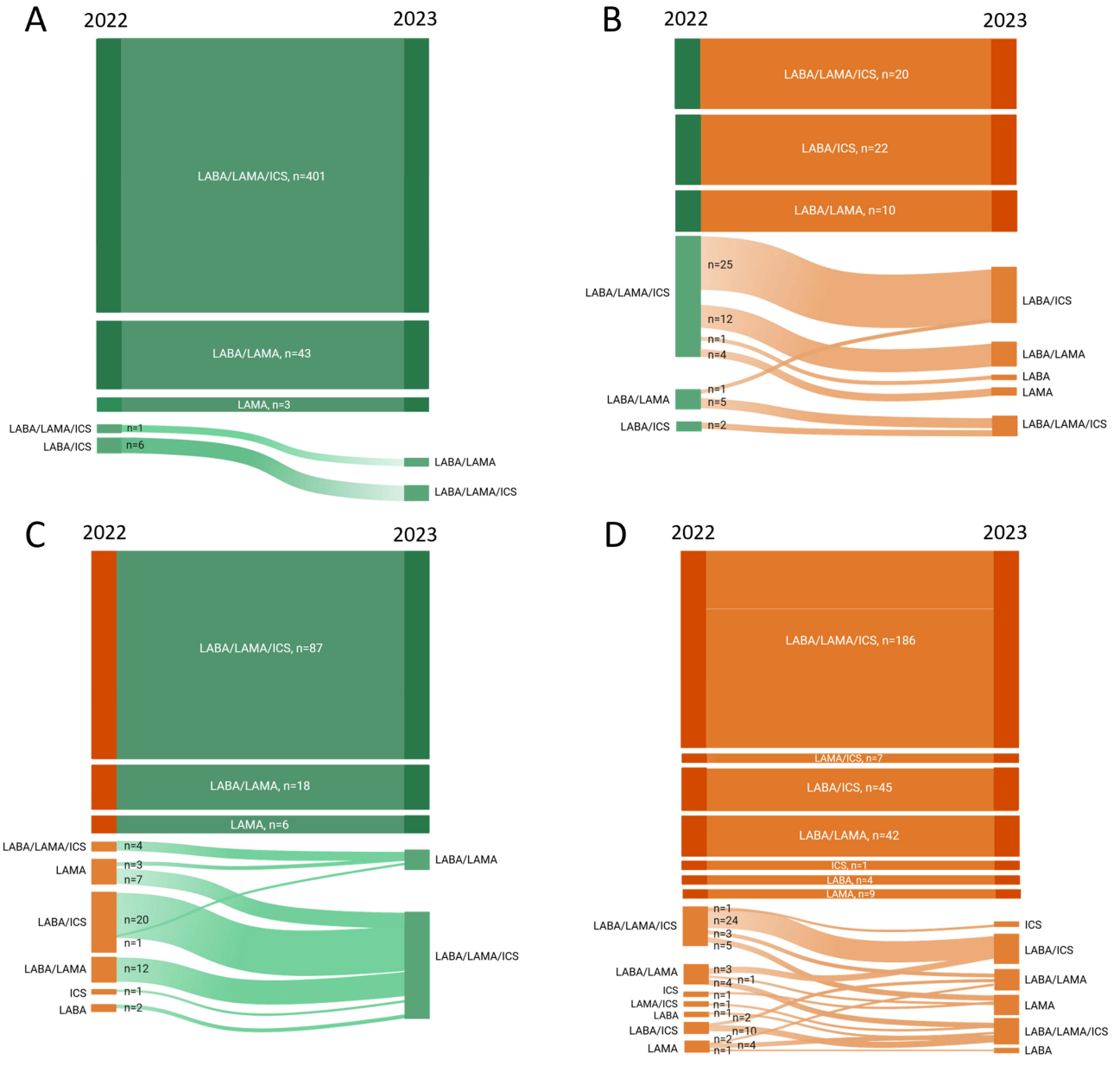


**Figure 3** Treatment patterns between 2022 and 2023. This figure illustrates the medication flows and treatment patterns between 2022 and 2023 among patients who were alive at both time points (n=1074): (**A**) Patients treated according to GOLD at both time points (n=454, 42.3%); (**B**) patients treated according to GOLD in 2022 but not in 2023 (n=102, 9.5%); (**C**) patients not treated according to GOLD in 2022 but are treated according to GOLD in 2023 (n=161, 15.0%); (**D**) patients not treated according to GOLD at either time point (n=357, 34.3%).

**Abbreviations**: LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting Beta-Agonist; ICS, Inhaled corticosteroids.


https://doi.org/10.2147/COPD.S543458

GOLD recommendations due to differences in exacerbations, hospitalizations, eosinophil counts, or CCQ scores between the 2022 and 2023 assessments. For example, a patient on LABA/LAMA with exacerbations had no indication for ICS in 2022 due to low eosinophil levels at the time, but became eligible for ICS in 2023 when higher eosinophil counts were measured. The 50 patients whose treatment went from adherent in 2022 to nonadherent in 2023 by changes in their medication, showed the following reasons for nonadherence to the guideline: de-escalating triple therapy to LABA/ICS (n=25), withdrawal of ICS despite exacerbations or hospitalizations (n=15) or in the presence of asthma as comorbidity (n=2), start of ICS treatment despite lack of exacerbations (n=5) or in case of eosinophils <0.1 $x10^9$/L (n=1), and escalating from LABA/ICS to triple therapy in absence of exacerbations (n=2).

One hundred sixty-one patients were not treated according to the GOLD 2022 strategy, but had treatment in line with the 2023 strategy. Of these, 50 (31.1%) had their medication adjusted, so actively conforming to the strategy, and the remaining 111 patients (68.9%) did not undergo any changes in their medication regimen, Figure 3C. The majority (n=76) of the treatments of these 111 patients were now adherent to the GOLD strategy due to the differences in the recommendations between the 2022 and 2023 strategy, which aligned their existing medications with the updated recommendations. Specifically, for 59 patients on triple therapy, GOLD 2022 recommended LABA/ICS but not triple therapy, whereas the GOLD 2023 now supports the triple therapy. Similarly, 17 patients previously on LABA or LABA/LAMA had an indication for ICS in 2022, but no longer required ICS following the GOLD 2023 revision. For the remaining 35 of the 111 patients whose medication was not changed, differences in exacerbations, hospitalizations, eosinophils, or CCQ scores between the 2022 and 2023 assessments led to a new recommendation in 2023, which coincidentally aligned with their existing medication regimen. For example, one patient experienced exacerbations in 2023, which justified the triple therapy he was already receiving.

### Extra Nuance of the 2025 Strategy: Clinically Stable Patients on LABA/ICS

Five of the 120 patients still on LABA/ICS in 2023 had no exacerbations, a low symptom load, and no features of asthma (4.2%), meaning that their medication regimen would have aligned with the recommendations if this current nuance of the 2025 strategy would have been valid at that time.

## Differences Between Specific Patient Groups

Certain patient groups were more often received inhaled medication not in accordance with the 2023 strategy, Figure 4. When categorized by eosinophil levels into low (<0.1 $x10^9$/L), medium (0.1–0.3 $x10^9$/L), and high (≥0.3 $x10^9$/L), there were 214 (19.9%), 513 (47.8%), and 347 (32.3%) patients in each subgroup, respectively. In the subgroup with low eosinophils, 69.6% (95% CI 63.2–75.4%) of the patients were not treated according to the 2023 strategy, compared to 40.2% (95% CI 36.0–44.5%) in the medium, and 30.0% (95% CI interval 25.4–35.0%) in the high eosinophil group (p<0.001). Patients who were treated according to the dyspnoea algorithm (n=288) were more likely to receive treatment not in line with the 2023 recommendations compared to patients who were treated according to the exacerbation algorithm (n=786): 68.4% (95% CI interval 62.8–73.5%) and 33.3% (95% CI interval 30.1–36.7%) were treated incorrectly, respectively (p<0.001). Furthermore, nonadherence to the GOLD 2023 strategy was higher in patients with less severe GOLD classifications: 56.6% (95% CI interval 46.7–65.9%) in GOLD I, 43.6% (95% CI interval 38.9–48.5%) in GOLD II, 42.8% (95% CI interval 38.2–47.5%) in GOLD III, and 28.1% (95% CI interval 20.6–36.9%) in GOLD IV subgroup (p<0.001). Among triple therapy users (n=769), 358 (46.6%) used a single device (SITT), while 411 (53.4%) used multiple devices (MITT). Nonadherence to the 2023 strategy was similar: 31.6% (95% CI interval 27.0–36.6%) in SITT compared to 29.2% (95% CI interval 25.0–33.8%) in MITT (p=0.476).

## In-Depth Evaluation of ICS Use

The cross-sectional analysis in 2023 showed that, among the patients alive in 2023 (n=1074), 898 patients (83.6%) were using an ICS. Of the total cohort, 625 patients (58.2%) used an ICS appropriately, while 125 patients (11.6%) correctly did not receive ICS treatment. Overtreatment was more prevalent than undertreatment: 273 patients (25.4% with 95% CI interval 22.9–28.1%) received ICS inappropriately, whereas 51 patients (4.7% with 95% CI interval 3.6–6.2%) did not receive and ICS despite having an indication according to the 2023 strategy. The highest ever recorded eosinophil value

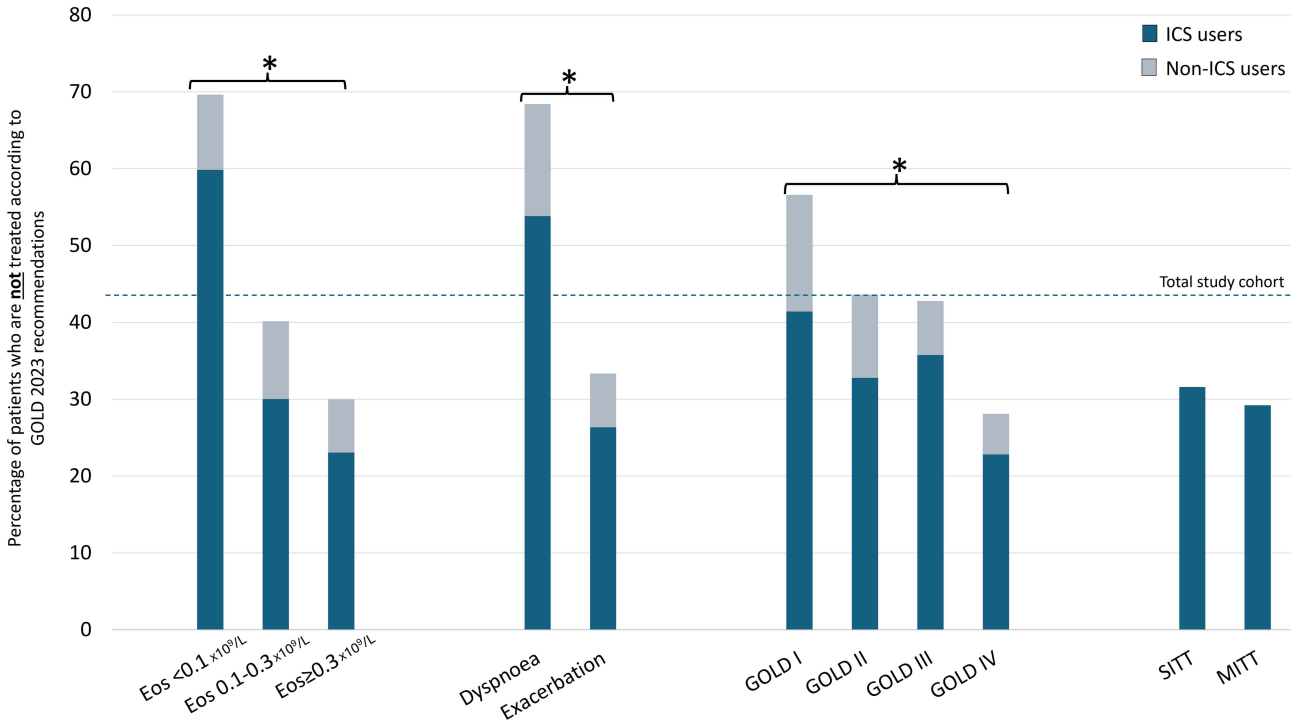


**Figure 4** Percentages of patients in different subgroups who are not treated according to the 2023 strategy. Patients are categorized four times: on the far left by eosinophil levels: low (<0.1 x$10^9$/L), medium (0.1–0.3 x$10^9$/L), and high (≥0.3 x$10^9$/L); second from the left those receiving treatment based on the dyspnoea algorithm and those treated according to the exacerbation algorithm in the GOLD strategy; second from the right by GOLD classification based on airflow obstruction severity; and on the far right, triple therapy users are divided into single-inhaler triple therapy (SITT) and multiple-inhaler triple therapy (MITT) users. The blue bars represent the proportion of ICS users, while the grey bars display those without ICS. The blue dotted lines shows the percentage (42.7%) of patients that is not treated according to the GOLD report in the total cohort (n=1074). *= *statistically significant difference.*

was used for the primary assessments. When instead only the most recent eosinophil count was considered, the proportion of patients classified as appropriate ICS users decreased from 58.2% to 43.8%, Figure 5A. A similar trend was seen when different timeframes for exacerbations and hospitalizations were applied: 48.4% when using data from the past year, 58.2% for the past three years, and 61.9% for the past five years, Figure 5B. Of the 898 ICS users in 2023, 59 patients (6.6%) had no exacerbations or hospitalizations in the past five years and consistently had an eosinophil count of less than 0.3.

When applying the 2022 and 2023 strategy at the same time point, which was the first measurement time point just before the 2022 strategy was replaced by the 2023 strategy, 1099 patients (83.4%) of the total study cohort (n=1318) were using an ICS. Among them, 88 patients had an indication for ICS at that moment according to the 2022 strategy, but would no longer have an indication once the 2023 strategy became applicable, Table 3. At the second measurement time point of this study, which occurred one year after the implementation of the 2023 strategy, 24 of these 88 patients had died. Of the 64 patients who were still alive, ICS was continued in 55 patients despite still having no indication according to the 2023 strategy, ICS was continued in five patients who had acquired an indication during that year (eg due to an exacerbation or hospitalisation), and it was appropriately discontinued in four patients.

## Discussion

In a real-world Dutch secondary care setting, this study demonstrated that only a small majority of patients were treated according to the GOLD recommendations, with a slight increase from 51.6% in 2022 to 57.3% in 2023. Some patient subgroups were at higher risk of receiving treatment that did not align with the GOLD strategy: patients with low eosinophil counts, those without exacerbations, and those with a less severe GOLD classification. Our in-depth evaluation of ICS revealed that overtreatment with ICS was common and more prevalent than undertreatment.

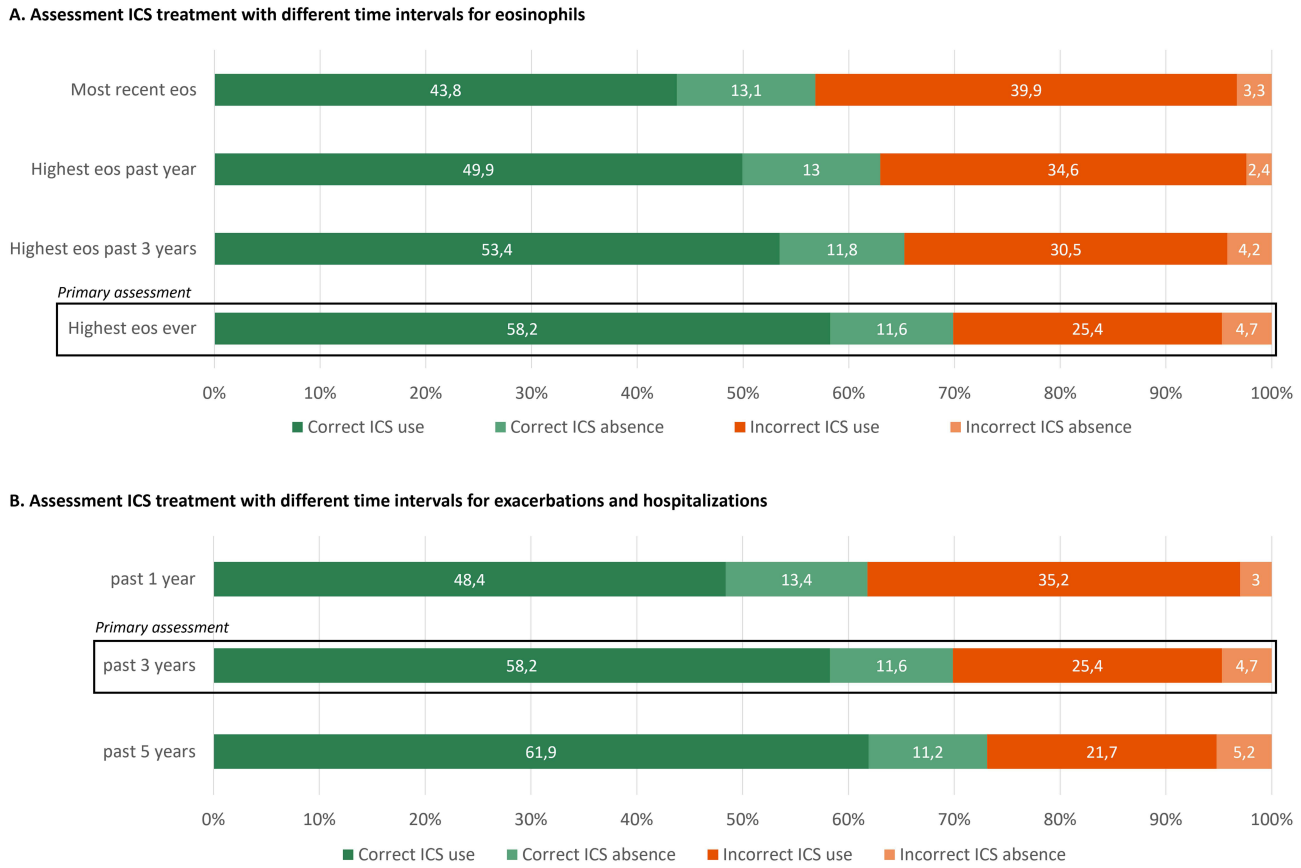


**Figure 5** Assessment of ICS treatment using different time intervals. (**A**) displays the proportion of patients with correct ICS use (dark green), correct ICS absence (light green), incorrect ICS use (dark Orange), and incorrect ICS absence (light orange) across different time intervals of eosinophil count. (**B**) presents these proportions based on various time intervals for exacerbations and hospitalizations. The black box highlights the values used for the primary assessment of inhalation treatment in this study.

The adherence rate of 57% is not particularly high. One previous study assessed adherence to the GOLD strategy since the introduction of the updated treatment algorithms in the 2023 report. This cohort study of 3477 patients from 54 hospitals in South Korea reported lower adherence rates than our findings: 31.3% for the GOLD 2019 strategy and 28.0% for the GOLD 2023 strategy. Interestingly, clinicians' adherence to the 2018 Korean national guideline was higher and more comparable (56.9%), indicating that it likely plays a more prominent role in guiding clinical practice in South Korea than the GOLD strategy.[15] Other studies investigating adherence to earlier versions of the GOLD strategy reported adherence rates ranging from 36% to 60.5%.[16–19] Consistent with our findings, several studies have shown that guideline

**Table 3** Longitudinal Comparison in ICS Users (n=1099) from 2022 to 2023

| First measurement point (end of 2022) | | |
|---|---|---|
| | **ICS indication 2023 strategy** | **No ICS indication 2023 strategy** |
| **ICS indication 2022 strategy** | 743 | 88 |
| **No ICS indication 2022 strategy** | 0 | 268 |

| Second measurement point (end of 2023) | |
|---|---|
| Deceased | 24 |
| ICS continued, still no indication | 55 |
| ICS continued, gained an indication | 5 |
| ICS discontinued | 4 |
| **Total** | **88** |

nonadherence by health care providers is more prevalent in lower-risk groups and in patients without exacerbations, in both primary and secondary care settings.[17–21] Additionally, similar to our results, overtreatment with ICS was frequently reported.[19–22]

It is important to consider the barriers to implementing the GOLD recommendations in clinical practice. For example, clinicians could be reluctant to change a winning combination when patients are clinically stable Patients may also have strong preferences regarding specific inhaled medications. Furthermore, as will be discussed in more detail later in this discussion, the criteria for stopping ICS treatment are unclear. The annual release of new GOLD strategies could pose a challenge for clinicians to stay up to date if recommendations change too frequently. Davis et al investigated the knowledge and application of the GOLD recommendations through a survey among primary care and secondary care physicians in 12 countries. Primary care physicians were less familiar with the GOLD strategies than respiratory specialists (58% vs 93%). Surprisingly, the respiratory physicians did not demonstrate more guideline-concordant prescribing practices for inhaled medication than the primary care physicians, suggesting that awareness does not necessarily result in greater adherence to guidelines.[10] Physicians may have followed national guidelines, which can differ from the GOLD recommendations.[15] For instance, a COPD questionnaire survey in Germany showed that most (51.4%) pulmonary specialists preferred national guidelines compared to the GOLD guidelines (40.2%).[23] It could be that not all physicians are always completely at ease with the GOLD strategy. After all, the complete strategy has been compiled by experts, but changes frequently, and, to our knowledge, has never been compared to other possible strategies.

Although we observed that some patients' inhaled medication had been appropriately adjusted in line with current guidelines, many patients without exacerbations or with low eosinophil counts were still receiving triple therapy, and others remained on LABA/ICS. The 2025 strategy offers additional nuance for the latter group, recommending the continuation of LABA/ICS for clinically stable patients without asthma, no exacerbations, and low symptom burden. However, only a small percentage (4.2%) of LABA/ICS users in our study cohort would have received the correct medication regimen if the 2025 nuances had been in effect at the time of the 2023 assessment. Adherence to the strategy changed between 2022 and 2023 in 263 patients, with some treatments going from adhering to the 2022 strategy to nonadhering to the 2023 strategy (n=102) and vice versa (n=161). Although we found that the guideline adherence rate improved slightly from 51.6% in 2022 to 57.3% in 2023, some of this improvement may be due to other factors than better adherence to the strategy per se. Not all changes in adherence could be attributed to intentional medication adjustments in response to updated recommendations, nor to the revised guidelines (in)validating existing treatment regimens. Furthermore, in a substantial proportion (n=60), changes between adherence to the 2022 and 2023 strategy were driven by variations in key clinical variables between the two assessment periods. For instance, a hospitalisation in 2019 could justify the prescription of an ICS in the 2022 assessment, as it occurred within the previous three years. However, since this hospitalisation occurred more than three years prior to the 2023 assessment, it no longer justified ICS use according to the 2023 GOLD strategy. The importance of the specific timeframes used for assessing appropriate medication was also demonstrated in our detailed assessment of ICS use within the study population.

The vast majority of our study population (83.6%) was treated with an ICS in 2023, with a substantial proportion seemingly being overtreated with ICS (25.4%), putting them at risk of side effects while probably having minimal or no benefit from the ICS. The GOLD strategies provide treatment algorithms and criteria for initiating ICS treatment, either as initial treatment or when escalation is required due to persistent exacerbations.[5,6] However, it is not specified in the GOLD strategy which eosinophil count to use for determination of treatment (eg most recent or highest value known), despite previous studies having demonstrated variability in eosinophil counts over time within individual COPD patients.[24–26] Furthermore, the GOLD strategies do not specify the timeframe for patients who are currently exacerbation-free on ICS treatment. In other words: after how many years without exacerbations is ICS treatment still justified? This absence of clear guidance regarding which eosinophil count and which timeframe for exacerbations should be applied for ICS indication is a key limitation of the current GOLD strategy. As shown by our study, increasing the timeframes for eosinophils and exacerbations increases the proportion of patients with an indication for ICS. It is possible that patients classified in our study as overtreated with ICS due to lack of recent exacerbations, originally had valid reasons for initiating ICS therapy, such as a history of multiple exacerbations at that time.

Currently, there is no conclusive evidence, and consequently no consensus, on how to manage ICS treatment once a patient becomes stable It is unclear after how many years of clinical stability without exacerbations ICS withdrawal should be considered, and whether this even should be considered if the initial indication for ICS was valid. Studies investigating the withdrawal of ICS in patients with COPD showed contradicting results.[27] Some studies showed that stopping ICS abruptly resulted in more exacerbations, a decline in lung function, and reduced quality of life. This was seen both in studies that compared ICS continuations to placebo,[27–29] as in one study that continued long-acting bronchodilators in both groups.[30] In contrast, other studies that continued long-acting bronchodilators reported no statistically significant differences in exacerbation rates between the ICS continuation and withdrawal group.[31–34] However, these results should be interpreted with caution due to the limited follow-up periods of 3 to 6 months,[31–34] observed trends toward increased exacerbations in patients who discontinued ICS,[34] and a higher risk of exacerbations in patients with elevated eosinophil counts.[33] The WISDOM trial is the largest trial to date investigating ICS withdrawal in COPD patients with prior exacerbations.[35] In contrast to the previous mentioned trials, this study first tapered the dose of ICS, rather than stopping abruptly. This approach aligns with the GINA guideline recommendations for ICS treatment in stable patients with asthma.[36] The WISDOM trial found no significant increase in exacerbations in the ICS withdrawal group (hazard ratio (HR) 1.06; 95% CI: 0.94–1.19). Post-hoc analysis of triple therapy users prior to enrolment showed similar results. However, the follow-up of less than one year and the observed trends towards more severe exacerbations (HR 1.20; 95% CI: 0.98–1.48), greater $FEV_1$ decline (−38 mL), and worse St. George's Respiratory Questionnaire (SGRQ) scores (+0.55 vs −0.42) in the withdrawal group raise potential concerns.

The GOLD strategy lacks a recommendation regarding the withdrawal of ICS in clinically stable patients with COPD. GOLD only recommends considering ICS de-escalation in cases of side effects such as pneumonia, with the sidenote that discontinuing ICS in patients with eosinophil counts above 0.3 $x10^9$/L could lead to more exacerbations.[1] Other guidelines provide more specific guidance on when ICS could be discontinued if patients remain free of exacerbations. For instance, the most recent Dutch COPD guidelines for both primary and secondary care suggest considering abrupt withdrawal of ICS after two years without exacerbations,[2,3] even though it is acknowledged in the latter that this recommendation is not supported by any evidence.[3] Since one of the primary reasons for initiating ICS is to reduce exacerbations, stopping treatment when it has been successful (ie no exacerbations) seems contradictory. In our study, only a small proportion of patients (6.6%) consistently had eosinophil counts below 0.3 $x10^9$/L and remained free of exacerbations and hospitalisations for at least five years. Furthermore, it should be noted that a recent systematic review and meta-analysis showed a reduction in all-cause mortality in COPD patients with ICS treatment.[37] The effect of discontinuing ICS on this mortality benefit is unknown. The lack of evidence on ICS withdrawal in stable patients may make clinicians reluctant to stop ICS therapy. This is reflected in our study by the small proportion of ICS users whose indication under the 2022 strategy no longer applied in 2023, and who actually had their ICS discontinued (4 out of 59). Conducting a prospective study with long-term follow-up to evaluate the impact of ICS discontinuation in clinically stable COPD patients could help fill this evidence gap.

Our study has some limitations. The data were extracted from a single secondary care centre in the Netherlands, yet including multiple prescribers. As shown in the baseline characteristics, our study population includes a relatively high proportion of triple therapy users, suggesting that our hospital may have a more severe COPD population, as indicated by the mortality rate. Although the hospital serves as a regional centre of expertise due to its coordination of care, its COPD population is comparable to those of general hospitals. In the Netherlands, COPD care is guided by either the GOLD strategy or the national guideline, which largely align with GOLD recommendations on pharmacological treatment.[2,3] Therefore, we expect that the findings of this study are also applicable to other countries where COPD care is guided by the GOLD strategy. This is supported by the similarity of our results to those of previous studies in a secondary care setting in other countries.[16–20,22] Consistent with previous studies, our study showed that clinicians were less likely to adhere to the GOLD recommendations regarding inhaled medication when treating low-risk patients.[17–21] Moreover, Rodrigues et al showed in a Dutch primary care setting that 36.4% of the COPD patients did not receive any inhaled medication within the first three months after diagnosis.[38] As most COPD patients in the Netherlands are treated in primary care, overall adherence to the GOLD strategy may be even lower in the general population than in our study cohort. Furthermore, patients with missing CCQ or eosinophil data were excluded from the study cohort. This may have

introduced some selection bias towards patients with more severe COPD, since these values are more likely to be missing in patients with stable, less severe disease. This is also reflected in treatment patterns, with the excluded cohort receiving triple therapy less frequently. One might argue that in most patients, according to the latest recommendations by GOLD, it is not possible to determine whether treatment is appropriate without knowing the eosinophil count and CCQ score or another disease burden questionnaire, such as the Medical Research Council (MRC) or COPD Assessment Test (CAT). Physicians should be encouraged to assess the eosinophil count and disease burden in all COPD patients, including those with less severe and more clinically stable disease, to determine appropriate treatment. Due to the design of the study, it was not possible to account for the potential use of systemic corticosteroids prior to eosinophil testing. Similarly, appropriate de-escalation of ICS treatment based on the presence of pneumonia or other side effects could not be assessed. Given that, according to our assessment, only a small number of patients were undertreated, we expect that this did not occur often. Also, prednis(ol)one prescriptions were used as a surrogate for exacerbations. Exacerbations could have been missed if pharmacy records were not available in the "Landelijk Schakelpunt (LSP)" or if exacerbations were not treated with prednis(ol)one. However, given that most pharmacies participate in the LSP (95%) and most patients granted consent (90%), we assume that the number of prednisone prescriptions not recorded in our dataset is limited.[12] Furthermore, based on our clinical experience and in line with GOLD and national guidelines, we anticipate that it is very uncommon for patients with COPD exacerbations to be treated with antibiotics without the use of prednisone. Due to the limitations of this retrospective study, our database did not contain all factors that could influence adherence to the guidelines at patient-, prescriber- or time-related levels. These factors, for instance, include patient preferences, side-effects, and previous ICS response. As a next step following this descriptive study, a prospective study incorporating these factors in a multivariate regression analysis or an in depth qualitative study would help clarify what drives guideline non-adherence.

## Conclusion

A substantial proportion of patients with COPD are not treated in accordance with prevailing recommendations in the GOLD strategy, particularly those with a low eosinophil count, those without exacerbations or hospitalisations, and those with a less severe GOLD classification. This study demonstrates that even after the 2023 updates to inhaled medication recommendations, guideline adherence improved only slightly and few had their medication actively adjusted, highlighting the real-world challenges of implementing guideline recommendations in daily practice. While there may be valid reasons for deviating from the guidelines, these findings should prompt treating physicians to reconsider the appropriateness of the current treatment for their patients. ICS overtreatment was frequent, posing an increased risk of unwanted short and long term side effects. This study highlighted key limitations of the current GOLD strategy, including the lack of consensus on whether to continue ICS treatment in stable COPD patients who initially had an appropriate indication, and the absence of clear guidance on which eosinophil count and which exacerbation timeframe should be use to guide ICS continuation. Conducting additional consensus studies on ICS tapering could provide clearer guidance for clinicians on which patients can safely discontinue ICS and which cannot, potentially leading to greater adherence to guidelines in clinical practice.

## Data Sharing Statement

All data relevant to the study are included in the article or uploaded as supplementary information. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

Ethics approval for this study was waived by the Institutional Research Board of the Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands (identification number 2023-037). This research was declared outside the scope of the Medical Research Involving Human Subjects Act, as it used routinely collected healthcare data that had been pseudonymized. The Institutional Research Board of Franciscus Gasthuis & Vlietland waived the requirement to obtain informed consent, because the data is collected in a coded (pseudonymized) form, and obtaining consent is not feasible due to the large number of patients.

## Acknowledgments

We are grateful to dr. Simone Rauh for her help in processing the data.

## Author Contributions

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

## Funding

The faculty received an unrestricted grant from Chiesi Pharmaceuticals B.V. Furthermore, the funding includes contributions from the research group in the Franciscus Gasthuis & Vlietland hospital and transformation funds from health insurance companies.

## Disclosure

LC: the faculty has received an unrestricted grant from Chiesi Pharmaceuticals B.V (outside the scope of this work). JvB: has received grants and/or consultancy fees from ALK-Abello, AstraZeneca, Chiesi, European Commission COST (COST Action 19132), GSK, Novartis, Pfizer, Teva, Trudell Medical, and Vertex, outside the submitted work and all paid to his institution (UMCG). HK: has received research/educational grants and served on advisory boards for Boehringer Ingelheim, GSK and Novartis, and has served on advisory boards for AstraZeneca and Chiesi. JiV: reports unrestricted faculty research grants from GSK, Teva, AZ, Chiesi, Sanofi, and speaker fees from AZ, GSK, Sanofi, Chiesi, Stichting RoLeX and Health Investment. The authors report no other conflicts of interest in this work.

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