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REVIEW

Real-World Outcomes of Single-Inhaler Triple Therapy Prescribed by General Practitioners in Managing Chronic Obstructive Pulmonary Disease: A Systematic Literature Review

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ABSTRACT

BACKGROUND: The benefits of triple therapy for Chronic Obstructive Pulmonary Disease (COPD) have been established in two 52-week phase-3 randomized controlled trials. The current systematic literature review (SLR) appraised available evidence on the real-world outcomes of single-inhaler triple therapy (SITT) when prescribed by general practitioners (GPs).
METHODS: Using the PICOS (Population, Intervention, Comparator, Study design) framework, a literature search was conducted to identify suitable studies for the review. PubMed and Embase databases were searched, and Rayyan was used to screen articles for inclusion. The study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.
RESULTS: 1,379 non-randomized clinical studies published between 2020 and 2024 were identified from the literature search. 1,367 articles were later excluded from the review (duplicates: n = 119; not eligible: n = 1,248), leaving 12 studies for inclusion. 10 studies were single-armed, while 2 were comparative. 7 studies were from Germany, 3 from the United Kingdom, and 1 each from France, Greece, and Belgium. The SITT combinations studied were beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide (n = 9) and fluticasone furoate/umeclidinium bromide/vilanterol (n = 3). One study did not specify this. One study reported on inhaler use, 8 on adherence, 2 on drug persistence, 5 on lung function, 3 on exacerbations, and 6 on health-related quality of life.
CONCLUSIONS: We found evidence of possible benefits for SITT prescribed by GPs on real-world outcomes. Nevertheless, the evidence is limited in quantity and quality, and future real-world studies need to confirm our findings.

Keywords

COPD, Fixed-dose combination triple therapy, Single-inhaler triple therapy, Real-world outcomes

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive heterogeneous condition characterized by symptoms of dyspnea and chronic cough with sputum which limits proper airflow in the lungs [1-6]. COPD affects about 300 to 400 million persons worldwide, with the disease burden predicted to increase due to the aging population and the sustained exposure to risk factors [1,2]. Though preventable and treatable, COPD is the world's third leading cause of death [1,2,7]. COPD underdiagnosis and undertreatment might lead to other non-communicable diseases such as lung cancer, lung infection, and heart problems which may worsen patients' health-related quality of life (HRQoL), with increased economic costs [2,6,7].

Often, dual combination therapy of inhaled corticosteroids plus long-acting beta-agonist (ICS + LABA) or long-acting beta-agonist plus long-acting muscarinic antagonist (LABA + LAMA) is prescribed for COPD maintenance. However, patients whose symptoms remain uncontrolled are escalated to triple therapy (multi-inhaler or single-inhaler) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations [1].

In Europe, Italy is the only EU5 country, and one of only two countries along with Austria, that restricts the prescription of single-inhaler triple therapy (SITT) to specialists, due to concerns about prescription appropriateness and fears of uncontrolled SITT use increase [8].

However, the vast majority of European countries have allowed general practitioners (GPs) to prescribe SITT, with a recent United Kingdom (UK) survey highlighting that GPs

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prescribed SITT to control COPD symptoms, ease treatment use, enhance quality of life, lessen exacerbation frequency, and improve lung function [9]. This approach aligns with the 2024 GOLD report, which summarizes the role of SITT in COPD management, and its potential to improve health-related outcomes, including HRQoL, noting that "single inhalers improve adherence to treatment and may be more effective and convenient than multiple inhaler therapy" [1]. Though three 52-week randomized controlled trials (RCTs) (IMPACT [10], ETHOS [11], and TRIBUTE [12]) have evidenced the benefits of SITT, some authors [13] questioned their applicability in real-life settings.

We therefore conducted a systematic literature review (SLR) to investigate and summarize existing evidence on the possible benefits of SITT prescribed by GPs on real-world outcomes.

METHODS

Search strategy and study selection criteria

The systematic literature (SL) search was conducted by two researchers (LAO and MB) who used the PICOS [14] (Population, Intervention, Comparator, Outcome, Study design) framework (Supplementary Table S1) to develop search strings from diverse related search terms and synonyms (Supplementary Table S2). The search strings incorporated Medical Subject Headings (MeSH) and Elsevier's authoritative life science thesaurus (Emtree) search terms used to search PubMed and Embase databases respectively (Supplementary Table S3).

The search results from PubMed and Embase were downloaded and uploaded to Rayyan [15], an artificial intelligence web tool for systematic reviews. Here, the reviewers identified and resolved duplicates, and then screened the title and abstract of the remaining articles to reach eligible studies for the review. The reviewers' results were harmonized where conflicts arose, with a third reviewer (LP) consulted where necessary.

Full-text and abstract publications of the eligible studies were sourced for further screening. Articles that could not be retrieved were excluded, alongside those that did not meet the inclusion criteria in Supplementary Table S4.

The study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [16] guidelines.

Data extraction and collection

Data extraction of the study characteristics and the reported preselected outcomes was accomplished by one researcher (LAO) who manually retrieved and collected data from the included studies and double-checked for validation by a second investigator.

Study outcomes

Data on the four preselected outcome domains, including drug utilization (inhaler use, medication adherence and persistence); lung function; COPD exacerbations; and HRQoL were collected pre- and post-study. The inhaler use (device error) data were fetched directly from the studies, and the medication adherence and persistence data were collected as reported using the test of adherence to inhalers (TAI) and the proportion of days covered (PDC) tools. The TAI tool rates adherence in points, as either good (50 points), intermediate (46–49 points), or poor (≤ 45 points); the PDC tool rates adherence as either high (≥ 80%) or low (< 80%).

The lung function parameters, including forced expiratory volume in one second (FEV1), percentage of the predicted value of FEV1 (FEV1%), forced vital capacity (FVC), the ratio of FEV1 to FVC (FEV1/FVC), the specific breathing resistance (sRtot), the specific airway resistance (sRaw), the residual volume (RV), the total lung capacity (TLC), and the inspiratory capacity (IC) were collected as reported by studies. The exacerbations in COPD data were collected from studies according to severity (mild, moderate, moderate-severe, and severe) and timepoint (at baseline and 6 or 12 months after the study). The HRQoL data were collected as reported by the various preselected indicators: the COPD assessment test (CAT) score; the COPD condition reported using the visual analogue scale (VAS); the treatment safety parameters, including, the on-treatment (SITT) adverse events (AEs), pneumonia incidence, mortality rate, and rescue medication use.

Data analysis and presentation

A descriptive analysis of post- versus pre-study changes in mean, median, and percentage was performed on the results of all four preselected outcomes reported by the studies, using Microsoft Excel [17]. The study outcomes were presented in tables as mean, median, or percentage differences from baseline.

Risk of bias in included studies

Two reviewers (LAO and MB) accomplished the risk of bias (RoB) assessment by inspecting the RoB involved in the studies using ROBINS-I [18] (Cochrane's RoB assessment tool for non-randomized studies of interventions—NRSIs). ROBINS-I investigated bias within the seven domains of bias: i) confounding, ii) selection of participants in the study, iii) classification of interventions, iv) deviations from intended interventions, v) missing outcome data, vi) measurement of outcomes, and vii) selection of the reported result.

The RoB present in the four preselected outcomes was determined by how well the domains' signaling questions were appraised, with the judgment of either *Low, Moderate, Serious,* or *Critical* applied to each domain. The outcomes' overall RoB followed the domains', with individual studies copying from outcomes. The RoB results were envisioned in robvis [19] (Cochrane's web-based visualization tool for RoB assessment).

RESULTS

Study identification and selection

The literature search identified 1,379 studies from PubMed (n = 143), Embase (n = 1,225), Google Scholar (n = 7), and manual search (n = 4). The search results from PubMed and Embase were uploaded to Rayyan for synthesis, deleting 119 duplicate articles and leaving 1,249 studies for screening. Articles screened for eligibility were 1,260 (PubMed and Embase: n = 1,249; Google Scholar: n = 7; manual search: n = 4), excluding 1,188 (PubMed and Embase) articles in the first round of screening. Of the 72 remaining studies, 60 articles were later excluded after full-text screening. In the end, 12 studies (ten [21,23-31] non-comparative and two [20,22] comparative) that met the inclusion criteria were included in the review. The study selection process and reasons for exclusion from the review are documented in Figure 1.

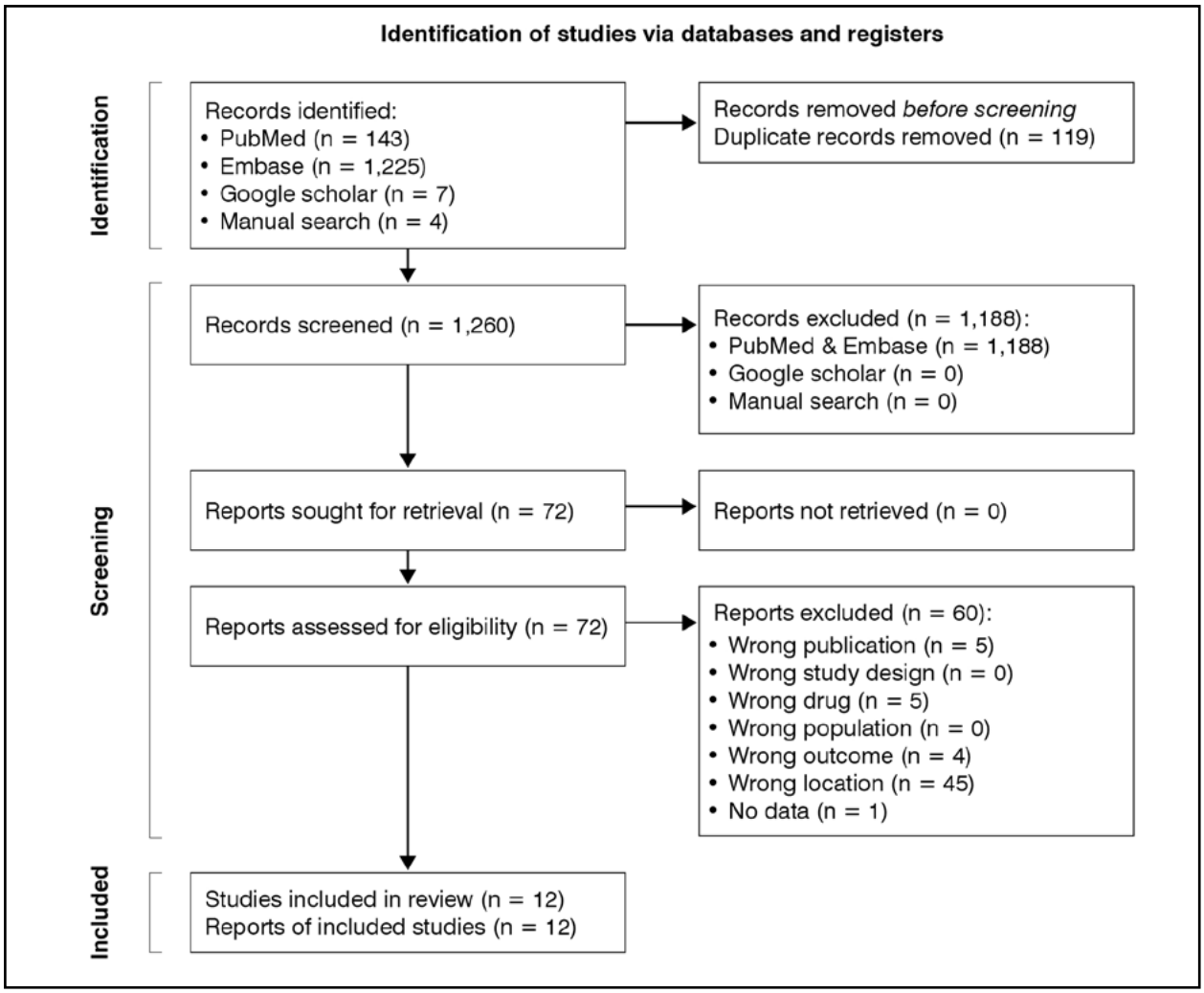

Figure 1. *The PRISMA flow diagram*

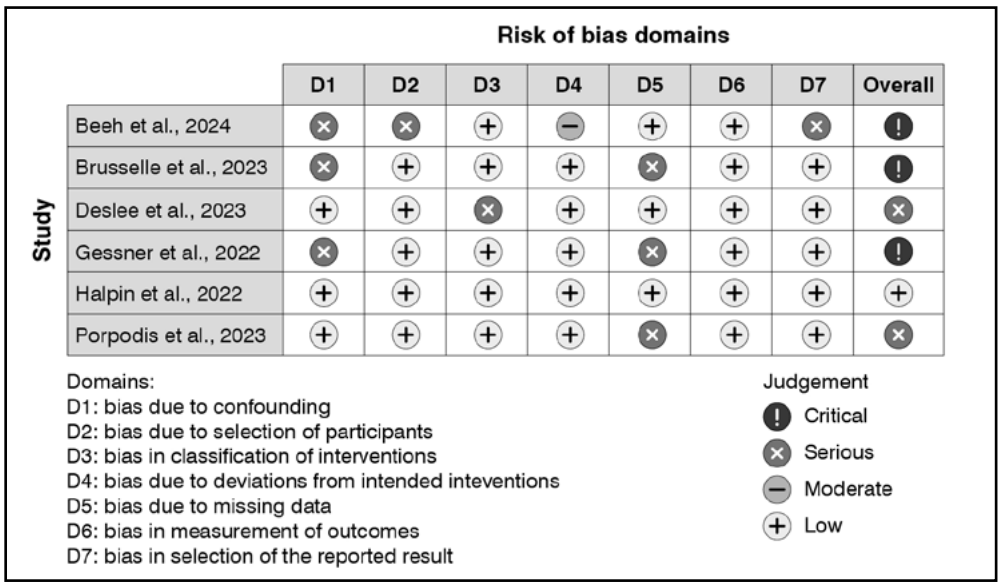

Figure 2. *Risk of bias (RoB) in included studies (n = 6)*
Note: Six full-text articles were screened for risk of bias, leaving out six abstract publications

Study characteristics

The twelve [20-31] studies (six abstracts [24-27,29,31] and six full-text [20-23,28,30]) included in this SLR were observational cohort studies written in English and published between 2020 and 2024. These studies from Germany (n = 7) [21,24-29], the UK (n = 3) [22,31], France (n = 1) [20], Greece (n = 1) [23], and Belgium (n = 1) [30] were conducted on adult COPD patients initiated on SITT (beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide—BDP/FF/G [22,23-30] and fluticasone furoate/umeclidinium bromide/vilanterol—FF/UMEC/VI [21,22,31]) in the primary care setting. The study participants were followed for over two months, and the reported preselected outcomes were inhaler use [23], medication adherence [20-23,25,28-30] and persistence [20,22]; lung function [21,23,24,28,30]; COPD exacerbations [21,23,31]; and HRQoL [21,23,26-28,30]. Supplementary Table S5 displays the study characteristics; Tables S6 and S7 show the baseline characteristics of the studied population.

Risk of bias in included studies

Six [20-23,28,30] full-text articles were assessed for RoB, leaving out six [24-27,29,31] abstract publications. The overall RoB exposed three (50%) [21,23,28] studies with critical, two (33.3%) [20,30] with serious, and one (16.7%) [22] with low RoB (Figure 2). The RoB in the four outcome domains is presented in weighted bar plots in Figures 3, 4, 5, 6, and 7.

In Figure 2, serious RoB was due to confounding (three studies [21,23,28]), selection of participants (one study [21]), classification of interventions (one study [20]), missing data (three studies [23,28,30]), and selection of the reported result (one study [21]). One study [21] had a moderate RoB due to deviations from the intended interventions.

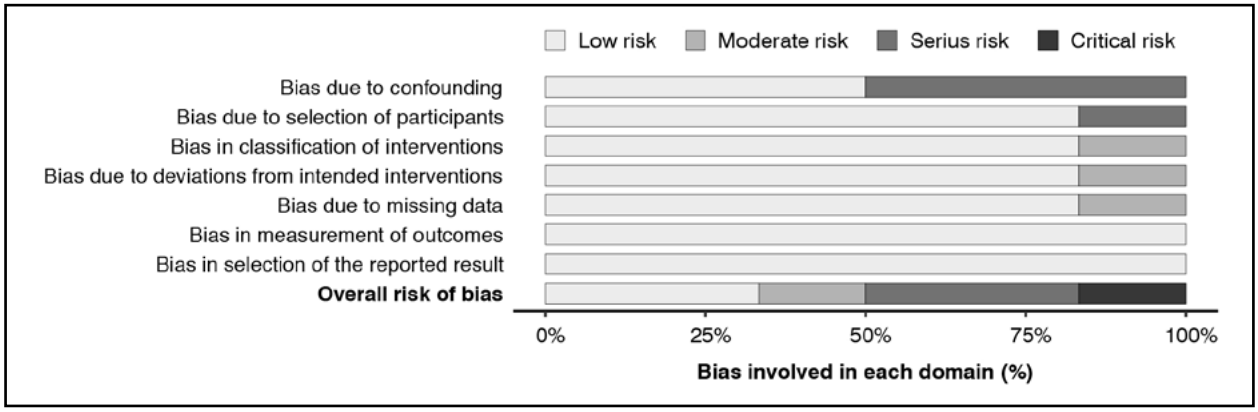

Figure 3. *Risk of bias (RoB) in outcomes: medication adherence (n = 6)*
Note: Six full-text articles were screened for risk of bias, leaving out six abstract publications.

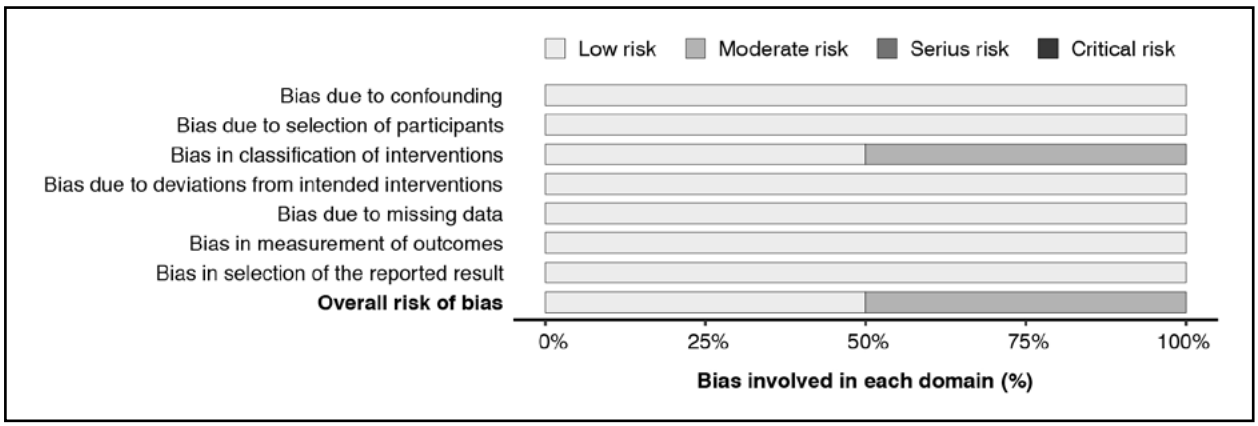

Figure 4. *Risk of bias (RoB) in outcomes: medication persistence (n= 2)*
Note: Six full-text articles were screened for risk of bias, leaving out six abstract publications

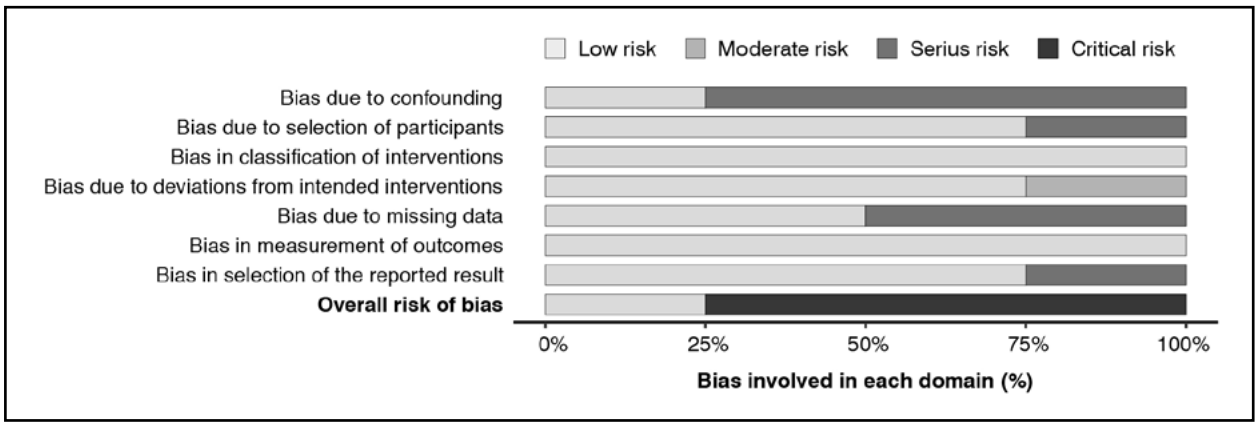

Figure 5. *Risk of bias (RoB) in outcomes: lung function: FEV1 (n = 4)*
FEV1: forced expiratory volume in one second
Note: Six full-text articles were screened for risk of bias, leaving out six abstract publications

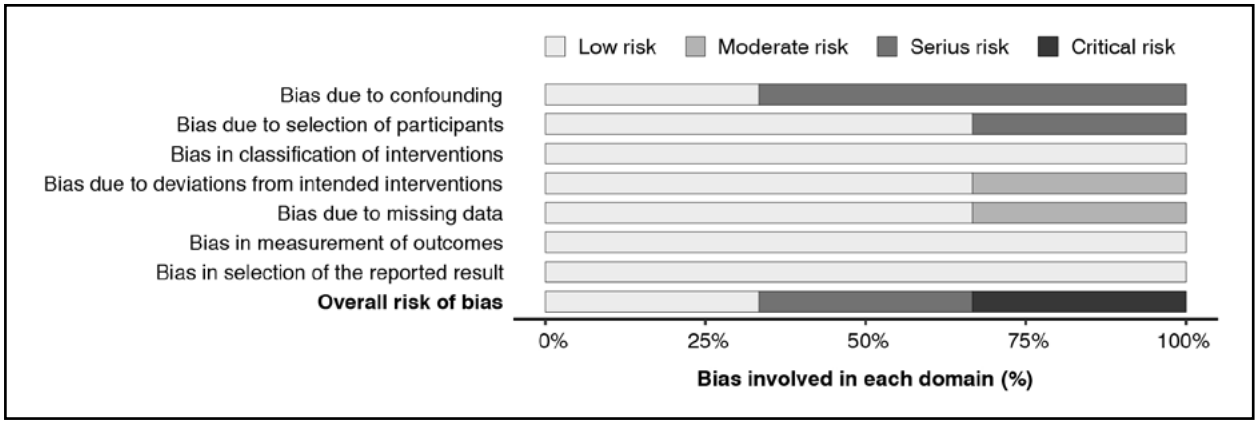

Figure 6. *Risk of bias (RoB) in outcomes: COPD exacerbation (n= 2)*
COPD: chronic obstructive pulmonary disease
Note: Six full-text articles were screened for risk of bias, leaving out six abstract publications

Still, in Figure 2, one study [21] had serious RoB in three RoB domains (confounding, selection of participants, and selection of the reported result), two studies [23,28] in two (confounding and missing data), and another two [20,30] in one each (classification of interventions and missing data respectively).

The serious RoB was cited in four outcomes, medication adherence (two domains: confounding and selection of participants; Figure 3), lung function (three domains: confounding, selection of participants, and missing data; Figure 5), COPD exacerbation (two domains: confounding and selection of participants; Figure 6), and HRQoL (four domains: confoun-

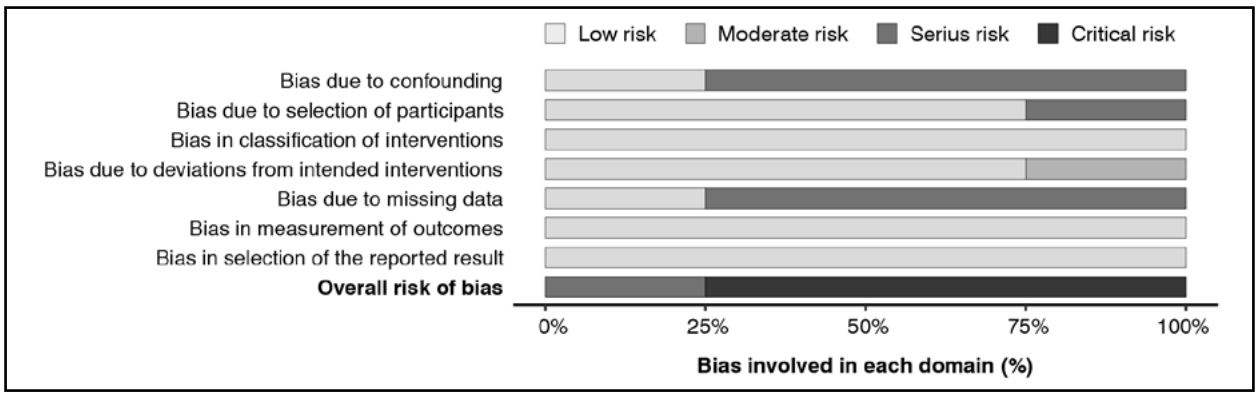

Figure 7. *Risk of bias (RoB) in outcomes: HRQoL—CAT, VAS (n = 4)*
COPD: chronic obstructive pulmonary disease; CAT: COPD assessment test; VAS: visual analogue scale
Note: Six full-text articles were screened for risk of bias, leaving out six abstract publications

ding, selection of participants, missing data, and selection of the reported result; Figure 7); apart from medication persistence which had a moderate RoB (one domain: classification of interventions; Figure 4).

Study outcomes

The real-world findings of these studies were documented at different time points (>2 [20], 3 [24], 6 [22,25-29,31], 12 [22], and 18 [22] months) or visits (V2 [21,23,30], V3 [21,23,30], V4 [21], and V5 [21]) depending on the study duration. Supplementary Tables S8 and S9 display the results of the four preselected outcome types reported by ten [21,23-31] non-comparative and two [20,22] comparative studies respectively.

Drug utilization

In this review, one study [23] reported on inhaler use; eight [20-23,25,28-30] on medication adherence [six [21,23,25,28-30] non-comparative studies measured adherence using the test of adherence to inhalers (TAI), while two [20,22] comparative studies used the proportion of days covered (PDC) tool]; and two [20,22] on medication persistence.

Inhaler use errors

Brusselle, 2023 [23] discovered a 12.5% (P = NR) reduction from baseline in the number of inhaler device errors among patients on SITT, with 0% (P = NR) critical inhaler device errors at the end of follow-up (Table I).

Adherence

Significant improvement in the overall mean TAI score from baseline was reported in one study, Beeh, 2024 [21] (1.60, P < 0.0001). Another study, Porpodis, 2023 [30] comparing the TAI score between visits 2 and 3 reported no significant improvement (0, P = 0.216) between visits. On the other hand, Halpin, 2022 [22] realized an overall improvement of 0.28 (P = NR) in the mean PDC score six months after switching MITT patients to SITT, almost similar to the significant improvements of SITT vs MITT in the 6- (0.22, P < 0.001), 12- (0.22, P < 0.001) and 18- (0.22, P < 0.001) month follow-up (Table I).

Regarding good adherence, Beeh, 2024 [21] (14.60%, P < 0.0001) and Criée, 2022 [25] (10.10%, P < 0.0001) reported a significant improvement in the percentage of SITT patients having good adherence. Brusselle, 2023 [23] (12.50%, P = NR), Gessner 2022 [28] (8.70%, P = NR), and Höevelmann, 2020 [29] (12.10%, P = NR) reported a positive percentage change in good adherence among SITT patients without reaching statistical significance. Again, Porpodis, 2023 [30], comparing visits 2 and 3 stated a 5.60% (P = NR) improvement in the percentage of SITT patients with good adherence between visits (Table I).

In the 18-month follow-up, Halpin, 2022 [22] revealed a significant improvement of 23.3% (P < 0.001) in high adherence (PDC ≥ 80%) among patients on SITT over their MITT counterparts. This significant trend was also observed earlier at 6- (22.7%, P < 0.001) and 12- (19.5%, P < 0.001) month follow-up respectively (Table I).

Interestingly, Deslee, 2023 [20] did not notice a significant change in adherence between SITT and MITT patients (−0.4%, P = 0.869) who stayed on treatment for more than 90 days (Table I).

Percentage change in inhaler use						
Study	**Overall inhaler error (%)**			**Critical error (%)**		
Brusselle, 2023 [23]	- 12.5 (P = NR)			- 9.6 (P = NR)		
Average change in TAI, PDC, and adherence ratings						
Study	**TAI, overall[1]**	**PDC, overall[2]**	**Good or high (%)**	**Intermediate (%)**	**Poor or low (%)**	**Responders (%)**
Beeh, 2024 [21]	1.60 (P < 0.0001)	NR	14.60 (P < 0.0001)	NR	NR	NR
Brusselle, 2023 [23]	NR	NR	12.50 (P = NR)	- 5.20 (P = NR)	- 7.30 (P = NR)	NR
Criée, 2022 [25]	NR	NR	10.10 (P < 0.0001)	- 4.90 (P = NR)	- 5.20 (P = NR)	NR
Deslee, 2023 [20][3,4]	NR	NR	- 0.4 (P = 0.869)[4]	NA	NR	NR
Gessner, 2022 [28]	NR	NR	8.70 (P = NR)	- 4.0 (P = NR)	- 4.60 (P = NR)	NR
Halpin, 2022 [22][3]	NR	0.28 (P = NR)[5]; 0.22 (P < 0.001)[6]	23.3 (P < 0.001)	NA	NR	NR
Höevelmann, 2020 [29]	NR	NR	12.10 (P = NR)	- 7.40 (P = NR)	- 4.70 (P = NR)	66.9
Porpodis, 2023 [30][7]	0 (P = 0.216)[7]	NR	5.60 (P = NR)[7]	4.10 (P = NR)[7]	1.60 (P = NR)[7]	NR
Median change in drug persistence between SITT and MITT patients						
Study			**Duration persisted on therapy**			
Deslee, 2023 [20]			46 days (P < 0.001)			
Halpin, 2022 [22]			4.1 months (P = NR)			
Median change in drug persistence (SITT vs MITT) stratified by the prescribing physician						
Study	**Initiating physician**		**Duration persisted on therapy (days)**			
Deslee, 2023 [20]	Primary care physician		61 (P < 0.001)			
	Pulmonologist		38 (P = 0.001)			
	Other/unknown		116 (P = 0.042)			

Table I. *Inhaler use, adherence, and persistence. Supplementary data in Tables S8 and S9*

MITT: multiple-inhaler triple therapy; NA: not applicable; NR: not reported; PDC: proportion of days covered; SITT: single-inhaler triple therapy; TAI: test of adherence to inhalers

[1] TAI adherence ratings: good (50 points), intermediate (46 – 49 points) or poor (≤ 45 points); [2] PDC adherence ratings: high (≥ 80%) or low (≤ 80%); [3] Adherence compared between SITT and MITT patients using the PDC tool; [4] Adherence measured amongst patients with ≥ 90 days of drug persistence; [5] Change in mean PDC pre- and 6 months post-SITT; [6] 18-month mean PDC change between groups; [7] Mean change in adherence between visits 2 and 3

About intermediate adherence, Brusselle, 2023 [23] (−5.20%, P = NR), Criée, 2022 [25] (−4.90%, P = NR), Gessner 2022 [28] (−4.0%, P = NR), and Höevelmann, 2020 [29] (−7.40%, P = NR) reported a reduction in the percentage of SITT patients having intermediate adherence, however, the levels of significance were not established. Still, Porpodis, 2023 [30], comparing visits 2 and 3 displayed a 4.10% (P = NR) reduction in the percentage of SITT patients with intermediate adherence between visits (Table I).

Concerning poor adherence, Brusselle, 2023 [23] (−7.30%, P = NR), Criée, 2022 [25] (−5.20%, P = NR), Gessner, 2022 [28] (−4.60%, P = NR), and Höevelmann, 2020 [29] (−4.70%, P = NR) reported a reduction in the percentage of SITT patients with poor adherence, though, no P-values were established. Porpodis, 2023 [30], comparing visits 2 and 3 also demonstrated a 1.60% (P = NR) reduction in the percentage of SITT patients with poor adherence between visits (Table I).

For adherence responders, Höevelmann, 2020 [29] reported that 66.9% (P = NR) of SITT patients previously on poor and intermediate adherence stepped up to higher levels of adherence respectively (Table I).

Medication persistence

Two studies, Deslee, 2023 [20] (46 days, P < 0.001) and Halpin, 2022 [22] (4.1 months, P = NR) reported pro-longed persistence on therapy amongst patients on SITT versus those on MITT (Table I). Moreover, for each prescribing physician [GPs: 61 days (P < 0.001); pulmonologists: 38 days (P = 0.001); others: 116 days (P = 0.042)], Deslee, 2023 [20] discovered a

Improvement in average lung function						
Study	**FEV1 (mL)**	**FEV1 (%)**	**FVC (mL)**	**FEV1/FVC**	**TLC (mL)**	**IC (mL)**
Beeh, 2024 [21][1]	93 (P < 0.0001)	4.10 (P < 0.0001)	64.0 (P < 0.0001)	NR	NR	NR
Brusselle, 2023 [23][1]	60 (P = NR)	NR	60.0 (PNR)	NR	NR	NR
Criée, 2020 [24][2]	73.42 (P = 0.0453)	NR	88.61 (P = 0.0069)	NR	44.66 (P = 0.4885)	76.26 (P = 0.1287)
Gessner, 2022 [28][1]	54.40 (P < 0.05)	2.0 (P < 0.05)	60.0 (P < 0.05)	1.21 (P < 0.05)	20 (P = NS)	20 (P = NS)
Porpodis, 2023 [30][1]	200 (P < 0.0001)	5.70 (P < 0.0001)	NR	NR	0.99 (P < 0.001)	NR

Reduction in average lung function			
Study	**RV (mL)**	**sRtot (kpa*s)**	**sRaw (kpa*s)**
Criée, 2020 [24][2]	- 50.57 (P = 0.8404)	NR	- 0.35 (P = 0.0013)
Gessner, 2022 [28]	- 100 (P < 0.05)	- 0.23 (P < 0.05)	NR

Average or percentage change in exacerbation					
Study	**Overall**	**Mild**	**Moderate**	**Moderate-severe**	**Severe**
Beeh, 2024[21, β]	- 1.20 (P = NR)	- 0.40 (P = NR)	- 0.60 (P = NR)	NR	- 0.10 (P = NR)
Brusselle, 2023[23, β]	NR	NR	- 0.80 (P = NR)	NR	- 0.27 (P = NR)
Rothnie, 2022[31, §]	NR	NR	- 4.30 (P < 0.0001)	- 6.90 (P < 0.0001)	- 3.30 (P < 0.0001)

Table II. *Lung Function and COPD Exacerbation.* Supplementary data in Tables S8 & S9
FEV1: forced expiratory volume in one second; FVC: forced vital capacity; kpa, kilopascal; IC: inspiratory capacity; NR: not reported; NS: not significant; sRaw: specific airway resistance; sRtot: specific breathing resistance; RV: residual volume. TLC: total lung capacity
[1] Data documented according to spirometry readings; [2] Weighted mean changes and highest p-value among the groups stratified by prior medication (ICS/LABA, LABA/LAMA, MITT);[3] Mean changes at 12 months follow-up, exacerbations classified according to GOLD (Global Initiative for Chronic Obstructive Lung Disease); [4] Percentage changes at 6 months follow-up.

significant difference in the days SITT patients persisted on therapy over their MITT counterparts (Table I).

Lung function

Five studies [21,23,24,28,30] reported the lung function of patients on SITT. Four [21,23,28,30] reported lung function according to the spirometry test results provided in the primary care databases. The remaining one [24] was an abstract article with no full-text information to verify this.

All five studies [21,23,24,28,30] (four [21,24,28,30] significant) reported an increase in the mean FEV1 (range: 54.40 to 200 mL), three [21,28,30] on FEV1% (range: 2.0% to 5.70%; P < 0.05), four [21,23,24,28] (three [21,24,28] significant) on FVC (range: 60.0 to 88.61 mL), one [28] on FEV1/FVC (1.21; P < 0.05), three [24,28,30] (one [30] significant) on TLC (range: 0.99 to 44.66 mL), and two [24,28] on IC (range: 20.0 to 76.26 mL; P = NS).

Two studies [24,28] (one [28] significant) reported a reduction in the mean RV (range: −50.57 to −100 mL), one [28] on sRtot (range: −0.23 kpa*s; P < 0.05), and one [24] on sRaw (range: −0.35 kpa*s; P = 0.0013) (Table II).

Exacerbations

In our review, three studies [21,23,31] reported exacerbations suffered by patients on SITT at the 6- or 12-month follow-up. Two studies [21,23] noticed a reduction in the mean number of exacerbation severity and one [31] in the percentage of patients suffering exacerbations (Table II).

HRQoL

Six [21,23,26-28,30] studies reported the health status of patients after SITT initiation using CAT. All studies experienced a reduction in the mean CAT score from baseline (Table III).

Two studies [21,23] reported the mean adverse events suffered, pneumonia incidence, and death among SITT patients. However, all deaths reported were declared causally not related to SITT treatment. Moreover, Porpodis, 2023 [30] recorded a significant improvement in the VAS (0.4 points; P < 0.001) from baseline, besides the decreased use of rescue medication (−1.3; P < 0.001) among patients on SITT (Table III).

The average change in CAT score						
Study	**Overall**	**Cough[1]**	**Dyspnea[1]**	**Phlegm[1]**	**Chest tightness[1]**	**Responders (%)**
Beeh, 2024 [21]	- 2.60 (P < 0.0001)	NR	NR	NR	NR	NR
Brusselle, 2023 [23]	- 2.70 (P = NR)	NR	NR	NR	NR	NR
Gessner, 2020 [26]	- 2.0 (P < 0.0001)	NR	NR	NR	NR	51.10
Gessner, 2020 [27]	- 2.40 (P < 0.0001)	NR	NR	NR	NR	50.0
Gessner, 2022 [28]	- 2.70 (P < 0.0001)	- 0.40 (P < 0.0001)	- 0.40 (P < 0.0001)	- 0.40 (P < 0.0001)	NR	56.0
Porpodis, 2023 [30]	- 7.90 (P < 0.001)	1.14 (P < 0.001)	NR	1.2 (P < 0.001)	0.99 (P < 0.001)	NR

The percentage of on-treatment adverse events							
Study	**AE, overall**	**AE leading to withdrawal**	**ADR**	**SAE**	**Fatal SAE**	**Rx-related fatal SAE**	**Infective/severe pneumonia**
Beeh, 2024 [21]	16.30	3.20	5.0	4.60	0.66	0	0.60
Brusselle, 2023 [23]	28.57	14.29	NR	4.76	NR	NR	0.79

Mortality rate and average change in VAS and rescue medication use			
Study	**Mortality rate[2]**	**COPD condition (VAS)[3]**	**Rescue medication use (days)**
Beeh, 2024 [21]	0.66	NR	NR
Brusselle, 2023 [23]	4.76	NR	NR
Porpodis, 2023 [30]	NR	0.4 (P < 0.001)	- 1.3 (P < 0.001)

Table III. *CAT Score, Adverse Events, and Mortality.* Supplementary data in Tables S8 & S9

AE: adverse event; ADR: adverse drug reaction; CAT: COPD assessment test; COPD: chronic obstructive pulmonary disease; NR: not reported; Rx, treatment; SAE: severe adverse event; VAS: visual analogue scale.

[1] CAT items; [2] All mortalities are all-cause, no reports for COPD-related mortalities; [3] Self-reported COPD condition measured using VAS between visits 2 and 3

DISCUSSION

This SLR assessed and summarized the available evidence on the real-world outcomes of SITT prescribed by GPs in the primary care setting. Twelve eligible studies were reviewed to investigate the evidence in four preselected outcome domains.

In summary, this review found homogeneity in the results of the included studies. Our investigation established evidence of the potential benefits of GP-prescribed SITT on adherence and persistence, lung function, COPD exacerbations, and HRQoL. Furthermore, we revealed that medication adherence and persistence presumably drove better clinical outcomes among SITT patients regarding lung function, COPD exacerbations, and HRQoL.

In terms of findings, though not much evidence was available, the only study that reported inhalation technique discovered that patients receiving SITT improved their inhaler use by 12.5% (P = NR) [23], a scenario seen in another real-world cohort study [32] conducted in Italy where SITT prescription is restricted to specialist care physicians, that reported 11.8% (P = NR) reduction in poor inhaler usability and compliance amongst patients initiated on SITT. Interestingly, the percentage of patients who exhibited numerous device errors while on MITT reduced upon switching to SITT (-12.5%; P = NR), though data is not shown in this review [23]. Improvement in medication adherence, largely reported by TAI, was evident at all levels. The percentage of patients with good adherence increased (range: 8.70% to 14.60%; P < 0.05: n = 2) [21,23,25,28,29], while those with poor adherence decreased (range: -4.60% to -7.30%; P = NR) [23,25,28,29] upon switching to SITT. These records reflect the findings of the TRITRIAL Italian study (good: 6.50%; poor: -11.8%; P = NR) [32]. Besides, patients on SITT stayed longer on medication over their MITT counterparts (46 days; P < 0.001 [20]; 4.1 months; P = NR [22]), a situation similar, but slightly above that of a Spanish study (22 days; P < 0.001) [33] conducted in 2022 when SITT prescription was still restricted to specialist physicians until June 2023. It is important to note that both patients on SITT and MITT attained good adherence (PDC > 80%) where drug persistence was ≥ 90 days [20].

In two Italian studies where SITT was prescribed by specialists only, the lung function parameters, in one study [32], FEV1 (1.3 L, mean absolute value) was stable through the second and third visits, with FEV1(%) recording a mean change of 2.8% from initiation; whereas in the other study [34], the mean FEV1 (200 mL; $P < 0.01$) and IC (210 mL; $P < 0.05$) improved, and RV (-430 mL; $P < 0.01$) reduced significantly from baseline. These findings are in agreement with the current review, where we discovered an improvement in the mean FEV1 (range: 54.40 mL to 200 mL; $P < 0.05$: n = 4) [21,23,24,28,30], FEV1% (range: 2.0% to 5.70%; $P < 0.05$: n = 3) [21,28,30] and IC (range: 20.0 mL to 76.26 mL; P = NS) [24,28]; and a reduction in RV (range: 50.57 mL to 100 mL; $P < 0.05$: n = 1) [24,28] when patients switched to SITT.

Moreso, the mean number (rate) of overall (-1.20; P = NR) [21], moderate (range: -0.60 to -0.80; P = NR [21,23]; -4.30%; $P < 0.0001$ [31]) and severe (range: -0.10 to -0.27; P = NR [21,23]; -3.30%; $P < 0.0001$ [31]) exacerbations suffered in the year after SITT initiation declined, a similar trend in the two Italian studies which reported a decline in the overall mean exacerbation severity (-1.83; $P < 0.0001$) [34] or the percentage of patients exacerbated (-80%; P = NR) [32]; and a decline in the proportion of patients suffering from moderate (-74.4%; P = NR) [32] and severe (-21.6%; P = NR) [32] exacerbations. However, the percentage decline in patients suffering from exacerbations recorded by Richieldi et al. [32] is higher than what we discovered in this review.

Lastly, the overall patients' health status improved, achieving the significant minimal clinically important difference (MCID) of -2.0 points in CAT (range: -2.0 to -7.90; $P < 0.05$: n = 5) [21,23,26-28,30], and an enhancement in the general COPD condition (VAS: 0.4; $P < 0.001$ [30]; dyspnea: -0.40; $P < 0.0001$ [28]), results which are in harmony with those of the two Italian studies (CAT: -6.3; $P < 0.0001$; VAS: 8.04; $P < 0.0001$ [32] and CAT: -8.18; $P < 0.0001$; dyspnea: -1.01; $P < 0.001$ [34]).

Despite limited literature, one study [20] compared the medication persistence of patients on SITT vs MITT drugs prescribed by GPs, pulmonologists, and other physicians. In their findings, all prescribing physicians had significant differences in the number of days patients persisted on SITT vs MITT (GPs: 61 days; $P < 0.001$; pulmonologists: 38 days; $P = 0.001$; other physicians: 116 days; $P = 0.042$).

On a side note, one study not included in this review reported contradicting findings. Suissa *et al.*, 2022 [13] comparing SITT with non-ICS single inhaler dual combination therapies concluded increased rates of first moderate-severe and severe exacerbations, severe pneumonia, and all-cause mortality amongst patients on SITT relative to their counterparts on dual therapies. The authors clarified their results claiming to be the first real-world findings where no patient previously on ICS was initiated on SITT, as opposed to the IMPACT [10,35] and ETHOS [11,36] randomized trials which reported reductions in moderate-severe exacerbations amongst patients on SITT, arguing that these trials enrolled patients already treated with triple therapy (40%) and those prior on ICS (70% – 80%).

Overall, this review's findings aligned with those obtained in settings where SITT prescription is regulated. Though we could not ascertain the misdiagnosis or undertreatment of the patients involved, the reported study population suffered from mild, moderate, and severe exacerbations while on dual or MITT maintenance therapy, apart from 120 patients [21] who were newly initiated on SITT as their first COPD treatment. In countries like Italy where GPs are still not permitted to prescribe SITT for COPD management , we recommend reevaluation of national health policies to remove such limitation. Evidence suggests that such a policy has potential benefits for all stakeholders – GPs gain in autonomy in choosing the best treatment for their COPD patients, with consequent improved clinical outcomes (e.g., reduced hospitalizations) for patients and reduced overall costs for the system. Practical steps for implementation of such a policy to permit GPs to prescribe also this treatment would be rather simple and mainly consist in training and diagnostic support, which in any case ought to be required also for the less effective MITT they're already prescribing.

While the integration of the entire health system is desired, the GPs' inclusivity in the prescription of SITT will bridge the gap in the healthcare system, allowing them to offer the comprehensive care needed to patients. Continuous Medical Education (CME) on the GOLD guidelines for SITT prescription will also benefit patients, especially those with uncontrolled COPD symptoms. GPs should also be equipped with the proper tools for patient identification, especially those for lung function tests and ranking of the exacerbations suffered. These changes will be pivotal to the patients and the entire healthcare system.

This SLR was not short of limitations. First, the review did not follow a registered protocol for its execution. Second, the RoB assessment methods were not conducted according to

the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines to judge the certainty of evidence in each outcome assessed. Third, our SL search only included studies published in English. Thus, though not known, the elimination of significant non-English articles from the review might have influenced our findings. Lastly, the results refer to observational studies, which carry an inherent risk of unadjustable selection bias.

CONCLUSIONS

This SLR has limitations in the methodology, and the availability of additional data could increase the reliability of our findings. Nevertheless, evidence currently available does not support in any way the restriction of SITT prescription by GPs, as patients on GP-initiated SITT attained improved inhaler use, adherence, and persistence; reduced COPD exacerbations and symptoms, and improved lung function and HRQoL. The current regulatory framework under Italian Note 99 limits appropriate COPD management. Specifically, general practitioners (GPs) are restricted from prescribing single-inhaler triple therapy (SITT) and can only prescribe the same medications individually as a multiple-inhaler triple therapy (MITT). This approach contrasts with recent GOLD recommendations that encourage single inhaler use, as noted above, and discourages using inhaled steroids with bronchodilators unless necessary, instead advocating for dual bronchodilator therapy for dyspneic patients and triple therapy for those prone to exacerbations. These recommendations underscore the importance of maximizing therapy to manage COPD effectively - Note 99, limiting the use of SITT to specialists, does not seem to pursue the same goal.

The clinical impact of these limitations is considerable. For some patients, initiating SITT is delayed due to the need for specialist consultation, as access is restricted by facility availability and regional criteria. Others, managed by their GP, may only receive MITT, which is inherently more complex, often leading to lower adherence. Both scenarios—delayed initiation and the use of multiple devices—can contribute to a higher risk of exacerbations, negatively affecting respiratory function and disease progression. The treatment plan must also be renewed annually following a specialist visit and spirometry. Delays in this review often result in the interruption of prescriptions, leading to a worsening of symptoms and an increased risk of exacerbations.

Economically, these restrictions have notable repercussions. The limited access to SITT and the increased reliance on MITT elevate both immediate and long-term costs. Delays due to waiting lists for specialist consultations can postpone appropriate treatment, increasing hospital expenditures associated with managing exacerbations. On top, MITT not only has a higher acquisition cost but also decreases adherence when compared to the GP-allowed MITT, further raising the likelihood of exacerbations and hospitalizations, which are among the costliest aspects of COPD care.

From a patient-centered perspective, these limitations impact quality of life. The need to wait for specialized care or travel to designated centers poses added burdens, while the use of multiple inhalers introduces complexity that decreases adherence. This situation can lead to a negative cycle of poor disease control, more frequent exacerbations, and reduced respiratory function, all of which add to patient stress and impact overall well-being. An update to Note 99 that aligns with the latest clinical guidelines could enable more effective, patient-centered, and cost-efficient COPD care.

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Conflicts of interest
LAO is employee of AdRes, which has received project funding by Chiesi for the conduct of the study.
LP is co-owner and employee of AdRes, which has received project funding by Chiesi for the conduct of the study.
CM is the President of the Italian Thoracic Society Member of the Regional Drug Commission; declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Menarini, Guidotti, Lusofarmaco, Roche, Chiesi, GSK, Sanofi, Berlin Chemie, Astrazeneca, Boehringher Ingelheim, Zambon; Support for attending meetings and/or travel from Sanofi, Astrazeneca, Menarini

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