Position Paper

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Single-Inhaler Triple Therapy (SITT) for COPD: An Italian expert opinion paper on improving clinical outcomes and equity of therapeutic access

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of global morbidity and mortality, with significant burden in Italy. Prevalence estimates vary by data source: Health Search data indicate a prevalence of 2.7% among adults, whereas population-based analyses report higher estimates of approximately 5.6%. Triple therapy combining a long-acting muscarinic antagonist (LAMA), a long-acting beta$_2$-agonist (LABA), and an inhaled corticosteroid (ICS) has been shown to improve lung function, reduce exacerbations, and potentially decrease mortality in moderate-to-severe COPD. Fixed-dose Single-Inhaler Triple Therapy (SITT) provides practical advantages over Multiple-Inhaler Triple Therapy (MITT), including improved treatment adherence, fewer inhaler technique errors, and comparable safety. This expert opinion review summarizes evidence from randomized controlled trials and real-world studies supporting the clinical, practical, and economic benefits of SITT.

While access to SITT in Italy is influenced by regulatory frameworks, optimizing prescription practices and aligning treatment strategies with clinical evidence could enhance continuity of care and patient outcomes. The paper highlights strategies to improve COPD management, reduce treatment discontinuation, and ensure equitable access to effective therapies.

Key words: Chronic Obstructive Pulmonary Disease (COPD), Multiple-Inhaler Triple Therapy (MITT), Single-Inhaler Triple Therapy (SITT), AIFA Note 99, treatment adherence, healthcare access equity

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Authors' contributions: AB contributed to the analysis of the validity of triple therapy and the comparison between MITT and SITT in COPD according to guideline documents. FPL and SD contributed to the topic of equity of care. CM handled the topic comparing MITT and SITT in COPD on additional outcomes, including lung function, error rates and selective discontinuation of individual COPD therapies. SP focused on the economic aspects of comparing MITT and SITT in COPD, addressing adherence, persistence, and costs. PP worked on the topic covering the foundations of guideline documents, from RCTs to real-world studies. All authors read and approved the final manuscript.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic respiratory condition characterized by persistent and progressive airway obstruction [1,2].

COPD is the fourth leading cause of death globally, accounting for about 3.5 million deaths in 2021, approximately 5% of all deaths worldwide [3]. In Italy, prevalence estimates vary according to the data source and diagnostic criteria used. Data from the Health Search database, based on clinically recorded diagnoses in primary care, indicate a prevalence of 2.7% among Italian adults in 2020–2021, with higher rates in males than females (3.2% vs 2.3%) and a marked increase with age, peaking in individuals over 85 years (16.6%) [4]. However, these figures likely underestimate the true burden of disease, as population-based analyses have reported a higher prevalence of approximately 5.6% among adults [5]. This discrepancy reflects the well-recognised underdiagnosis of COPD in routine clinical practice, particularly in the absence of systematic spirometric screening.

Its incidence appears to be increasing, likely due to the aging population and the rising prevalence of external risk factors such as pollution, with approximately 50% of COPD cases attributable to non-tobacco-related risk factors [6].

COPD is characterized by persistent respiratory symptoms such as dyspnea, cough, and excessive mucus production, as well as chronic inflammation of lung tissue [7].

While treatment strategies depend on disease severity, the overall goal in COPD management is to maintain lung function, alleviate symptoms, and prevent exacerbations, thereby improving the patient's functional status and quality of life [8,9]. However, despite effective therapies, suboptimal adherence, incorrect inhaler use, and inadequate techniques are common in patients with COPD, significantly contributing to therapeutic failure and increased healthcare costs [10,11].

Pharmacological management of moderate-to-severe COPD involves mono- or combination therapies of long-acting β_2-agonists (LABA), long-acting muscarinic antagonists (LAMA) and/or inhaled corticosteroids (ICS).

Several clinical trials have shown that triple-inhaler therapy, combining three active ingredients (LABA+LAMA+ICS), is more effective in reducing the risk of moderate-to-severe exacerbations compared to dual therapy ICS+LABA [12-14] and LAMA+LABA [13-15].

In Italy, according to health authorities (AIFA Note 99), escalation to triple therapy is allowed for COPD patients with persistent symptoms or exacerbations despite dual therapy, but the prescription of fixed-dose LABA+LAMA+ICS combinations must strictly and exclusively be handled by a specialist (pulmonologist, allergist, geriatrician, and internist [16-18]) working at facilities recognized by the Regions with appropriate diagnostic facilities [19].

While both Multiple-Inhaler Triple Therapy (MITT) and Single-Inhaler Triple Therapy (SITT) are available, growing evidence supports SITT for its clinical and practical benefits, particularly in improving adherence and reducing inhaler technique errors. By simplifying treatment, SITT enhances patient compliance, optimizes drug delivery, and lowers the risk of exacerbations, ultimately leading to better symptom management and improved lung function compared to MITT [20].

Despite supportive evidence favoring SITT over MITT, its widespread adoption remains challenging, especially in countries where regulatory policies, such as Italy's Note 99, impose restrictions on access. These limitations contribute to disparities in care and may hinder optimal disease management, particularly in primary care settings [21].

This paper aims to provide an expert opinion on the benefits of SITT in COPD management, examining clinical evidence, real-world data, and economic implications. Furthermore, it advocates for aligning treatment guidelines and Italian healthcare policies with current evidence to ensure equitable access to this effective therapeutic approach. Addressing these gaps can improve outcomes for COPD patients and enhance the sustainability of healthcare systems.

To guide the development of this expert opinion, a preliminary advisory board meeting was held in November 2024. During this meeting, the expert panel identified key topics in COPD diagnosis and management and discussed strategies to optimize treatment approaches and address barriers to equitable care.

A narrative approach was subsequently adopted to provide a comprehensive synthesis of the latest international and Italian clinical guidelines, randomized controlled trials (RCTs), real-world evidence (RWE) studies, and relevant policy documents, including AIFA Note 99. The narrative review was conducted through a thorough analysis of the current literature using the PubMed/MEDLINE Embase database, and complemented by the authors' clinical experience and personal insights. Literature sources were identified with keywords such as *"COPD," "single-inhaler triple therapy", "SITT", "multiple-inhaler triple therapy", "MITT", "adherence", "real-world evidence",* and *"AIFA Note 99",* focusing on publications in English or Italian between January 2016 and May 2025. No formal inclusion or exclusion criteria were applied; studies were selected based on their relevance, clinical significance, and applicability to the Italian healthcare context.

Following the meeting, the expert panel communicated via e-mail to discuss, review, and finalize the document.

Guideline recommendations and the role of SITT in COPD management

The 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations underscore that COPD diagnosis must be confirmed through post-bronchodilator spirometry, demonstrating a FEV_1/FVC ratio <0.7. Treatment goals focus on reducing symptoms such as dyspnea, enhancing exercise tolerance, and improving overall health status as well as mitigating risks like disease progression, exacerbations, and mortality [8].

In patients categorized within Group E – those with ≥2 moderate exacerbations per year or at least one leading to hospitalization – initial triple therapy LABA+LAMA+ICS should be if blood eosinophil counts are ≥ 300 cells/μL, as since the effect of ICS on exacerbation prevention is correlated to eosinophil levels [13]. For patients with persistent exacerbations despite dual therapy with LABA+LAMA and a blood eosinophil count ≥100 cells/μL, escalation to triple therapy is recommended as follow-up treatment.

While SITT provides distinct clinical and practical advantages over MITT, its explicit promotion within the guidelines remains understated. Rather, GOLD guidelines suggest minimizing the number of different inhaler devices per patient, noting that single-inhaler combinations may help improve health status and adherence compared to multiple-inhaler regimens. Therefore, the recommendation for SITT use is implicit and presented as an option to simplify therapy, without a direct or prescriptive endorsement.

The Canadian Thoracic Society (CTS) guidelines strongly recommend LABA+LAMA+ICS triple therapy for patients with stable COPD who have moderate to high symptoms and reduced lung function (FEV_1 < 80%), both for those at low risk and high risk of exacerbations [22]. For low-risk patients, step-up to triple therapy is advised when symptoms persist despite LAMA+LABA or ICS+LABA therapy, as it significantly improves dyspnea and health status. For high-risk patients, triple therapy is strongly recommended as initial maintenance therapy due to its demonstrated benefits in reducing moderate and severe exacerbations.

Moreover, patients with moderate-to-severe disease at high risk of acute exacerbations (AECOPD) should be treated with SITT, which has been shown to improve health status and lung function more effectively than MITT [23].

These guidelines point out that SITT is favored over multiple inhalers due to its potential benefits such as improved adherence and persistence, as observed in various retrospective observational studies [24-29], potentially leading to better clinical outcomes [24,27,28].

The CTS recommendations align with those of other recent guidelines, including the National Institute for Health and Care Excellence (NICE) and the American Thoracic Society (ATS), which recommend minimizing the number of inhalers and the number of different types of inhalers used by each patient as far as possible [30,31] (Table 1).

In conclusion, although many guidelines recognize the advantages of SITT over MITT, its adoption as a valid therapeutic option is not only inadequately considered but is also often hindered in daily practice,

Table 1. Statements from national and international COPD guidelines highlighting key concepts on the use of multiple inhalers versus single inhalers containing multiple active ingredients.

Guidelines on COPD management	Statements directly extracted from the respective documents listed
Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report 2025 [8]	• "Fixed dose triple inhaled combination therapy in one inhaler may help improve health status compared to treatment using multiple inhalers" (p. 61). • "Although patient preferences may vary, prescribing strategies that could help improve adherence often include selecting devices with a similar inhalation technique (in the case of multiple inhalers) and combination therapy. Single inhalers improve adherence to treatment" (p. 84). • "The number of different device types should be minimized for each patient" (p. 62, Fig. 3.11).
Canadian Thoracic Society (CTS) guideline 2023 [22]	• "Triple inhaled LAMA/LABA/ICS therapy, in a single inhaler triple therapy (SITT), is favored over multiple inhalers, because of potential increased benefits, increased adherence and reduced chance of errors in inhaler technique" (p. 1176)
National Institute for Health and Care Excellence (NICE) guideline 2019 [30]	• "Minimise the number of inhalers and the number of different types of inhalers used by each person as far as possible" (p.19, Rec. 1.2.21)
American Thoracic Society (ATS) guideline 2020 [31]	• "If a physician chooses to prescribe two or three separate inhalers rather than a single combination triple therapy inhaler, this could increase the complexity and burden of medication use for patients" (p. e61)

potentially limiting its broader implementation in clinical settings due to bureaucratic burdens.

Single-inhaler triple therapy (SITT) in COPD: from clinical trials to real-world evidence

The efficacy and safety of triple therapy in a single inhalation device have been evaluated in large multinational RCTs, demonstrating greater exacerbation reduction and lung function improvement compared to dual therapy with ICS+LABA [12-14] or LAMA+LABA [13-15], as well as LAMA monotherapy [32].

Although the IMPACT [13] and ETHOS [14] trials suggested a potential reduction in mortality with triple therapy, these findings have been critically discussed in the scientific literature and by regulatory authorities, as mortality was a secondary endpoint and the studies were not specifically powered to assess mortality outcomes [33-35]. Consequently, no individual randomized trial has provided conclusive evidence of a mortality benefit with triple therapy. To address this limitation, several meta-analyses have pooled data from multiple trials to increase statistical power and evaluate the consistency of mortality outcomes [36].

To date, eleven meta-analyses have addressed this question, both regarding triple therapy in general [37-42] and specifically in relation to SITT [43-47]. These analyses consistently show that triple therapy, compared with LABA+LAMA, significantly reduces mortality, with a decrease of 22-34% with SITT/MITT, and 24-31% specifically with SITT [37-47].

These trials, involving over 6,000 patients, have consistently shown that fixed-dose triple therapy provides significant benefits for individuals with severe to very severe COPD, including improved lung function and reduced exacerbation rates. However, the highly controlled conditions of these studies, such as strict inclusion criteria and high adherence to treatment protocols, may not fully represent real-world

clinical practice. To address these limitations, non-interventional studies have been conducted with broader inclusion criteria and real-world clinical settings, allowing healthcare providers to determine patient eligibility and follow standard treatment practices. These multicenter, single-arm, open-label cohort studies provide valuable insights into the safety, effectiveness, and adherence of fixed-dose triple therapy in routine COPD management (Table 2) [48,49].

While the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach is currently the gold standard for assessing evidence quality, the evidence pyramid remains a useful conceptual framework for ranking study designs within a hierarchy of evidence [50], with observational studies generally considered lower-level evidence than RCTs [51] (Figure 1). In the context of this manuscript, however, the different study designs address distinct clinical and policy-relevant questions and should therefore be interpreted as complementary rather than strictly hierarchically ranked.

However, rather than being viewed as inferior, observational studies should be considered complementary to RCTs, addressing different research questions. While RCTs are primarily designed to assess the specific effects of interventions under highly controlled conditions, observational studies reflect real-world clinical practice by evaluating treatment outcomes in broader, less-selected patient populations. These studies bridge the gap between clinical trials and routine practice by showing how pharmacological effects, placebo responses, and patient-physician interactions influence adherence, persistence, and overall efficacy [53,54].

The findings from these RWE studies reinforce the clinical validity of SITT compared with previous MITT-based approaches in COPD management [27,53-59]. Considering differences in healthcare systems, settings, and routine clinical practice across countries, generating local real-world data on the use of fixed inhaled triple therapy can further confirm its applicability and expand the results in larger populations and settings [60]. RWE studies increasingly support SITT as a practical and effective strategy for COPD management, highlighting the need to integrate such data into future guidelines to improve patient care and treatment access.

Advantages of SITT

SITT has emerged as a practical and clinically beneficial alternative to multiple-device regimens in COPD management, offering a range of well-recognized advantages.

Improved lung function

Several studies have demonstrated that using a single inhaler instead of multiple devices improves lung function in patients with moderate-to-severe COPD. A meta-analysis demonstrated that SITT led to a significantly greater improvement in FEV_1 from baseline compared to separate triple therapy (mean difference = 0.02 L; $p<0.01$) [61]. These findings suggest that SITT may provide superior lung function benefits while maintaining a similar safety profile compared to MITT. However, the +20 mL FEV_1 improvement is far below the 100 mL Minimal Clinically Important Difference (MCID), indicating limited clinical relevance despite statistical significance.

Better therapeutic adherence and reduced treatment discontinuation

Adherence to therapy is crucial for chronic conditions like COPD, where consistent therapy is essential for symptom control and the prevention of exacerbations. Poor adherence in COPD is strongly associated with worse clinical outcomes, including a higher risk of exacerbations, increased hospitalizations, and greater long-term mortality [62].

According to OsMed 2021 data, adherence to COPD drug therapy in Italy is suboptimal, with an annual coverage of 80% and a persistence rate of only 8%, markedly lower than that observed for other drug classes (Figure 2) [63].

Adherence to inhalation therapy is generally poor, and adherence to MITT remains particularly low, with 85% of patients classified as non-adherent [64,65].

Table 2. Summary of prospective cohort study in COPD patients treated with SITT

Study	Country	Duration	Enrolled Patients	Diagnosis	Previous Therapies	Main Results
TRIOPTIMIZE [55]	Germany	24 weeks	2,623	Moderate-severe COPD (GOLD B 45.6%, GOLD D 32%) Comorbidities 76.9%	Free ICS+LABA+LAMA (57.5%), LABA/LAMA (18.6%), ICS/LABA (23.9%)	Mean CAT score reduction of 2.7 points Adherence to therapy increased from 67.8% to 76.5%. FEV_1%pred increased by 2.0 points.
TRIVOLVE [56]	Belgium	52 weeks	126	Moderate-severe COPD (GOLD B 54.8%, GOLD D 41.3%) Comorbidities 72%	Free ICS+LABA+LAMA (76.2%), LABA/LAMA (19%), ICS/LABA (4.8%)	Device errors decreased to 16.3% Adherence to therapy increased from 67.5% to 80%. Improvements in lung function, symptom scores, and patient satisfaction. Exacerbation rates significantly decreased.
TRIBUNE [57]	Greece	24 weeks	1,195	Moderate-severe COPD, with at least one exacerbation in the past year Comorbidities 33.8%	LABA/LAMA (48.5%), ICS/LABA (48.6%)	Mean CAT score reduction of 7.9 points 85.9% of patients achieved MCID (≥2) in CAT Adherence to therapy increased from 58.4% to 64%
TRITRIAL [53]	Italy	52 weeks	655	Moderate-severe COPD Comorbidities 77%	Fixed ICS/LABA (25.6%), LABA/LAMA (21.4%), ICS/LABA/LAMA (9.5%) Free ICS + LABA + LAMA (24.7%), LABA + LAMA (7.2%), ICS + LABA (4.1%)	Mean CAT score reduction of 6.3 points Adherence to therapy increased from 51.8% to 58.3%
TRICOP [58]	Austria	52 weeks	265	Moderate-severe COPD (GOLD B 62.3%, GOLD D 34%) Comorbidities 69%	Free ICS + LABA + LAMA (23%), LABA + LAMA (12.5%), ICS + LABA (17.8 %)	Mean CAT score reduction of 7.2 points FEV_1 increase of +138 mL and FVC of 198 mL (in GOLD grade 3 and 4 patients) Reduction in moderate exacerbations (-57.4%) and severe exacerbations (-27.3%)
TRIWIN [27]	Greece	24 weeks	475	Moderate-severe COPD Comorbidities 31%	Free ICS/LABA/LAMA (3.6%), LABA/LAMA + ICS (29.7%), LABA/ICS + LAMA (66.7%)	Mean CAT score reduction of 6.3 points FEV_1 increase of +300 mL Adherence to therapy increased from 33.7% to 58.3%
ELLITHE [54]	Germany	52 weeks	931	Moderate-severe COPD (GOLD B 68.6%, GOLD D 31.4%) Comorbidities 67%	Free or fixed triple ICS/LABA /LAMA (22.8%), LAMA/LABA (49.6%), LABA/ICS (14.3%)	Mean CAT score reduction of 2.6 points
RESTART [59]	Korea	24 weeks	91	Moderate-severe COPD (GOLD B 71%, GOLD D 15%) Comorbidities 49%	Free or fixed triple ICS/LABA/ LAMA	Mean CAT score reduction of 1.4 points

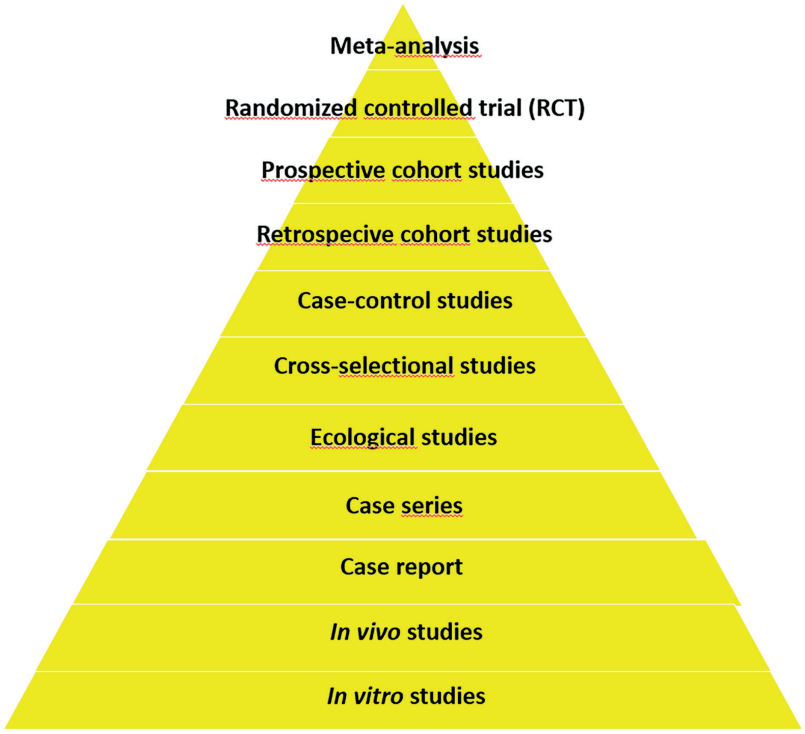

Figure 1. Modified version of the evidence-based medicine pyramid, illustrating the hierarchy of evidence, with more rigorous and reliable evidence at the top. Adapted from Lucas & Harris, 2018[52]. Licensed under CC BY 4.0.

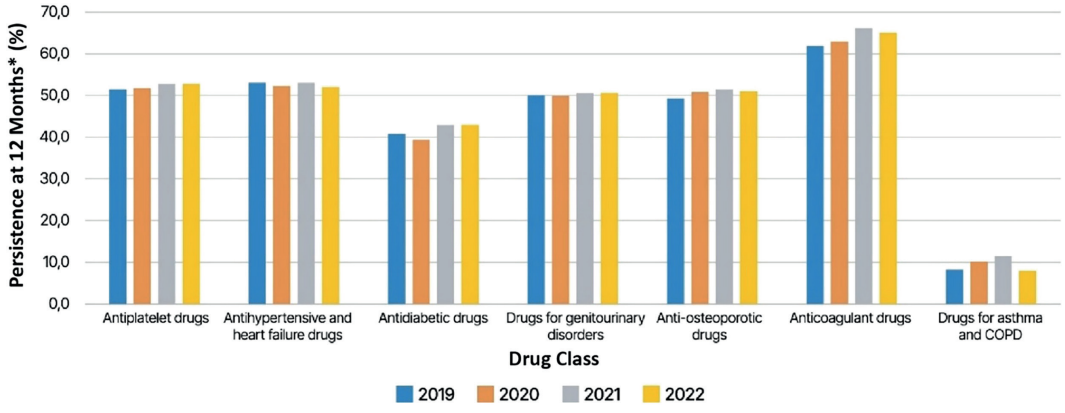

Figure 2. Persistence on therapy at 12 months for COPD drugs compared with other drug classes (data from OsMed Rapporto Nazionale 2022 [63]).

*Persistence defined as the proportion of patients remaining on treatment after 12 months.

A U.S. retrospective cohort study of 14,000 COPD patients using MITT found low adherence (measured as the proportion of days covered, PDC), with only 14% maintaining PDC ≥0.8 after 12 months, and 86% discontinuing therapy during follow-up [64]. Similarly, a study conducted in Italy, involving 3,177 COPD patients, reported that 85% of patients showed poor adherence to open triple inhaler therapy, defined as a PDC lower than 80% [65].

The complexity of using multiple inhalers with different active ingredients, dosages, and inhalation techniques, significantly contributes to non-adherence. Non-persistence, defined as selective discontinuation of individual therapies, also compromises treatment efficacy and disease control [66,67]. In this context, SITT offers a valuable alternative by simplifying the treatment regimen, reducing device handling and confusion, improving adherence, and promoting more stable disease control with a lower likelihood of complications.

Clinical evidence supports these advantages.

A retrospective cohort study in England found that patients using SITT had significantly higher adherence compared to MITT users over 18 months, with median persistence being higher for SITT (5.09 *vs*. 0.99 months) [25]. A German observational cohort study showed that SITT users exhibited an adherence 19% points higher versus MITT users [29].

Similarly, a retrospective cohort study in Japan reported a significantly higher adherence in SITT users than MITT users at 6, 12, and 18 months, with higher median persistence for SITT (2.0 *vs*. 1.0 month) [68]. Real-world data from a French retrospective study indicate that SITT users had higher treatment persistence than MITT users (181 *vs.* 135 days) and a significantly greater one-year persistence rate (33% *vs*. 18%), indicating reduced risk of premature discontinuation [26].

Further evidence from a multicenter, prospective observational study in China found that SITT patients had higher adherence rates (86.5% *vs*. 79.8%), greater treatment persistence (72.5% *vs*. 57.6%; p< 0.001), and a lower risk of moderate and severe exacerbations compared to MITT users. Moreover, SITT was associated with reduced all-cause mortality over a 12-month follow-up period [69]. Similarly, a Spanish observational study found that SITT was associated with significantly higher persistence at 12 months (62.4% *vs*. 53.8%; p <0.001), along with a lower risk of exacerbations and all-cause mortality compared to MITT [24].

A U.S.-based retrospective study of over 9,000 COPD patients further confirmed these trends, showing that adherence was notably higher among SITT users (PDC: 0.66 *vs*. 0.48; p<0.001). Moreover, SITT users were twice as likely to be adherent (46.5% *vs*. 22.3%; p<0.001) and demonstrated significantly higher persistence at 12 months (35.7% *vs*. 13.9%) compared to MITT users [70].

Another Spanish retrospective study shows that at the 12-month follow-up, patients in the SITT cohort were significantly more adherent (75.22% vs 70.1%; OR = 1.33), more persistent (64.32% vs 52.4%; HR = 1.56) and had a lower incidence of moderate exacerbations (53.53% vs 64.07%; OR = 0.65) than patients in the MITT cohort [20].

Reduced risk of errors

Errors in inhalation technique are well-documented and significantly impact COPD management, leading to inadequate medication delivery, poor symptom control, and increased exacerbation risk [71,72].

Critical errors are mistakes that result in little or no medication reaching the lungs, such as failing to exhale fully before inhalation, not actuating the device properly, or not holding the breath after inhalation; these errors vary by device type. The use of multiple inhalers with different techniques further increases the likelihood of errors, particularly among elderly with comorbidities or cognitively impaired patients who may struggle with device coordination [73].

Notably, a study comparing COPD patients using similar inhalation devices found significantly fewer exacerbations than in those using different types of inhalers, suggesting that reducing therapeutic complexity with SITT may improve disease management and lower exacerbation risk compared to MITT [74].

Several studies emphasize the importance of correct inhaler use, showing that improper technique, especially without adequate education, is associated with worse outcomes [75]. A large-scale study analyzing 659 video-recorded demonstrations of inhaler use in 364 COPD patients revealed that 66% made at least one critical error with at least one device model, with error rates increasing according to the number of inhalers used: 43% for one device, 70% for two, and 86% for three or more. The only factor significantly associated with making ≥1 critical error was the simultaneous use of multiple inhaler models [76].

These findings underscore the importance of assessing patients' inhaler technique and minimizing different devices prescribed, as SITT, reduced device heterogeneity, and enhanced patient education can help decrease errors and improve treatment outcomes.

Synergistic interactions between active ingredients

In vitro studies have shown that the SITT combining an ICS, LABA and LAMA exerts a synergistic effect on airway smooth muscle relaxation, whereas similar evidence is lacking for MITT.

Rogliani et al. showed that beclomethasone/formoterol/glycopyrronium combination induces a strong synergistic relaxation of medium bronchi and small airways, mediated by the activation of intracellular glucocorticoid receptors and G-protein of β_2 - adrenoceptors, leading to the modulation of cyclic AMP-dependent PKA pathway [77].

Further research confirmed that ICS+LABA+LAMA combination synergistically enhances airway relaxation and reduce inflammation in hyperresponsive airways, with ICS concentration influencing the extent of these effects [78,79].

However, these findings, based on *ex vivo* mechanistic studies, highlight a potential benefit of SITT but do not provide direct clinical evidence of its superiority over MITT, underscoring the need for further research.

Environmental impact of inhalers

The environmental impact of inhalers varies depending on the type and usage. Each inhaler has its own environmental footprint, including greenhouse gas emissions, waste production, and energy consumption [80]. Therefore, it can be reasonably concluded that using fewer inhalers would help reduce this impact. Whenever possible, minimizing the number of inhalers used can significantly decrease their overall environmental footprint, underscoring the importance of thoughtful consideration in both their usage and disposal.

In this context, the use of a SITT versus MITT results in a more positive environmental impact as a single inhaler reduces device numbers, and therefore waste and resource use, making it a more sustainable option [81].

Pharmacoeconomic aspects of SITT in COPD management

The increasing prevalence of chronic diseases, an aging population, and limited healthcare resources are challenging for healthcare systems. Addressing these issues requires a strategy that optimizes efficiency, reduces waste, and enhances adherence and persistence to chronic therapies [82,83].

Chronic diseases require long-term treatment, but prevention through risk factor modification and appropriate and timely medications use can reduce their impact. In Italy, 24 million people suffer from chronic conditions, with 85% over 75 requiring complex therapies, contributing to €66 billion in healthcare costs [84].

COPD has significant pharmacoeconomic implications due to its chronic nature, resource-intensive management of exacerbations - often requiring hospitalization - and its frequent associated comorbidities [83]. In an Italian real-world administrative analysis, the average annual cost per COPD patient was mainly driven by hospitalizations (42%) and long-term pharmacological treatment (41%), with outpatient specialist services accounting for a smaller proportion (16%) [5].

Poor adherence is a key factor in economic burden, as it is associated with inadequate disease control and an increased risk of exacerbations and hospitalizations, leading to higher healthcare resource consumption [85,86].

Although adherence and persistence to maintenance therapy are essential for optimal clinical outcomes [87,88], in real-world settings, the complexity of MITT regimens is a major barrier, leading to poor adherence and persistence, and, consequently, higher healthcare utilization, increased costs, and poorer health-related quality of life [64,89-91].

Real-world data showed that simplifying therapy to a single inhaler significantly reduces inhaler technique errors and improves treatment compliance, leading to fewer exacerbations and hospitalizations, which translates into substantial savings in hospitalization costs. For example, one study found that SITT was associated with a significant decrease in healthcare resource utilization compared to MITT, including fewer medical visits, shorter hospital stays, and lower

hospitalization rates, resulting in an average annual cost savings of €403 per patient [24]. Similarly, a systematic review found that SITT, compared to multiple inhalers for the same COPD medications, was associated with lower healthcare resource use and greater cost-effectiveness [92].

A recent systematic review found that SITT is a cost-effective choice compared to dual therapy for COPD, particularly for patients with advanced COPD, as it reduces exacerbations, improves quality of life, and extends life expectancy [93]. Although the direct treatment costs were slightly higher, the overall financial burden – accounting for hospitalizations and productivity loss – was lower.

In conclusion, SITT represents a high-value therapeutic option that aligns with both clinical and economic goals in COPD management.

Legislative framework and AIFA Note 99 for triple therapy of COPD

AIFA Note 99 (effective from September 1, 2021 and updated in 2022) regulates the prescription of triple therapy for COPD in Italy, establishing the reimbursement criteria for inhaled medications under the National Health Service [19].

Note 99, in line with the 2020 GOLD Report, emphasizes accurate COPD diagnosis by requiring spirometry with bronchodilation to confirm persistent bronchial obstruction (FEV_1/FVC <70%) in suspected cases.

However, AIFA Note 99 permits general practitioners (GPs) to prescribe medications from the R03 class for COPD, but limits fixed-dose triple combinations (LABA+LAMA+ICS) prescriptions to specialists. Triple therapy in a single inhaler can only be prescribed by a pulmonologist, allergist, geriatrician, and internist working at facilities recognized by the Regions, equipped with the necessary instrumentation to perform second-level exams, and requires periodic therapeutic plans.

GPs cannot initiate SITT without a therapeutic plan prescribed by a specialist; following a full respiratory assessment, GPs can only prescribe the medication for a 12-month duration, after which it must be renewed by a specialist. Revision of Note 99 appears relevant not only to ensure alignment with the most recent versions of the GOLD Report (e.g. the 2025 GOLD Report), but also to allow GPs to renew therapeutic plans that could improve disease management by preventing therapy discontinuation due to delayed specialist renewals and may also help reduce MITT overprescription.

At the same time, broader GP involvement may raise concerns regarding the risk of inappropriate prescribing. In this context, evidence from previous experiences suggests that supportive measures – such as targeted educational initiatives, guideline-based decision aids, and monitoring mechanisms – may help mitigate these risks while preserving patient safety and adherence to best clinical practice.

While global recommendations and real-world evidence support SITT over open triple therapy, debate still exists regarding the regulatory framework in Italy. European data suggest removing therapeutic plans does not lead to misuse or increased costs but optimizes resource allocation and improves outcomes [94].

This study analyzed the payer-driven differences in access criteria for triple therapy in primary care across Europe, focusing on GOLD guidelines application and economic implications. Most national payers either do not apply access criteria or reimbursement rules for triple therapy (England, Germany, Belgium, Netherlands, and Portugal) or have recently lifted them (France and Spain), allowing GPs to initiate treatment. In contrast, Italy and Austria still maintain such limitations, particularly regarding SITT, which restricts GPs' ability to start treatment with triple therapy without specialist initiation or a treatment plan.

The implementation of payer-driven access criteria for COPD treatment may lead to unintended consequences, including reduced autonomy for primary care providers who cannot prescribe the full range of available treatments without specialist involvement, a lack of awareness among GPs about better options, interrupted care for patients due to difficulties in accessing specialists, and delayed access to guideline-directed medical therapies, potentially resulting in suboptimal outcomes and higher long-term costs.

Moreover, a study conducted in England assessed the prescription of triple therapy by GPs, supporting the idea that, despite concerns about increased costs and potential inappropriate use, liberalizing access to this therapy is appropriate [95].

Based on the considerations above, the potential impact of removing the current restrictions on the renewal of triple therapy prescriptions by GPs, while maintaining the requirement that the initial prescription be made within a specialist setting, could be further examined within the context of AIFA Note 99, particularly in relation to its possible implications for the therapeutic management and continuity of care of patients with COPD.

The current legislative and regulatory framework poses challenges for clinical management and impacts healthcare equity, resource allocation, and patient outcomes, highlighting the need for streamlined COPD care that removes unnecessary administrative barriers, improves access to effective therapies, and enhances long-term outcomes across the entire population.

Conclusions

COPD remains a major public health challenge with significant clinical, social, and economic implications. Evidence from real-world studies suggests that SITT can improve adherence and reduce inhaler technique errors in COPD patients, while maintaining similar efficacy and safety to MITT, and may support better disease control by simplifying treatment.

Despite these benefits and strong alignment with international guidelines, the current Italian regulatory framework – particularly the restrictions imposed by AIFA Note 99 – hinders widespread adoption of SITT by limiting its prescription to specialists and requiring periodic therapeutic plans. This not only contributes to unequal access to care and may delay appropriate treatment escalation in primary care settings, but also increases MITT use, associated with higher costs and lower adherence. Italy remains one of the few European countries with such limitations, departing from the practices of nations that have removed access barriers without negative consequences. Revising Note 99 to allow GPs to initiate or renew treatment plans could improve care continuity, reduce exacerbations, and enhance healthcare sustainability, aligning policy with evidence and international standards.

This expert opinion review is subject to several limitations. First, the article does not follow a fully systematic methodology: while the evidence was gathered from leading guidelines, published RCTs, and real-world studies, the literature review was narrative, without a prespecified protocol or risk-of-bias assessment. Second, although the focus is on the Italian healthcare context, some clinical results, real-world evidence, and pharmacoeconomic data were derived from international studies, which may limit generalizability to the Italian population. Despite these limitations, the available data indicate that a revision of access policies and greater integration of real-world evidence and international guidelines could help improve therapeutic equity and clinical outcomes for COPD patients in Italy.

References

1. Celli BR, Wedzicha JA. Aspects of Chronic Obstructive Pulmonary Disease. N Engl J Med 2019;381:1257-66.
2. Confalonieri M, Braga L, Salton F, Ruaro B, Confalonieri P. Chronic Obstructive Pulmonary Disease Definition: is it time to incorporate the concept of failure of lung regeneration? Am J Respir Crit Care Med 2023;207:366-7.
3. World Health Organization (WHO). The top 10 causes of death 2024. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death (2024).
4. Società Italiana dei Medici di Medicina Generale e delle Cure Primarie (S.I.M.G.) XVI Report Health Search Edizione 2023. https://www.simg.it/hs-report/XVI.pdf (2023).
5. Calabria S, Ronconi G, Dondi L, Pedrini A, Piccinni C, Esposito I, et al. Real-world analysis of obstructive respiratory tract disorders: characterization, health care and costs. Recenti progressi in medicina 2021;112:285-93.
6. Yang IA, Jenkins CR, Salvi SS. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. Lancet Respir Med 2022;10:497-511.
7. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet 2007;370:765-73.
8. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for prevention, diagnosis and management of COPD: 2025 Report. https://goldcopd.org/2025-gold-report/ (2025).
9. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. Lancet 2007;370:786-96.
10. Darbà J, Ramírez G, Sicras A, Francoli P, Torvinen S, Sánchez-de la Rosa R. The importance of inhaler devices:

the choice of inhaler device may lead to suboptimal adherence in COPD patients. Int J Chron Obstruct Pulmon Dis 2015;10:2335-45.
11. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med 2011;105:930-8.
12. Singh D, Papi A, Corradi M, Pavlišová I, Montagna I, Francisco C, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. Lancet 2016;388:963-73.
13. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med 2018;378:1671-80.
14. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to- very-severe COPD. N Engl J Med 2020;383:35-48.
15. Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet 2018;391:1076-84.
16. Agenzia Italiana del Farmaco DETERMINA 24 agosto 2018 - Classificazione del medicinale per uso umano "Trimbow", ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 1358/2018). (18A05984) (GU Serie Generale n.218 del 19-09-2018); Articolo 3. https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2018-09-19&atto.codiceRedazionale=18A05984&elenco30giorni=false (2018)
17. Agenzia Italiana del Farmaco DETERMINA 19 febbraio 2019 - Riclassificazione del medicinale per uso umano "Trelegy Ellipta", ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 288/2019). (19A01476) (GU Serie Generale n.58 del 09-03-2019); Articolo 3. https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2019-03-09&atto.codiceRedazionale=19A01476&elenco30giorni=true (2019)
18. Agenzia Italiana del Farmaco DETERMINA 10 gennaio 2022 - Riclassificazione del medicinale per uso umano "Trixeo Aerosphere", ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 2/2022). (22A00192) (GU Serie Generale n.8 del 12-01-2022); Articolo 3. https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2022-01-12&atto.codiceRedazionale=22A00192&elenco30giorni=true (2022)
19. Agenzia Italiana del Farmaco. Nota 99. https://www.aifa.gov.it/documents/20142/1728122/nota-99.pdf (2022).
20. González-González MA, Pedrosa-Naudín MA, Fernández-Lázaro D, Planelles ID, Álvarez FJ, Gutiérrez-Abejón E. Single-versus multiple-inhaler triple therapy in patients with COPD in Spain: a retrospective cohort study comparing adherence, persistence, risk of exacerbations and economic outcomes. Front Pharmacol 2025;16:1642470.
21. Di Marco F, Shahaj O, Valipour A, Legrand B, Jommi C, Micheletto C, et al. Single-Inhaler Triple Therapy in Primary Care Across Europe: Expert Panel Consensus on the Consequences of Payer-Driven Access Rules and Call to Action. Int J Chron Obstruct Pulmon Dis 2025;20:1595-612.
22. Bourbeau J, Bhutani M, Hernandez P, Aaron SD, Beauchesne MF, Kermelly SB, et al. 2023 Canadian Thoracic Society Guideline on Pharmacotherapy in Patients with Stable COPD. Chest 2023;164:1159-83.
23. Halpin DMG, Worsley S, Ismaila AS, Beeh KM, Midwinter D, Kocks JWH, et al. INTREPID: single-versus multiple-inhaler triple therapy for COPD in usual clinical practice. ERJ Open Res 2021;7:00950-2020.
24. Alcázar-Navarrete B, Jamart L, Sánchez-Covisa J, Juárez M, Graefenhain R, Sicras-Mainar A. Clinical characteristics, treatment persistence, and outcomes among patients with COPD treated with single- or multiple- inhaler triple therapy: a retrospective analysis in Spain. Chest 2022;162:1017-29.
25. Halpin DMG, Rothnie KJ, Banks V, Czira A, Compton C, Wood R, et al. Comparative adherence and persistence of single- and multiple- inhaler triple therapies among patients with chronic obstructive pulmonary disease in an English real-world primary care setting. Int J Chron Obstruct Pulmon Dis 2022;17:2417-29.
26. Deslee G, Fabry-Vendrand C, Poccardi N, Thabut G, Eteve Pitsaer C, et al. Use and persistence of single and multiple inhaler triple therapy prescribed for patients with COPD in France: a retrospective study on THIN database (OPTI study). BMJ Open Respir Res 2023;10:e001585.
27. Steiropoulos P, Georgatou N, Krommidas G, Bartziokas K, Korkontzelou A, Katerelos P, Efstathopoulos P, et al. Extrafine single inhaler triple therapy effectiveness in COPD patients previously treated with multiple-inhaler triple therapy: the TRIWIN study. Ther Adv Respir Dis 202;18:17534666241263439.
28. Cabrer CE, López García J, Vega Lizarazo DE, Benítez-Cano Gamonoso M, Segura Romero M, Sanchez Martín S, et al. Inhaled Triple Therapy with Extrafine Single Inhaler Versus Multiple Devices in Chronic Obstructive Pulmonary Disease (TRIPOLI): A Post-Authorization Retrospective Study. Int J Chron Obstruct Pulmon Dis 2025;20:1737-47.
29. Vogelmeier CF, Beeh KM, Schultze M, Kossack N, Richter LM, Claussen J, et al. Evaluation of Adherence and Persistence to Triple Therapy in Patients with COPD: A German Claims Data Study. Int J Chron Obstruct Pulmon Dis 2024;19:1835-48.

30. National Institute for Health and Care Excellence (NICE). Chronic Obstructive Pulmonary Disease in Over 16s: Diagnosis and Management. NICE Guideline, No. 115. https://www.nice.org.uk/guidance/ng115 (2019).
31. Nici L, Mammen MJ, Charbek E, Alexander PE, Au DH, Boyd CM, et al. Pharmacologic management of chronic obstructive pulmonary disease. An official American thoracic society clinical practice guideline. Am J Respir Crit Care Med 2020;201:e56-e69. Erratum in: Erratum: Pharmacologic Management of Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 2020;202:910.
32. Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, Cohuet G, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): A double-blind, parallel group, randomised controlled trial. Lancet 201;389:1919-29.
33. Soumagne T, Zysman M, Karadogan D, Lahousse L, Mathioudakis AG. Impact of triple therapy on mortality in COPD. Breathe (Sheff) 2023;19:220260.
34. US Food and Drug Administration. Final Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting, August 31, 2020 https://www.regulations.gov/document/FDA-2020-N-0626-0003 (2020).
35. US Food and Drug Administration. Warning Letter: AstraZeneca Pharmaceuticals LP. MARCS-CMS 664789 – August 04, 2023. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/astrazeneca-pharmaceuticals-lp-664789-08042023 (2023).
36. Haidich AB. Meta-analysis in medical research. Hippokratia 2010;14:29-37.
37. Lee HW, Park J, Jo J, Jang EJ, Lee CH. Comparisons of exacerbations and mortality among regular inhaled therapies for patients with stable chronic obstructive pulmonary disease: Systematic review and Bayesian network meta-analysis. PLoS Med 2019;16:e1002958.
38. Axson EL, Lewis A, Potts J, Pang M, Dickinson S, Vioix H, et al. Inhaled therapies for chronic obstructive pulmonary disease: a systematic review and meta-analysis. BMJ Open 2020;10:e036455.
39. Koarai A, Yamada M, Ichikawa T, Fujino N, Kawayama T, Sugiura H. Triple versus LAMA/LABA combination therapy for patients with COPD: a systematic review and meta-analysis. Respir Res 2021;22:183.
40. Chen H, Deng ZX, Sun J, Huang Q, Huang L, He YH, et al. Association of Inhaled Corticosteroids with All-cause Death Risk in COPD Patients: A Meta-analysis of Sixty Randomized Controlled Trials. Chest 2023;63:100-14.
41. Pan Q, Sun J, Gao S, Liu Z, Huang Y, Lian Y. Incremental long-term benefit of drug therapies for chronic obstructive pulmonary disease in quality of life but not mortality: a network meta-analysis. Arch Med Sci 2024;20:1586-96.
42. Calderón-Montero A, García Fernández M, García-Velasco ME, Joshi M, Khan K, Calderón-Ferrer C, et al. Effect of triple inhaled therapy on cardiovascular and all-cause mortality compared with dual inhaled therapy in COPD: A systematic review and meta-analysis. Semergen 2025;51:102478.
43. Li Y, Li J, Yang H, Zhang Y. Effect of triple therapy on mortality and cardiovascular risk in patients with moderate to severe COPD: a meta-analysis of randomized controlled trials. BMC Pulm Med 2025;25:345.
44. Long H, Xu H, Janssens JP, Guo Y. Single-inhaler triple vs single-inhaler dual therapy in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized control trials. Respir Res 2021;22:209.
45. Lai CC, Chen CH, Chen KH, Wang CY, Huang TM, Wang YH, et al. The Impact of 52 Week Single Inhaler Device Triple Therapy versus Dual Therapy on the Mortality of COPD Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Life (Basel) 2022;12:173.
46. van Geffen WH, Tan DJ, Walters JA, Walters EH. Inhaled corticosteroids with combination inhaled long-acting beta2-agonists and long-acting muscarinic antagonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2023;12:CD011600.
47. Hammadi A, Hoyas-Sánchez C, Romero-Linares A, Álvarez-Muro L, Menéndez-Lobo A, Romeral-Navarro D, et al. All-Cause and Cardiovascular Mortality With Single Inhaler Triple Therapy Versus Double Therapies for COPD: A Systematic Review and Metanalysis. Arch Bronconeumol 2025;61:594-602.
48. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and Impact of Real-World Clinical Data for the Practicing Clinician. Adv Ther 2018;35:1763-74.
49. Rogliani P, Manzetti GM, Cazzola M, Calzetta L. Real-World Effectiveness of Triple Extrafine Fixed-Dose Combination with Beclomethasone/Formoterol/Glycopyrronium on Symptoms and Lung Function in COPD: A Systematic Review and Meta-Analysis. Int J Chron Obstruct Pulmon Dis 2025;20:1723-36.
50. Murad MH, Montori VM. Synthesizing evidence: shifting the focus from individual studies to the body of evidence. JAMA 2013;309:2217-8.
51. Poehling GG, Jenkins CB. Levels of evidence and your therapeutic study: what's the difference with cohorts, controls, and cases? Arthroscopy 200;20:563.
52. Lucas RM, Rodney Harris RM. On the Nature of Evidence and 'Proving' Causality: Smoking and Lung Cancer vs. Sun Exposure, Vitamin D and Multiple Sclerosis. Int J Environ Res Public Health 2018;15:1726.
53. Richeldi L, Schino P, Bargagli E, Ricci A, Rocca A, Marchesani F, et al. TRITRIAL: The Impact of Fixed Triple Therapy with Beclometasone/Formoterol/Glycopyrronium on Health Status and Adherence in Chronic Obstructive Pulmonary Disease in an Italian Context of Real Life. Int J Chron Obstruct Pulmon Dis 2024;19:475-87.
54. Beeh KM, Scheithe K, Schmutzler H, Krüger S. Real-World Effectiveness of Fluticasone Furoate/Umeclidinium/Vilanterol Once-Daily Single-Inhaler Triple Therapy for Symptomatic COPD: The ELLITHE Non

-Interventional Trial. Int J Chron Obstruct Pulmon Dis 202;19:205-16.
55. Gessner C, Trinkmann F, Bahari Javan S, Hövelmann R, Bogoevska V, Georges G, et al. Effectiveness of Extrafine Single Inhaler Triple Therapy in Chronic Obstructive Pulmonary Disease (COPD) in Germany - The TriOptimize Study. Int J Chron Obstruct Pulmon Dis 2022;17:3019-31.
56. Brusselle G, Himpe U, Fievez P, Leys M, Perez Bogerd S, Peché R, et al. Evolving to a single inhaler extrafine LABA/LAMA/ICS - Inhalation technique and adherence at the heart of COPD patient care (TRIVOLVE). Respir Med 2023;218:107368.
57. Porpodis K, Bartziokas K, Chatziapostolou P, Korkontzelou A, Katerelos P, Efstathopoulos P, et al. Extrafine single inhaler triple therapy effect on health status, lung function and adherence in COPD patients: A Panhellenic prospective non-interventional study - The TRIBUNE study. Respir Med 2023;212:107219.
58. Marth K, Renner A, Pohl W. TRICOP - A Real-world effectiveness study with a single-inhaler extrafine triple therapy over 52 weeks in Austrian patients with COPD. Respir Med 2021;182:106398.
59. Lim H, Kim DH, Hong SH, Shin J, Lee H, Shin K, et al. Real-world effectiveness of single-inhaler triple treatment through assorted respiratory outcomes when switched from multiple-inhaler triple therapies (RESTART): a prospective cohort study of Korean patients with COPD. Int J Chron Obstruct Pulmon Dis 2025;20:1039-50.
60. Roche N, Anzueto A, Bosnic Anticevich S, Kaplan A, Miravitlles M, Ryan D, et al. The importance of real-life research in respiratory medicine: manifesto of the respiratory effectiveness group: endorsed by the international primary care respiratory group and the world allergy organization. Eur Respir J 2019;54:1901511.
61. Zhang L, Wang X, Zhang Y, Chen W. Efficacy and Safety of Single Inhaler Triple Therapy Versus Separate Triple Therapy in Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis. Clin Ther 2022;44:859-73.
62. Turégano-Yedro M, Trillo-Calvo E, Navarro I Ros F, Maya-Viejo JD, González Villaescusa C, Echave Sustaeta JM, et al. Inhaler Adherence in COPD: A Crucial Step Towards the Correct Treatment. Int J Chron Obstruct Pulmon Dis 2023;18:2887-93.
63. Osservatorio Nazionale sull'impiego dei Medicinali. L'uso dei Farmaci in Italia. Rapporto Nazionale Anno 2021. Roma: Agenzia Italiana del Farmaco https://www.aifa.gov.it/documents/20142/1740782/Rapporto-OsMed-2021.pdf (2022).
64. Bogart M, Stanford RH, Laliberté F, Germain G, Wu JW, Duh MS. Medication adherence and persistence in chronic obstructive pulmonary disease patients receiving triple therapy in a USA commercially insured population. Int J Chron Obstruct Pulmon Dis 2019;14:343-52.
65. Zucchelli A, Vetrano DL, Bianchini E, Lombardo FP, Piraino A, Zibellini M, et al. Adherence to COPD free triple inhaled therapy in the real world: a primary care-based study. Clin Respir J 2020;14:732-9.
66. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. Value Health 2008;11:44-7.
67. Restrepo RD, Alvarez MT, Wittnebel LD, Sorenson H, Wettstein R, Vines DL, et al. Medication adherence issues in patients treated for COPD. Int J Chron Obstruct Pulmon Dis 2008;3:371-84.
68. Jokšaitė S, Wood R, Ismaila A, Camidge L, Mizukami A, Czira A, et al. Comparative adherence and persistence of single-inhaler and multiple-inhaler triple therapies among patients with chronic obstructive pulmonary disease in Japan: a retrospective cohort study. BMJ Open 2024;14:e080864.
69. Lin L, Liu C, Cheng W, Song Q, Zeng Y, Li X, et al. Comparison of treatment persistence, adherence, and risk of exacerbation in patients with COPD treated with single-inhaler versus multiple-inhaler triple therapy: A prospective observational study in China. Front Pharmacol 2023;14:1147985.
70. Mannino D, Bogart M, Wu B, Germain G, Laliberté F, MacKnight SD, et al. Adherence and persistence to once-daily single-inhaler versus multiple-inhaler triple therapy among patients with chronic obstructive pulmonary disease in the USA: A real-world study. Respir Med 2022;197:106807.
71. Pollack M, Rapsomaniki E, Anzueto A, Rhodes K, Hawkins NM, Vogelmeier CF, et al. Effectiveness of Single Versus Multiple Inhaler Triple Therapy on Mortality and Cardiopulmonary Risk Reduction in COPD: The SKOPOS-MAZI Study. Am J Med 2025;138:650-9.e10.
72. Usmani OS, Lavorini F, Marshall J, Dunlop WCN, Heron L, Farrington E, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. Respir Res 2018;19:10.
73. Sanchis J, Gich I, Pedersen S. Aerosol Drug Management Improvement Team (ADMIT). Systematic Review of Errors in Inhaler Use: Has Patient Technique Improved Over Time? Chest 2016;150:394-406.
74. Bosnic-Anticevich S, Chrystyn H, Costello RW, Dolovich MB, Fletcher MJ, Lavorini F, et al. The use of multiple respiratory inhalers requiring different inhalation techniques has an adverse effect on COPD outcomes. Int J Chron Obstruct Pulmon Dis 2016;12:59-71. Erratum in: The use of multiple respiratory inhalers requiring different inhalation techniques has an adverse effect on COPD outcomes [Corrigendum]. Int J Chron Obstruct Pulmon Dis 2019;14:1739.
75. Roggeri A, Micheletto C, Roggeri DP. Inhalation errors due to device switch in patients with chronic obstructive pulmonary disease and asthma: critical health and economic issues. Int J Chron Obstruct Pulmon Dis 2016;11:597-602.

76. Sulku J, Bröms K, Högman M, Janson C, Lisspers K, Malinovschi A, et al. Critical inhaler technique errors in Swedish patients with COPD: a cross-sectional study analysing video-recorded demonstrations. NPJ Prim Care Respir Med 2021;31:5.
77. Rogliani P, Matera MG, Facciolo F, Page C, Cazzola M, Calzetta L. Beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide: Synergy of triple combination therapy on human airway smooth muscle ex vivo. Br J Pharmacol 2020;177:1150-63.
78. Rogliani P, Ritondo BL, Facciolo F, Matera MG, Nikolaev I, Calzetta L. Indacaterol, glycopyrronium, and mometasone: Pharmacological interaction and anti-inflammatory profile in hyperresponsive airways. Pharmacol Res 2021;172:105801.
79. Rogliani P, Ora J, Frugoni C, Melis E. Facciolo F, Calzetta L. Modulating the Level of ICS in Triple ICS/LABA /LAMA FDC: Effect Against Airway Hyperresponsiveness in a Human Ex Vivo Model of Severe Eosinophilic Asthma. Am J Respir Crit Care Med 2023;207:A1311.
80. Cançado JED, Usmani OS. Choice of inhaler device and its disposal have a significant impact on the environment. J Bras Pneumol 2024;50;e20240092.
81. Sposato B, Ricci A, Lacerenza LG, Petrucci E, Cresti A, Baratta P, et al. Triple Therapy in COPD in Real Life: Is It Better to Use Single or Multiple Inhalers? J Clin Med 2024;13:6191.
82. Ministero della Salute. Piano Nazionale della Cronicità (PNC). https://www.quotidianosanita.it/allegati/allegato1721737583.pdf (2024).
83. Istituto Superiore di Sanità. EpiCentro - L'epidemiologia per la sanità pubblica. Broncopneumopatia cronica ostruttiva. https://www.epicentro.iss.it/broncopneumopatia/
84. CittadinanzAttiva, 2022. XX Rapporto sulle politiche della cronicità – Fermi al piano. https://www.cittadinanzattiva.it/comunicati/15423-presentato-il-xx-rapporto-nazionale-sulle-politiche-della-cronicita-fermi-al-piano.html (2022).
85. Osservatorio Nazionale sull'impiego dei Medicinali. L'uso dei farmaci in Italia. Rapporto Nazionale Anno 2022. Roma: Agenzia Italiana del Farmaco. https://www.aifa.gov.it/documents/20142/1967301/Rapporto-OsMed-2022.pdf (2023).
86. Mäkelä MJ, Backer V, Hedegaard M, Larsson K. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. Respir Med 2013;107:1481-90.
87. Ismaila A, Corriveau D, Vaillancourt J, Parsons D, Dalal A, Su Z, et al. Impact of adherence to treatment with tiotropium and fluticasone propionate/salmeterol in chronic obstructive pulmonary diseases patients. Curr Med Res Opin 2014;30:1427-36.
88. Vestbo J, Anderson JA, Calverley PM, Celli B, Ferguson GT, Jenkins C, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. Thorax 2009;64:939-43.
89. Yu AP, Guérin A, Ponce de Leon D, Ramakrishnan K, Wu EQ, Mocarski M, et al. Therapy persistence and adherence in patients with chronic obstructive pulmonary disease: multiple versus single long-acting maintenance inhalers. J Med Econ 2011;14:486-96.
90. Sanduzzi A, Balbo P, Candoli P, Catapano GA, Contini P, Mattei A, Puglisi G, et al. COPD: adherence to therapy. Multidiscip Respir Med 201;9:60.
91. Toy EL, Beaulieu NU, McHale JM, Welland TR, Plauschinat CA, Swensen A, et al. Treatment of COPD: relationships between daily dosing frequency, adherence, resource use, and costs. Respir Med 2011;105:435-41.
92. Zhang S, King D, Rosen VM, Ismaila AS. Impact of single combination inhaler versus multiple inhalers to deliver the same medications for patients with asthma or COPD: a systematic literature review. Int J Chron Obstruct Pulmon Dis 2020;15:417-38.
93. Rana RH, Alam K, Keramat SA, Gow J. Cost-effectiveness of single-inhaler triple therapy for patients with severe COPD: a systematic literature review. Expert Rev Respir Med 2022;16:1067-84.
94. International Primary Care Respiratory Group (IPCRG). Variations in the pharmacological management of COPD due to payer-driven access criteria for triple therapy: Pan-European cross-expertise qualitative insights. https://www.ipcrg.org/24157 (2024).
95. Rothnie KJ, Wood RP, Czira A, Banks VL, Camidge LJ, Massey OKI, et al. Outcomes of patients with COPD switching from multiple-inhaler to once-daily single-inhaler triple therapy in a real-world primary care setting in England: a retrospective pre-post cohort study. BMJ Open Respir Res 2024;11:e001890.

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