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Review Article

Universal Triple Therapy in COPD: A Paradigm Shift or an Unnecessary Escalation?

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Abstract: Triple therapy comprising an inhaled corticosteroid (ICS), a long-acting β_2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA) has become an important treatment option for chronic obstructive pulmonary disease (COPD). Major randomized controlled trials have demonstrated reductions in exacerbations, improvements in lung function, and better health-related quality of life in selected patients. However, uncertainty remains regarding whether triple therapy should be prescribed universally as first-line treatment for symptomatic COPD or reserved for patients most likely to benefit from ICS. This narrative review evaluates contemporary GOLD recommendations, major clinical trials, blood eosinophils as a treatment-response biomarker, mortality outcomes, and ICS-associated pneumonia risk. Evidence from IMPACT, ETHOS, TRIBUTE, FULFIL, TRILOGY, and other studies supports triple therapy in appropriately selected patients with established COPD, particularly those with previous exacerbations. However, most pivotal trials enrolled patients receiving maintenance inhalers, limiting direct extrapolation to treatment-naïve patients. Blood eosinophil counts, exacerbation history, concomitant asthma, and infection susceptibility should guide treatment selection. Indian publications additionally highlight challenges involving COPD awareness, diagnostic practices, inhaler access, and rational prescribing. LABA/LAMA remains the preferred initial treatment for most symptomatic patients without a compelling indication for ICS, whereas initial triple therapy may be considered in selected high-risk patients, particularly those with blood eosinophils ≥300 cells/μL. A phenotype-directed approach offers the most rational balance between exacerbation prevention, symptom control, and treatment-related harm.

Keywords: COPD, Triple Therapy, Inhaled Corticosteroids, LABA/LAMA, Exacerbations, Blood Eosinophils, GOLD 2026, India, Pneumonia.

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INTRODUCTION

Chronic obstructive pulmonary disease is a heterogeneous respiratory disorder characterized by persistent airflow obstruction, chronic respiratory symptoms, and variable contributions from airway inflammation, mucus hypersecretion, small-airway disease, and emphysema. Clinical presentations differ according to tobacco exposure, occupational and biomass exposure, previous respiratory infections, comorbidities, and individual inflammatory characteristics.

Long-acting bronchodilators remain the foundation of pharmacological treatment. LABA/LAMA combinations provide complementary bronchodilation, improve lung function, reduce dyspnea, and prevent exacerbations in appropriate patients. Adding an ICS creates triple therapy, combining bronchodilation with suppression of corticosteroid-responsive airway inflammation [1, 2].

The availability of single-inhaler triple therapy has changed COPD management. Trials such as IMPACT and ETHOS demonstrated clinically important reductions in moderate-to-severe exacerbations compared with selected dual inhaler regimens [3, 4]. Subsequent analyses have also suggested potential mortality benefits in particular trial populations [13, 14].

Nevertheless, the increasing availability of triple therapy raises an important clinical question: should every symptomatic patient receive all three medications from the beginning, or should ICS be added

selectively according to exacerbation history, blood eosinophil counts, and other clinical characteristics?

Three decisions must be distinguished: initial treatment in newly diagnosed COPD, escalation in patients who continue to exacerbate despite dual bronchodilation, and continuation or withdrawal of ICS in patients already receiving triple therapy. These decisions involve different populations and evidence bases. Demonstrating efficacy in exacerbation-prone patients receiving established maintenance treatment does not automatically establish universal triple therapy as the best initial treatment for all symptomatic patients.

The present review examines the evidence supporting triple therapy, evaluates its limitations, and proposes an individualized approach to treatment selection, including considerations relevant to Indian clinical practice.

Pharmacological Rationale for Triple Therapy

Triple therapy combines three complementary pharmacological mechanisms.

Long-acting β_2-Agonists:

LABAs stimulate β_2-adrenergic receptors in airway smooth muscle, promoting sustained bronchodilation. They improve expiratory airflow and may reduce dynamic hyperinflation and exertional dyspnea.

Long-Acting Muscarinic Antagonists:

LAMAs inhibit muscarinic receptor-mediated bronchoconstriction, principally through antagonism of M3 receptors. Their complementary effects improve airflow and lung volumes.

Inhaled Corticosteroids:

ICS suppress several components of airway inflammation and are particularly useful in patients with corticosteroid-responsive inflammation. Their clinical benefit in COPD varies according to exacerbation history, blood eosinophil counts, and concomitant asthma [1-16].

The central distinction is that LABA/LAMA primarily addresses persistent airflow limitation and symptoms, whereas adding ICS is principally intended to improve outcomes in patients likely to experience a clinically meaningful corticosteroid-associated reduction in exacerbations.

Consequently, the rationale for triple therapy should be based on the expected incremental benefit of ICS rather than symptoms alone.

Contemporary Guideline Recommendations
GOLD 2026

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends selecting pharmacological treatment according to symptoms, exacerbation risk, treatment response, and relevant biomarkers [1].

For most symptomatic patients, initial treatment emphasizes long-acting bronchodilation, generally LABA/LAMA when symptoms warrant dual therapy.

GOLD 2026 permits consideration of initial triple therapy in selected patients at high exacerbation risk, particularly those with blood eosinophil counts ≥300 cells/μL. However, the available evidence is derived predominantly from trials involving previously treated patients. Direct evidence in newly diagnosed, treatment-naïve patients remains limited [1-4].

For patients who continue to exacerbate despite LABA/LAMA, adding ICS should be considered according to the clinical context and blood eosinophil count. The expected exacerbation-prevention benefit generally increases with higher eosinophil counts [1-16].

Patients with concomitant asthma should receive treatment appropriate for asthma, for which ICS is an essential component [25].

American Thoracic Society Recommendations

The American Thoracic Society clinical practice guideline recommends LABA/LAMA over monotherapy in patients with COPD who have dyspnea or exercise intolerance. For patients who continue to experience exacerbations despite LABA/LAMA, the guideline conditionally recommends triple therapy when at least one exacerbation in the preceding year required antibiotics, oral corticosteroids, or hospitalization [2].

ATS also conditionally supports ICS withdrawal in selected patients receiving triple therapy who have not experienced exacerbations during the preceding year [2].

These recommendations emphasize the distinction between bronchodilation for symptoms and ICS use for exacerbation prevention.

Interpreting Differences between Guidelines

International recommendations generally support long-acting bronchodilators as the foundation of COPD treatment and reserve ICS-containing regimens for selected patients [1, 2].

The practical interpretation is:

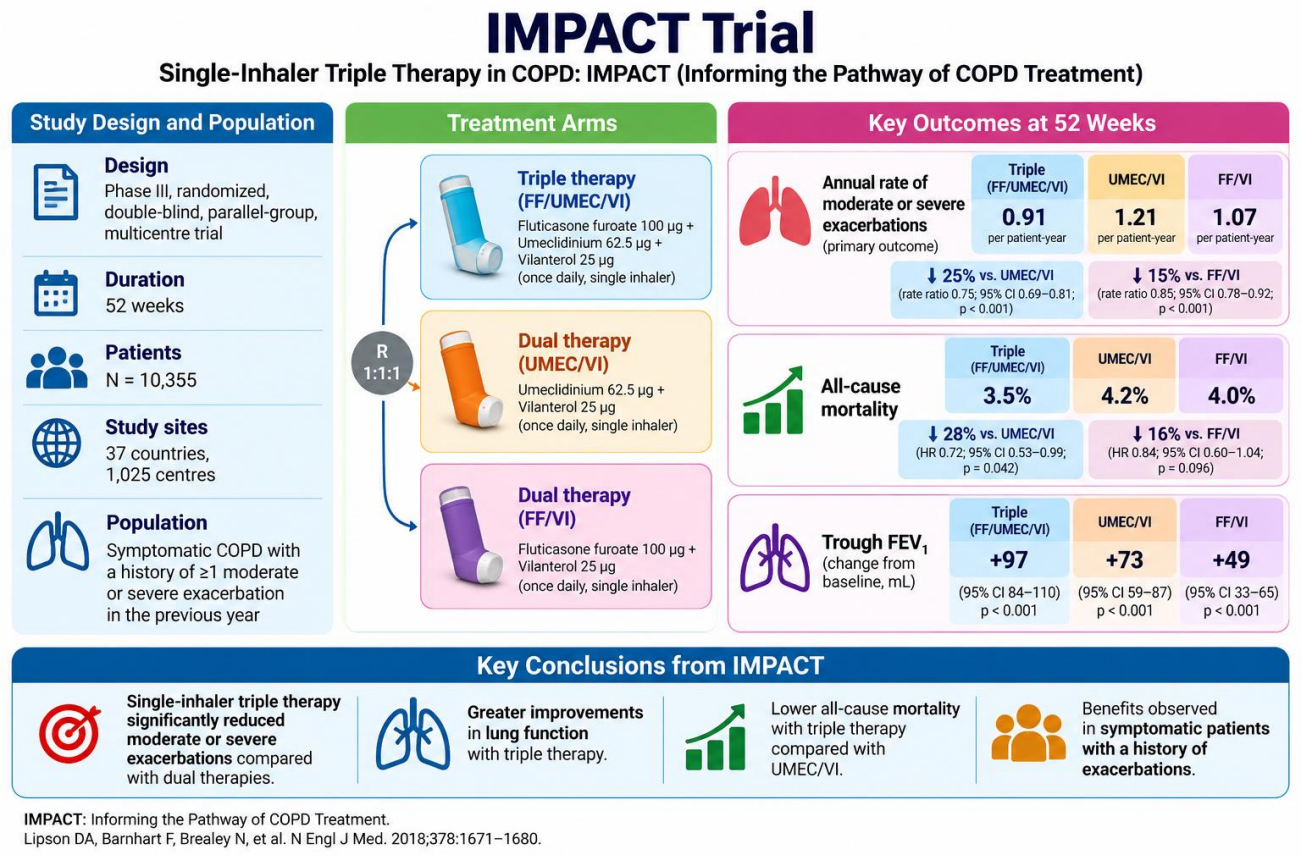
- **LABA/LAMA:** Preferred for most symptomatic patients without a compelling indication for ICS.
- **Triple Therapy:** Appropriate for selected patients with recurrent exacerbations despite optimized bronchodilation when the clinical profile supports ICS.
- **Initial Triple Therapy:** May be considered in selected high-risk patients, particularly those with eosinophils ≥300 cells/μL.

- **ICS Withdrawal:** May be considered when the original indication is weak or adverse effects outweigh benefits, with caution in patients at high risk of exacerbations.

Major Randomized Controlled Trials of Triple Therapy

1. IMPACT Trial

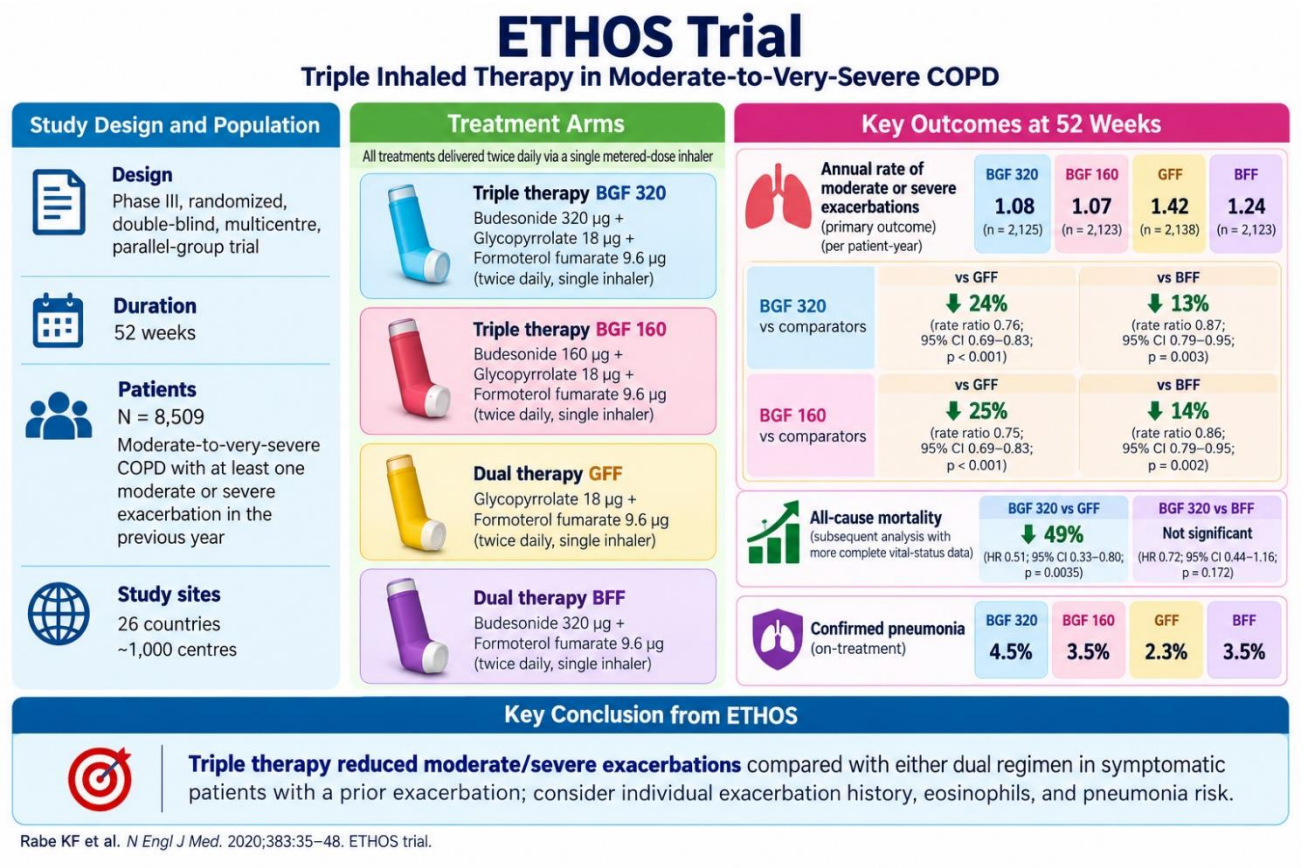
Lipson and colleagues conducted the IMPACT trial, a 52-week randomized study involving 10,355 patients with COPD [3]. Participants received fluticasone furoate/umeclidinium/vilanterol, fluticasone furoate/vilanterol, or umeclidinium/vilanterol. The annual moderate-to-severe exacerbation rates were 0.91, 1.07, and 1.21 per patient-year, respectively. Triple therapy reduced the exacerbation rate by 15% compared with ICS/LABA and by 25% compared with LABA/LAMA [3]. IMPACT provided strong evidence for triple therapy in symptomatic patients with established COPD and an exacerbation history. However, many participants were already receiving ICS-containing treatment before enrollment. Withdrawal of pretrial ICS in patients assigned to LABA/LAMA may have influenced early differences between treatment groups [3]. The results therefore support triple therapy in an appropriate high-risk population but do not prove that all treatment-naïve symptomatic patients should start triple therapy.



2. ETHOS Trial

The ETHOS trial evaluated budesonide/glycopyrrolate/formoterol at two ICS dose levels in 8,509 patients with moderate-to-very-severe COPD and a history of exacerbations [4].

The annual moderate-to-severe exacerbation rates were approximately 1.08 with higher-dose triple therapy, 1.07 with lower-dose triple therapy, 1.42 with glycopyrrolate/formoterol, and 1.24 with budesonide/formoterol [4]. Both triple-therapy regimens reduced exacerbations compared with LABA/LAMA. The trial also generated interest because subsequent analyses reported lower all-cause mortality with the higher-dose triple regimen than with LABA/LAMA [14]. Nevertheless, mortality was not the primary endpoint of the original trial, and these findings should be interpreted in the context of the enrolled population and the analyses performed.

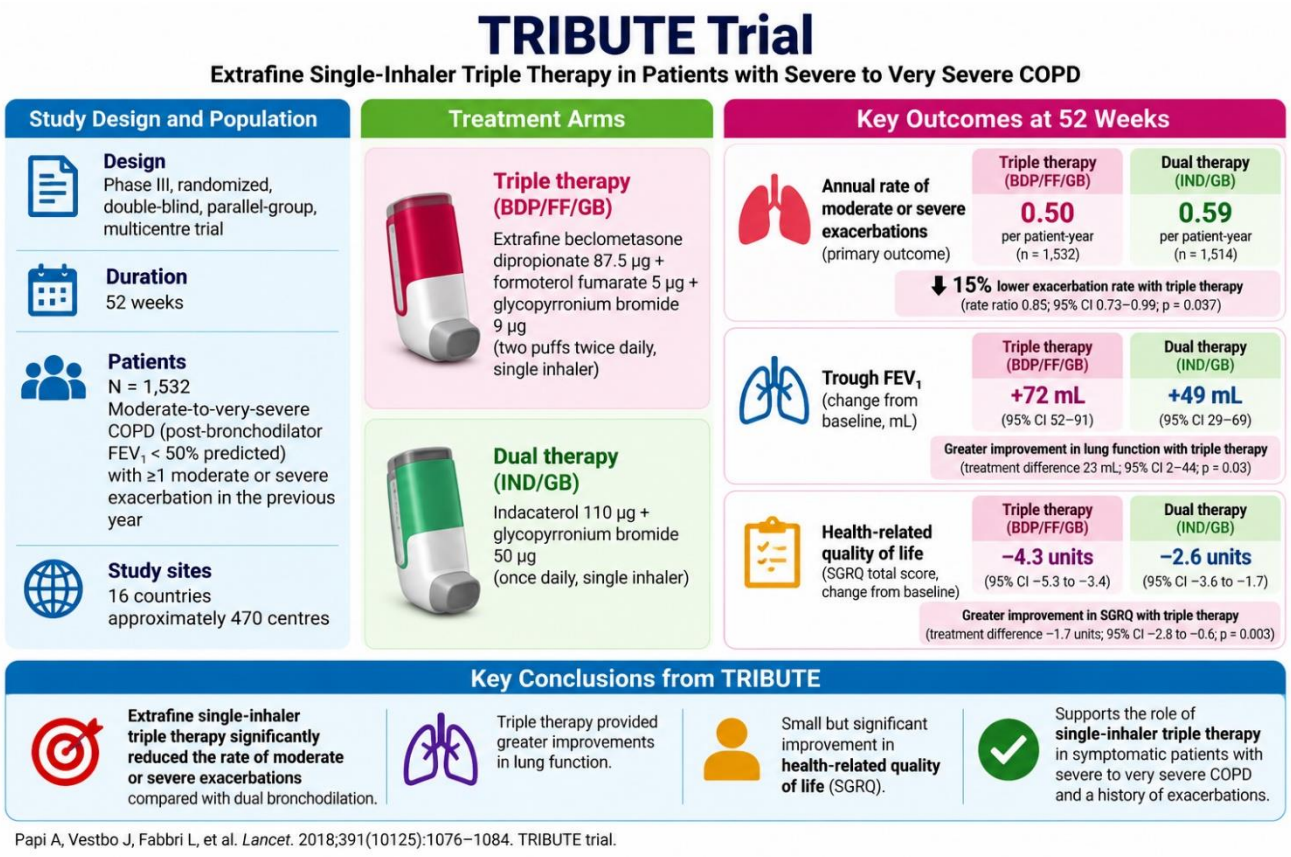


3. TRIBUTE Trial

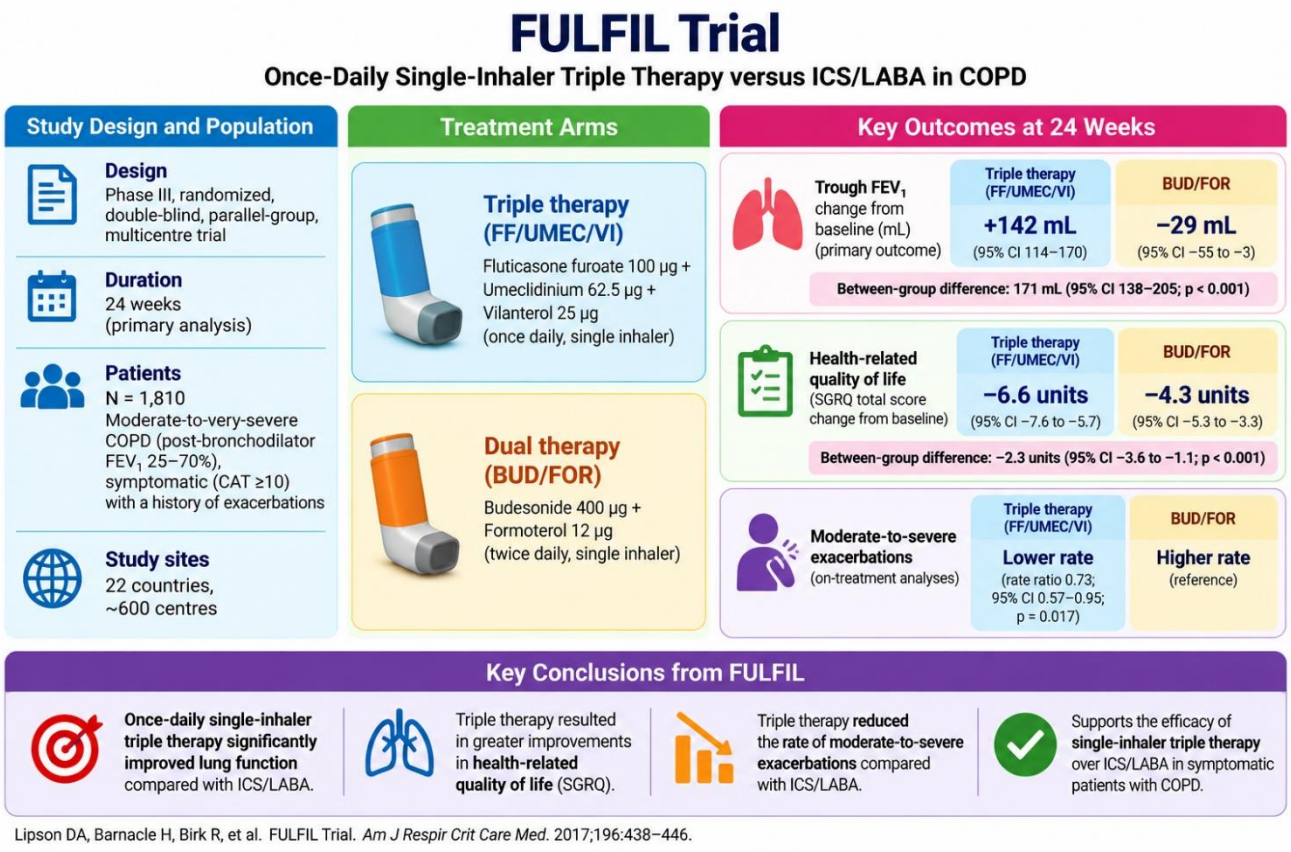
TRIBUTE compared extrafine beclometasone/formoterol/glycopyrronium with indacaterol/glycopyrronium in patients with severe or very severe airflow limitation and a history of exacerbations [5]. The annual moderate-to-severe exacerbation rate was 0.50 per patient-year with triple therapy and 0.59 with dual bronchodilation, corresponding to an approximately 15% relative reduction [5]. The trial supports triple therapy in appropriately selected patients with established, exacerbation-prone COPD. However, it does not establish universal first-line treatment.

4. FULFIL Trial

FULFIL compared once-daily fluticasone furoate/umeclidinium/vilanterol with twice-daily budesonide/formoterol [6]. At 24 weeks, triple therapy produced greater improvements in trough FEV_1 and health-related quality of life. Mean FEV_1 changes were 142 mL with triple therapy and −29 mL with the comparator. Corresponding St George's Respiratory Questionnaire changes were −6.6 and −4.3 points [6]. The trial supports the efficacy of triple therapy compared with the tested ICS/LABA regimen. However, because the comparator was not LABA/LAMA, the findings do not independently establish universal superiority over dual bronchodilation.



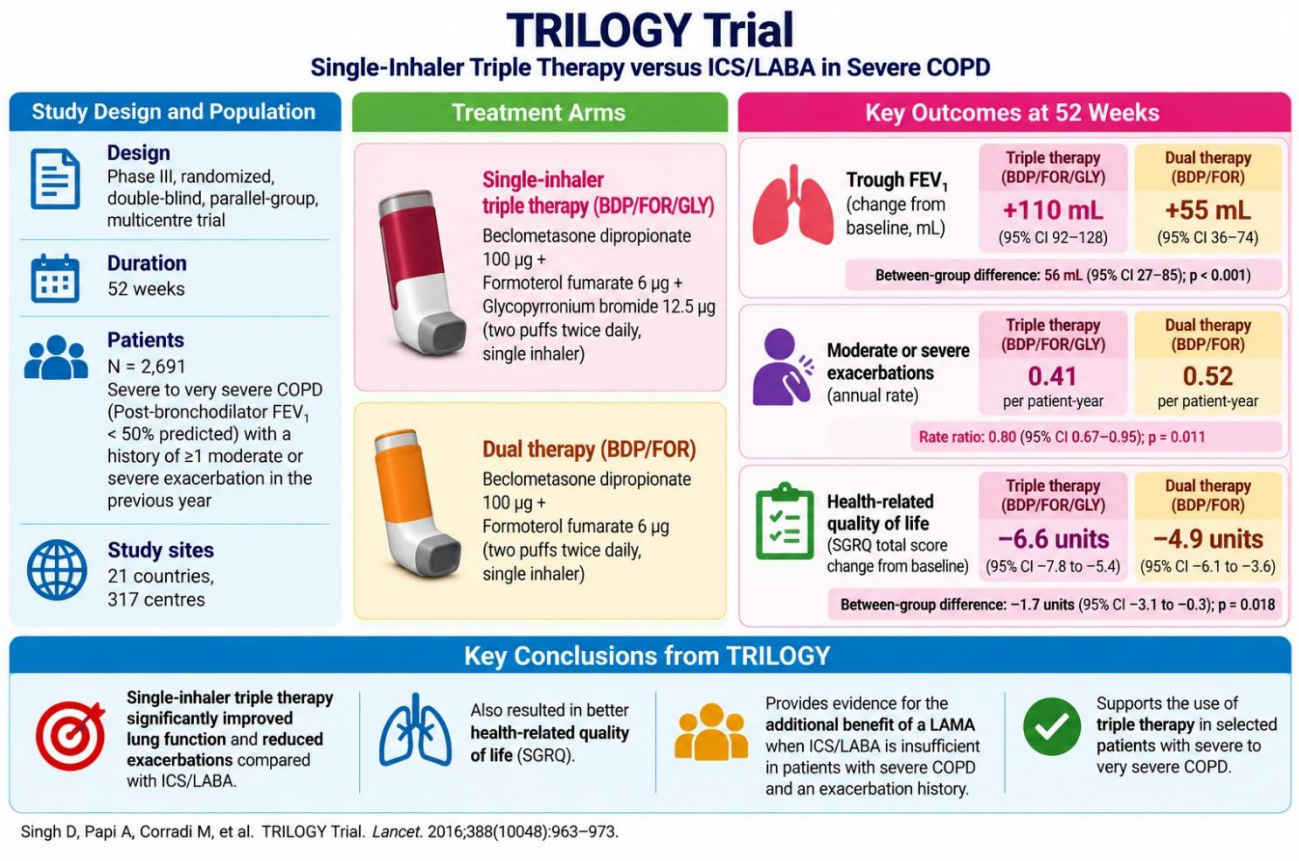
Papi A, Vestbo J, Fabbri L, et al. *Lancet*. 2018;391(10125):1076–1084. TRIBUTE trial.



Lipson DA, Barnacle H, Birk R, et al. FULFIL Trial. *Am J Respir Crit Care Med*. 2017;196:438–446.

5. TRILOGY Trial TRILOGY compared beclometasone/formoterol/glycopyrronium with

beclometasone/formoterol in patients with severe COPD [7]. Triple therapy improved lung function and reduced exacerbations compared with ICS/LABA. The trial demonstrated the additional benefit of including a LAMA in an ICS/LABA regimen for appropriately selected patients.



Singh D, Papi A, Corradi M, et al. TRILOGY Trial. *Lancet*. 2016;388(10048):963–973.

6. TRINITY Trial

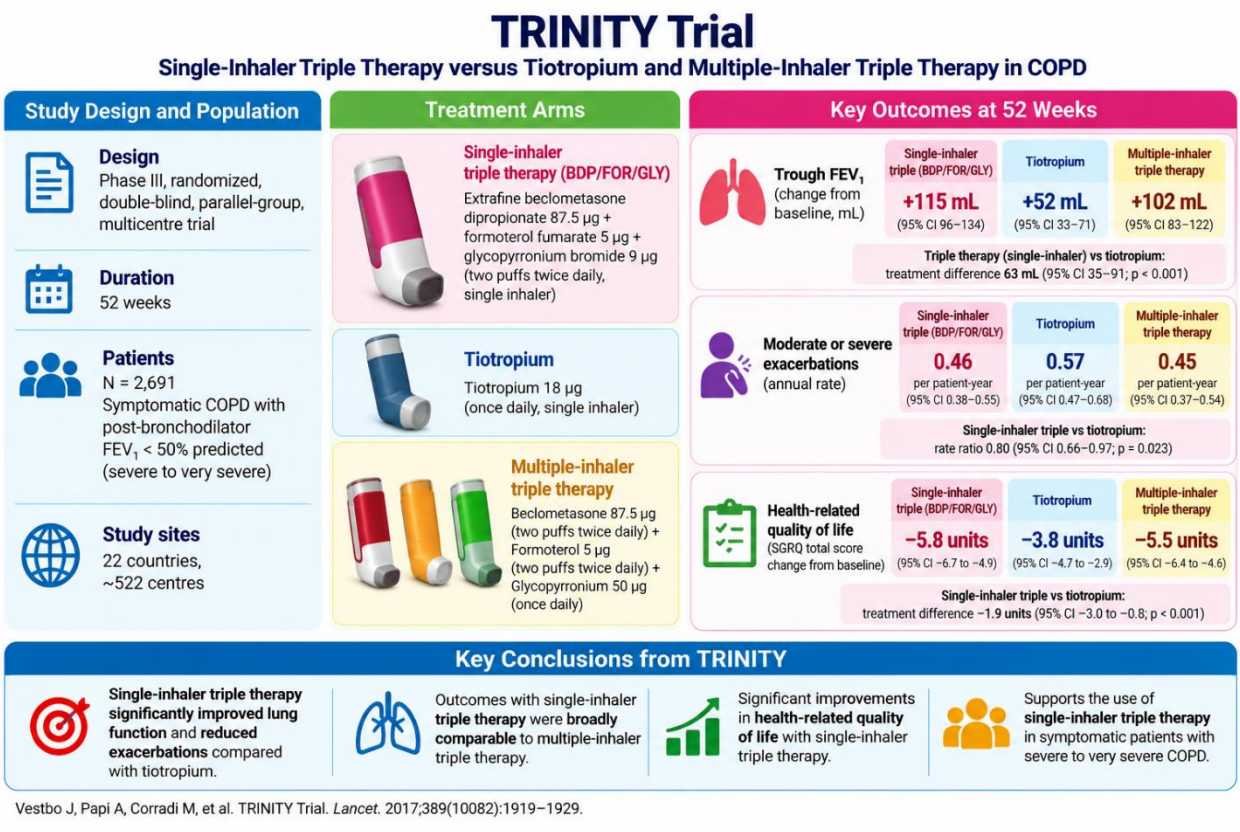
TRINITY evaluated extrafine triple therapy against tiotropium and an open-label multiple-inhaler triple regimen in patients with severe COPD [8]. The study provided additional evidence that triple therapy can improve disease control compared with LAMA monotherapy in selected patients. Outcomes were broadly comparable between the single-inhaler triple regimen and the multiple-inhaler triple regimen. Its findings support the efficacy of triple therapy in selected patients but do not establish that all symptomatic patients require three inhaled agents from the outset.

7. KRONOS Trial

KRONOS compared budesonide/glycopyrrolate/formoterol with dual inhaler regimens in patients with moderate-to-very-severe COPD [9]. Unlike some pivotal triple-therapy studies, the trial did not require a previous exacerbation history for enrollment. Triple therapy improved lung function compared with the dual regimens, and some exacerbation analyses favored triple therapy. However, the 24-week duration and the study's principal lung-function focus limit its ability to establish universal first-line treatment for treatment-naïve patients.

8. WISDOM Trial

WISDOM investigated ICS withdrawal in patients with severe COPD receiving triple therapy [17]. Participants underwent stepwise withdrawal of ICS while long-acting bronchodilation was maintained. ICS withdrawal was associated with a modest decline in lung function, while the primary analysis did not demonstrate a significant overall increase in the risk of moderate or severe exacerbations [17]. Subsequent analyses showed that withdrawal outcomes differed according to blood eosinophil counts, with greater concern in patients with higher eosinophil levels [16]. WISDOM informs treatment de-escalation rather than the selection of initial therapy. It supports careful consideration of ICS withdrawal in selected stable patients while highlighting the need to assess exacerbation history and inflammatory phenotype.



9. SUNSET Trial

SUNSET investigated ICS withdrawal in patients with COPD receiving long-term triple therapy who were not frequent exacerbators [18]. Patients switched to indacaterol/glycopyrronium or continued triple therapy. Withdrawal produced a small reduction in lung function without a significant overall increase in moderate or severe exacerbations. Patients with higher blood eosinophil counts appeared to have greater risk following withdrawal [18]. These findings support selective de-escalation in stable patients without frequent exacerbations, while emphasizing caution in patients with higher eosinophil counts or other indications for ICS.

Overall Interpretation of the Trials

The pivotal efficacy trials consistently support triple therapy in selected symptomatic patients with established COPD, particularly those at increased risk of exacerbations [3–9].

However, many participants had previous exacerbations, substantial disease burden, and prior exposure to maintenance inhalers. WISDOM and SUNSET primarily address ICS withdrawal rather than initial treatment selection [17, 18].

Therefore, the evidence for escalation to triple therapy is stronger than the direct evidence for universal initial triple therapy in treatment-naïve patients.

KRONOS Trial

Triple Therapy vs Dual Therapies in Moderate-to-Very-Severe COPD

Study Design and Population

Design
Phase III, randomized, double-blind, parallel-group, multicentre trial

Duration
24 weeks

Patients
N = 1,902
Moderate-to-very-severe COPD (post-bronchodilator FEV_1 25–80%)
Previous exacerbations not mandatory

Study sites
24 countries
~351 centres

Treatment Arms

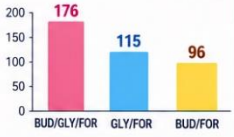
Triple therapy (BUD/GLY/FOR)
Budesonide 320 µg + Glycopyrrolate 18 µg + Formoterol fumarate 9.6 µg (two puffs twice daily, single inhaler)

Dual bronchodilator (GLY/FOR)
Glycopyrrolate 18 µg + Formoterol fumarate 9.6 µg (two puffs twice daily, single inhaler)

ICS/LABA (BUD/FOR)
Budesonide 320 µg + Formoterol fumarate 9.6 µg (two puffs twice daily, single inhaler)

Key Outcomes at 24 Weeks

Trough FEV_1 (change from baseline, mL)



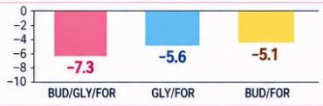
Triple therapy increased FEV_1 by **+61 mL** vs GLY/FOR ($p < 0.001$) and by **+80 mL** vs BUD/FOR ($p < 0.001$)

Moderate or severe exacerbations (annual rate, exploratory analysis)



Lower exacerbation rate with triple therapy vs GLY/FOR (rate ratio 0.57; 95% CI 0.36–0.92; p = 0.021) and vs BUD/FOR (rate ratio 0.64; 95% CI 0.40–1.03; p = 0.064)

Health-related quality of life (SGRQ total score change from baseline)



Greater improvement in SGRQ with triple therapy vs GLY/FOR (treatment difference −1.7 units; 95% CI −2.8 to −0.6; p = 0.002) and vs BUD/FOR (treatment difference −2.2 units; 95% CI −3.3 to −1.1; p < 0.001)

Key Conclusions from KRONOS

- **Single-inhaler triple therapy significantly improved lung function** compared with dual bronchodilator and ICS/LABA regimens.
- Exacerbation analyses **favoured triple therapy** (exploratory outcome).
- Demonstrated the efficacy of triple therapy in a broader **population**, as previous exacerbations were not mandatory for enrolment.
- Supports the role of **single-inhaler triple therapy** for improved lung function and disease control in moderate-to-very-severe COPD.

Ferguson GT, Rabe KF, Martinez FJ, et al. KRONOS Trial. *Lancet Respir Med.* 2018;6(10):747–758.

WISDOM Trial

Withdrawal of Inhaled Corticosteroids in Triple Therapy in Patients with COPD

Study Design and Population

Design
Phase III, randomized, double-blind, parallel-group, multicentre trial

Duration
52 weeks

Patients
N = 2,485
Severe to very severe COPD (Post-bronchodilator $FEV_1 \leq 50\%$)
on stable triple therapy (LABA/LAMA/ICS) for ≥ 6 months with a history of exacerbations in the previous year

Study sites
34 countries,
454 centres

Treatment Arms

Continued triple therapy (LABA/LAMA/ICS)
Salmeterol 50 µg + Fluticasone propionate 500 µg (confers 1,000 µg/day) + Tiotropium 18 µg (two puffs twice daily, single inhaler)

Stepwise ICS withdrawal to dual therapy (LABA/LAMA)
Gradual withdrawal of fluticasone over 12 weeks (reduction by 500 µg every 6 weeks) followed by maintenance with salmeterol 50 µg + tiotropium 18 µg (two puffs twice daily, single inhaler)

Key Outcomes at 52 Weeks

	Continued triple therapy (ICS)	ICS withdrawal to dual therapy
Trough FEV_1 (change from baseline, mL) (primary outcome: non-inferiority)	**+6 mL** (95% CI −8 to 21)	**−16 mL** (95% CI −32 to 0)
Moderate or severe exacerbations (annual rate)	**0.20** per patient-year	**0.22** per patient-year
Health-related quality of life (SGRQ total score, change from baseline)	**−5.5 units** (95% CI −6.3 to −4.8)	**−4.8 units** (95% CI −5.6 to −4.0)

Between-group difference: **22 mL** (95% CI 0–43) Met criteria for non-inferiority (upper limit < 50 mL)

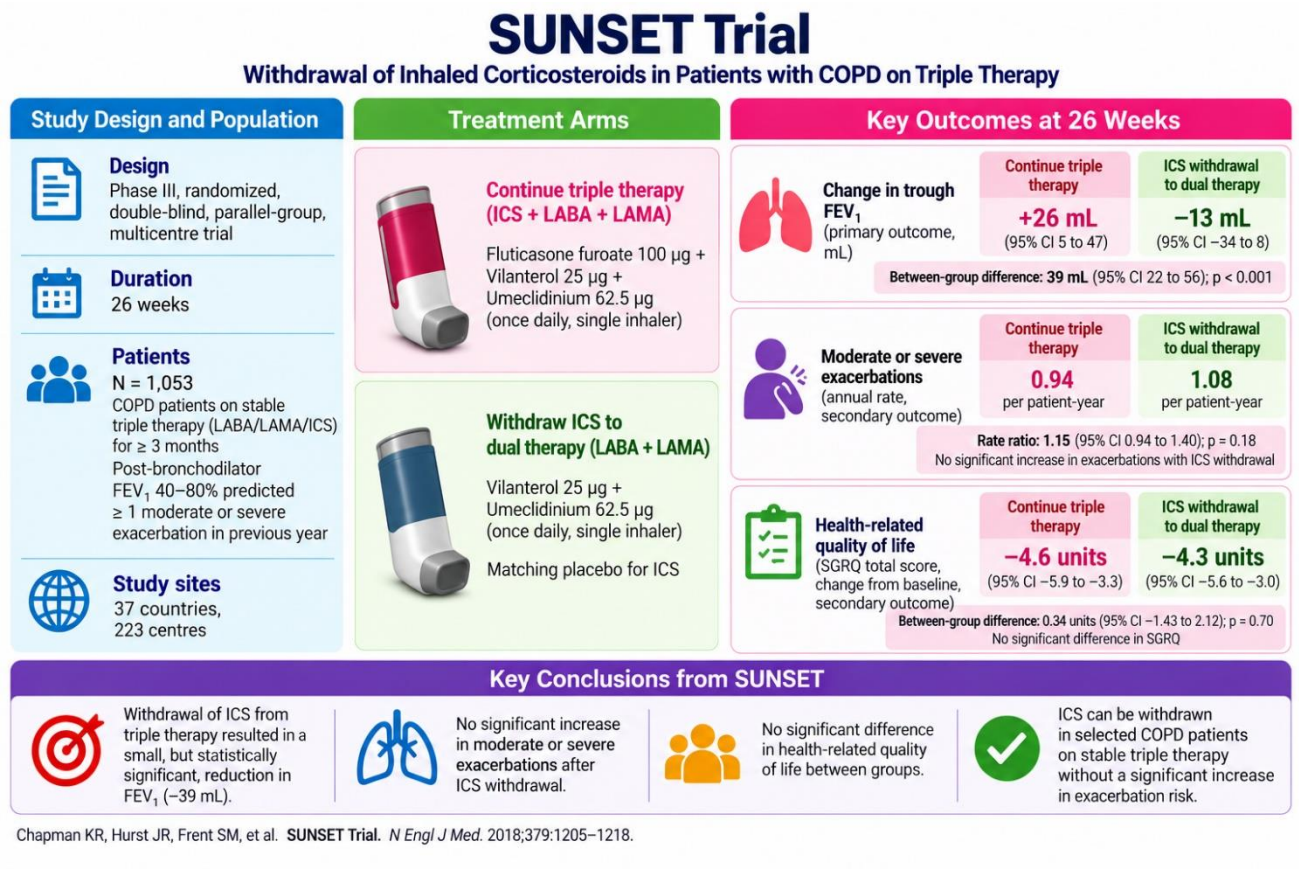
Rate ratio: 1.06 (95% CI 0.94–1.19); p = 0.35 No significant difference

Between-group difference: 0.52 units (95% CI −0.41 to 1.45); p = 0.27 No significant difference

Key Conclusions from WISDOM

- **Gradual withdrawal of ICS** from **triple therapy** was **non-inferior** to continued **triple therapy** for lung function (FEV_1) over 52 weeks.
- **No significant increase** in **moderate or severe exacerbations** after ICS withdrawal.
- **Health-related quality of life** was comparable between groups.
- Supports that **in selected** patients with **stable COPD**, **ICS can be withdrawn** from **triple therapy** without clinically important loss of control.

Magnussen H, Disse B, Rodriguez-Roisin R, et al. **WISDOM Trial.** *N Engl J Med.* 2014;371:1285–1294.



Triple Therapy for Symptom Control Alone

Persistent dyspnea is clinically important but does not automatically justify adding ICS.

LABA/LAMA provides complementary bronchodilation and can improve airflow, reduce dynamic hyperinflation, and improve exercise tolerance [2]. For patients whose principal problem is exertional breathlessness without recurrent exacerbations, optimizing bronchodilation may be preferable to adding ICS.

Before escalating treatment, clinicians should assess inhaler technique, adherence, device suitability, smoking and occupational exposure, pulmonary rehabilitation, physical deconditioning, and comorbid conditions such as cardiac disease, anemia, and obesity.

If symptoms persist without exacerbations, a change in device or bronchodilator regimen may be more appropriate than automatic escalation to triple therapy.

Blood Eosinophils and ICS Responsiveness

Blood eosinophil counts help estimate the likelihood that ICS will prevent COPD exacerbations. The relationship is continuous rather than an absolute biological threshold [15, 16].

Eosinophils below 100 cells/µL:

The expected exacerbation-prevention benefit from ICS is generally limited, especially in patients without recurrent exacerbations or concomitant asthma.

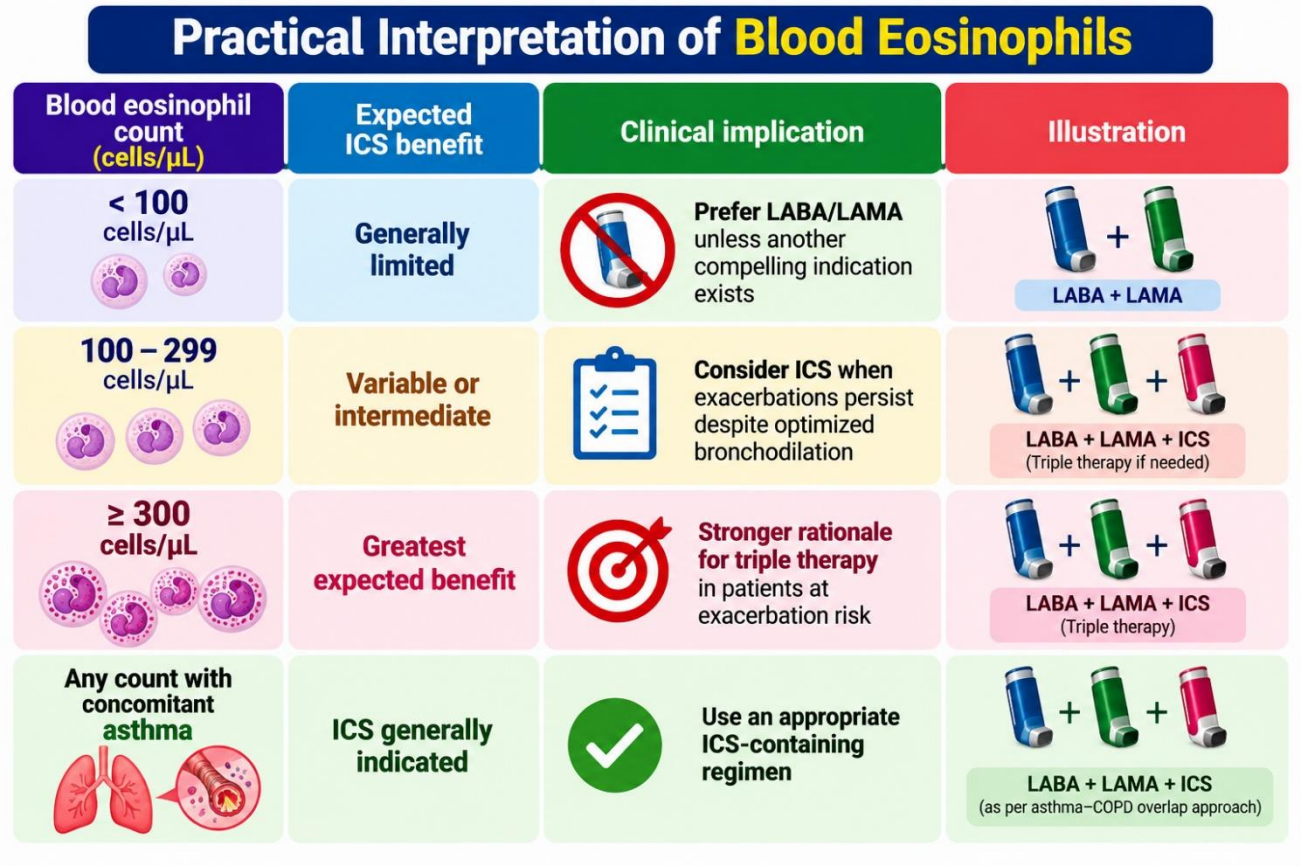
Eosinophils between 100 and 299 cells/µL:

The expected benefit is intermediate and depends on exacerbation burden, previous treatment response, and other clinical characteristics.

Eosinophils ≥300 cells/µL:

The probability of an exacerbation-prevention benefit is greatest. In patients with recurrent exacerbations, this count strengthens the rationale for triple therapy and may support consideration of initial triple therapy in selected high-risk patients [1-16].

Eosinophil counts should not be interpreted in isolation. Exacerbation history, concomitant asthma, previous pneumonia, and treatment response remain important.



Pneumonia and Other Adverse Effects

ICS use is associated with an increased risk of pneumonia in COPD, although the magnitude varies according to the molecule, dose, duration, patient characteristics, and study design [22–24].

Patients requiring particular caution include those with previous pneumonia, advanced airflow limitation, low body mass index, current smoking, older age, recurrent respiratory infections, or coexisting bronchiectasis.

Bronchiectasis does not automatically prohibit ICS use, particularly when asthma or a compelling eosinophilic indication exists. However, recurrent infections and chronic airway colonization warrant careful assessment of the indication for ICS.

Other potential adverse effects include oral candidiasis, dysphonia, skin bruising, and systemic corticosteroid effects with prolonged exposure, particularly at higher doses.

The appropriate strategy is selective prescribing, use of the lowest effective ICS dose when possible, preventive vaccination, and periodic reassessment rather than indiscriminate avoidance of triple therapy.

Mortality Benefits: What Can Be Concluded?

Mortality findings from IMPACT and ETHOS have contributed to interest in the broader benefits of triple therapy [3-14].

ETHOS reported lower all-cause mortality with the higher-dose triple regimen than with LABA/LAMA. IMPACT also reported fewer deaths in the triple-therapy group than in the LABA/LAMA group [13, 14].

However, mortality was not the primary endpoint of these pivotal exacerbation trials. Participants had substantial disease burden and were frequently receiving ICS-containing treatment before randomization. Withdrawal of pretrial ICS in some participants may have influenced outcomes.

Triple therapy may confer a survival benefit in selected patients with severe, exacerbation-prone COPD. Current evidence does not justify prescribing it to all symptomatic patients solely to improve survival.

Initial Triple Therapy versus Escalation

The distinction between initial therapy and escalation is central to the current debate.

Evidence for Escalation:

The evidence is strongest for patients who continue to experience clinically significant exacerbations despite appropriate maintenance bronchodilation. In these patients, exacerbation history

and blood eosinophil counts help identify those most likely to benefit from adding ICS [1-15].

Evidence for Initial Triple Therapy:

Direct randomized evidence comparing immediate triple therapy with initial LABA/LAMA in treatment-naïve patients remains limited. GOLD 2026 permits consideration of initial triple therapy in selected high-risk patients, particularly those with eosinophils ≥300 cells/µL, based partly on extrapolation from trials involving previously treated patients [1-4].

Clinical implication: A guideline-supported option for selected high-risk patients is not equivalent to a universal first-line standard.

Universal triple therapy would expose many patients who are unlikely to benefit from ICS to its adverse effects, cost, and treatment burden. Conversely, withholding ICS from patients with recurrent exacerbations, substantial eosinophilia, or concomitant asthma could result in preventable morbidity.

The rational strategy is individualized treatment based on the probability of benefit and harm.

COPD Management in India: Implications for Triple Therapy

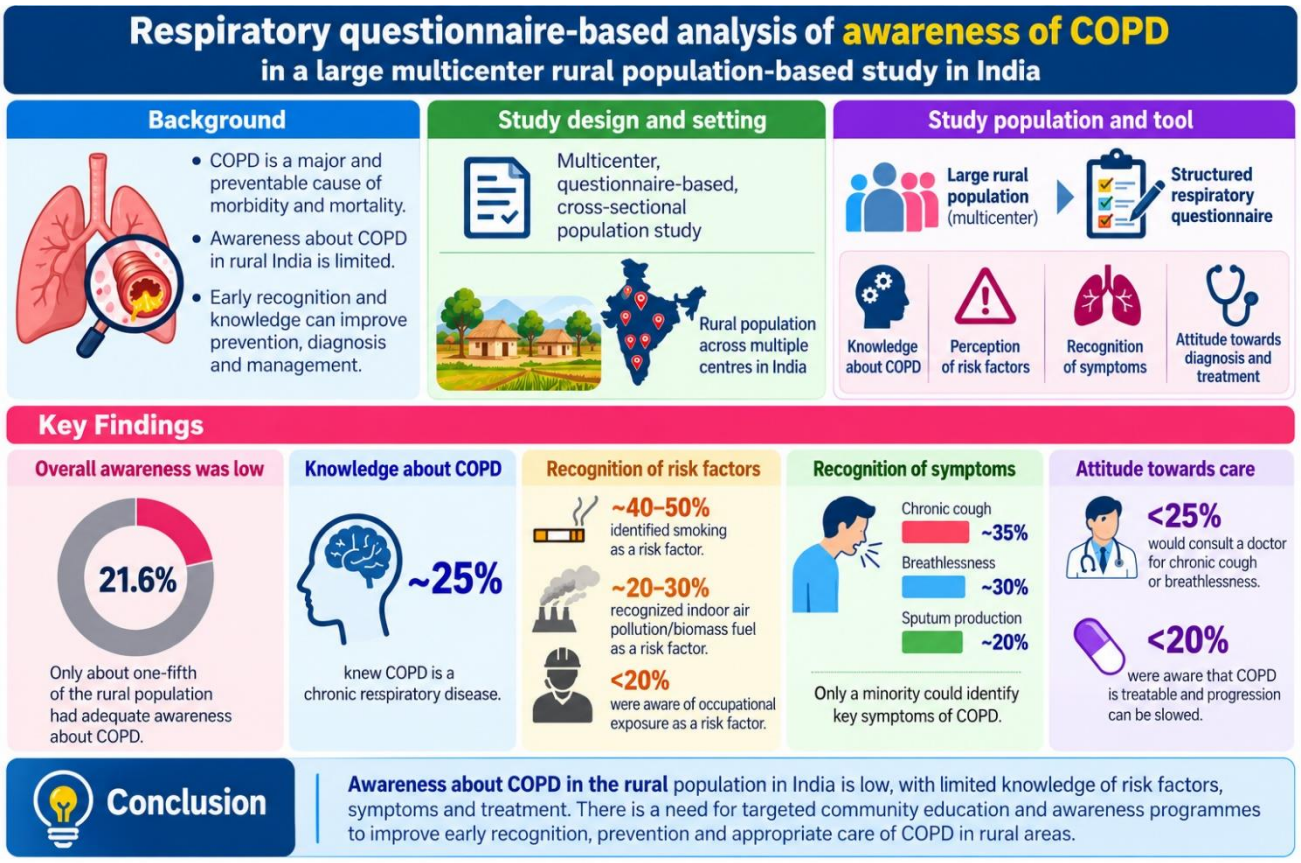
The application of international COPD recommendations in India requires consideration of disease recognition, diagnostic accuracy, inhaler access, affordability, treatment adherence, and the heterogeneity of risk exposures.

Underdiagnosis and Treatment Gaps

Patil and colleagues have reported substantial challenges in COPD diagnosis, disease awareness, and treatment practices in rural Indian settings [27-30].

Their multicentre questionnaire-based study of 6,000 patients examined COPD awareness and respiratory health knowledge in a rural population [28]. Their research on diagnosis and treatment trends and on COPD as a neglected and underestimated chronic lung disease further emphasizes the importance of recognizing and treating COPD appropriately [27-30].

These studies are relevant because escalation to triple therapy cannot compensate for an incorrect diagnosis, poor inhaler technique, inadequate adherence, or failure to provide appropriate bronchodilation.



Rational Inhalation Therapy

Patil and Pawar discussed the challenges of implementing rational inhaled treatment in India, including patient beliefs, prescribing practices, and access to inhaled medications [29].

These concerns are particularly relevant when choosing between dual and triple therapy. The convenience of a single-inhaler formulation may improve adherence in selected patients who require all three components, but a more complex or expensive inhaler regimen may not improve outcomes when the principal problem is poor access, incorrect technique, or inappropriate prescribing.

The initial priority should be accurate diagnosis, smoking cessation, education, appropriate bronchodilation, vaccination, and regular follow-up.

Indian COPD Phenotypes and ICS Selection

Patil *et al*., argued that Indian COPD populations may differ from Western trial populations in exposure patterns and inflammatory characteristics and advocated greater consideration of ICS in selected Indian COPD populations [31]. This perspective is relevant to the heterogeneity of COPD in India, where tobacco smoking, biomass smoke, occupational exposures, previous respiratory infections, and other environmental factors may contribute to disease.

However, a proposed difference in phenotype does not establish that all Indian patients respond better to ICS. The evidence should be interpreted in the context of study design, patient selection, inflammatory characterization, and the absence of large randomized trials demonstrating universal superiority of initial triple therapy in Indian COPD populations.

Blood eosinophils, exacerbation history, concomitant asthma, infection risk, and treatment response remain important considerations.

Practical Implications for Indian Clinical Practice

A rational approach should include:

- Confirming COPD with post-bronchodilator spirometry.
- Assessing symptoms and exacerbation history systematically.
- Providing appropriate long-acting bronchodilation.
- Considering ICS according to exacerbation risk, blood eosinophils, and concomitant asthma.
- Assessing inhaler technique, adherence, affordability, and device suitability.
- Evaluating pneumonia risk and coexisting bronchiectasis.
- Improving patient awareness and access to pulmonary rehabilitation and vaccination.

The Indian literature supports improving the quality and consistency of COPD diagnosis and inhaled treatment. It should not be used as a substitute for direct evidence comparing initial triple therapy with LABA/LAMA in treatment-naïve patients.

Practical Treatment Algorithm

Confirm the Diagnosis: Establish COPD using compatible clinical features and post-bronchodilator spirometry demonstrating persistent airflow obstruction.

Assess Symptoms and Exacerbation Risk:

Document symptom burden using the COPD Assessment Test or modified Medical Research Council scale. Record exacerbations during the preceding 12 months, including episodes requiring systemic corticosteroids, antibiotics, emergency assessment, or hospitalization.

Select Initial Treatment:

- Most symptomatic patients without recurrent exacerbations or a compelling indication for ICS: initiate LABA/LAMA when appropriate.
- Selected patients with high exacerbation risk and eosinophils ≥300 cells/μL: consider initial triple therapy after discussing the limitations of direct treatment-naïve evidence.
- Patients with concomitant asthma: use an ICS-containing regimen appropriate to the combined disease presentation.

Reassess Treatment Response: If exacerbations persist despite LABA/LAMA, review adherence, inhaler technique, comorbidities, and eosinophil counts before considering escalation to triple therapy.

Consider ICS Withdrawal When Appropriate:

In selected patients who remain stable without exacerbations, particularly when the original ICS indication is weak or adverse effects are significant, consider withdrawal with appropriate monitoring. Exercise caution in patients with asthma, higher eosinophil counts, or recurrent exacerbations [17, 18].

Clinical Decision Framework

Clinical presentation	Preferred approach	Rationale
Persistent dyspnea without recurrent exacerbations	LABA/LAMA	Targets symptoms while avoiding unnecessary ICS exposure
Recurrent exacerbations despite LABA/LAMA and eosinophils ≥300 cells/μL	Triple therapy	High probability of ICS-associated exacerbation reduction
Recurrent exacerbations despite LABA/LAMA and eosinophils 100–299 cells/μL	Consider triple therapy	Benefit depends on exacerbation burden and clinical context
Recurrent exacerbations with eosinophils <100 cells/μL	Individualized alternative strategy	Expected ICS benefit is lower; investigate other drivers

COPD with concomitant asthma	ICS-containing treatment	Asthma provides an independent indication for ICS
Previous pneumonia, infrequent exacerbations, and low eosinophils	Favor bronchodilation and reassess ICS indication	Potential infection harm may outweigh benefit
Stable on triple therapy without recent exacerbations	Reassess continued ICS need	Avoid unnecessary long-term corticosteroid exposure

Evidence Gaps and Future Research

Several unanswered questions limit confidence in universal first-line triple therapy.

First, adequately powered randomized trials are needed to compare initial triple therapy directly with LABA/LAMA in treatment-naïve patients.

Second, future trials should stratify participants by blood eosinophil counts, exacerbation history, asthma features, smoking status, and coexisting bronchiectasis.

Third, longer-term studies should clarify mortality effects, pneumonia risk, treatment persistence, and the consequences of initiating ICS early in the disease course.

Fourth, real-world studies from low- and middle-income countries are needed to evaluate affordability, inhaler access, adherence, infectious comorbidities, and effectiveness outside highly selected clinical trial populations.

Finally, research should identify which patients can safely discontinue ICS after sustained clinical stability without increasing exacerbation risk.

These questions are particularly relevant in settings where COPD is complicated by prior tuberculosis, bronchiectasis, recurrent bacterial infection, or substantial exposure to biomass smoke.

Recommendations for Clinical Practice

Avoid universal triple therapy. Symptoms alone do not establish an indication for ICS.

Use LABA/LAMA as the preferred initial approach for most symptomatic patients without concomitant asthma or another compelling indication for ICS [1, 2].

Consider initial triple therapy in selected high-risk patients, particularly those with substantial exacerbation risk and blood eosinophils ≥300 cells/µL. Explain that direct evidence in treatment-naïve patients remains limited [1-4].

Escalate to triple therapy when exacerbations persist despite optimized LABA/LAMA and the clinical profile suggests an ICS-responsive phenotype [1-15].

Interpret eosinophils alongside exacerbation history. Counts ≥300 cells/µL indicate the greatest likelihood of benefit, whereas counts <100 cells/µL generally indicate a lower expected response [15, 16].

Assess pneumonia risk before and during ICS treatment. Consider previous pneumonia, recurrent infections, coexisting bronchiectasis, and the strength of the ICS indication [22–24].

Reassess ICS periodically. Consider withdrawal in appropriately selected stable patients, but exercise caution in those with asthma, higher eosinophil counts, or recurrent exacerbations [17, 18].

Optimize nonpharmacological management. Smoking cessation, vaccination, pulmonary rehabilitation, adherence, and inhaler technique remain essential regardless of the inhaler regimen.

Individualize treatment. Consider exacerbation burden, symptoms, treatment preferences, affordability, comorbidities, and adverse-effect susceptibility.

CONCLUSION

Triple therapy has an established role in selected patients with symptomatic COPD, particularly those with recurrent exacerbations and evidence of corticosteroid-responsive inflammation. Major trials, including IMPACT, ETHOS, TRIBUTE, FULFIL, and TRILOGY, support its efficacy in appropriately selected patients with established disease [3–7].

However, these findings should not be interpreted as evidence that triple therapy is the optimal initial treatment for every symptomatic patient. The pivotal trials largely enrolled previously treated patients with substantial disease burden, and direct randomized evidence comparing initial triple therapy with LABA/LAMA in treatment-naïve patients remains limited.

Current GOLD guidance allows initial triple therapy to be considered in selected high-risk patients, particularly when blood eosinophils are ≥300 cells/µL [1]. For most symptomatic patients without these features, LABA/LAMA remains the preferred initial strategy.

Indian publications highlight important challenges in COPD awareness, diagnosis, and rational inhaled treatment [27–31]. These findings reinforce the need for better diagnosis, appropriate bronchodilation,

patient education, and individualized prescribing. They do not establish universal first-line triple therapy as the preferred strategy for Indian patients.

The most defensible approach is selective, phenotype-directed triple therapy rather than universal first-line prescribing or an inflexible restriction to frequent exacerbators alone. This strategy preserves the potential benefits of ICS for patients most likely to respond while limiting unnecessary exposure to corticosteroid-associated adverse effects.

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