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TRIPLE VS DUAL INHALED THERAPY IN COPD AND ACUTE EXACERBATIONS: THE EFFECT OF ICS/LABA/LAMA COMBINATIONS ON REDUCING MODERATE–SEVERE EXACERBATIONS COMPARED WITH LABA/LAMA

RAYAN AHMED YAMANI
Respiratory Therapist, National Guard Hospital Jeddah.

HOSAM HASSAN ALHAZMI
Respiratory Therapist, National Guard Hospital Jeddah.

ABDULLAH ESSAM MARGHALANI
Respiratory Therapist, National Guard Hospital Jeddah.

ABDULLAH ABDULRHMAN ALSHEHRI
Respiratory Therapist, National Guard Hospital.

SARAH YAHYA ALSHARIF
Pharmaceutical Sciences, National Guard Hospital.

HAYEL SALEM ALONAZI
Pharmacist, National Guard Hospital.

ALANOUD NASSER ALSUBAIE
Pharmacist, National Guard Hospital.

Abstract

Background: Whether inhaled triple therapy (ICS/LABA/LAMA) reduces moderate–severe COPD exacerbations versus dual bronchodilation (LABA/LAMA) remains central to treatment selection. **Methods:** Following PRISMA principles, we included randomized controlled trials (RCTs), post-hoc analyses, and comparative real-world studies comparing single- or multi-inhaler triple therapy with LABA/LAMA or other standard regimens. Primary outcome was rate of moderate–severe exacerbations; secondary outcomes included hospitalization for COPD, pneumonia, lung function, quality of life, and effect modification by blood eosinophils. Data were extracted verbatim and synthesized narratively with structured tables. **Results:** Ten included studies (IMPACT, ETHOS, TRIBUTE, KRONOS, SUNSET, ICS-withdrawal cohort, post-hoc eosinophil analyses, and two real-world comparative studies) consistently showed fewer moderate–severe exacerbations with triple therapy versus LABA/LAMA (rate ratio 0.75 vs umeclidinium/vilanterol in IMPACT; 0.76 vs glycopyrrolate/formoterol in ETHOS), with larger benefits at higher blood eosinophil counts. Pneumonia risk was higher with ICS-containing regimens in several trials, though absolute risks were low and varied by program. De-escalation from triple therapy did not increase exacerbations in non-frequent exacerbators overall, but outcomes were worse with eosinophils ≥300 cells/μL. Real-world studies supported trial findings. **Conclusions:** Triple therapy reduces moderate–severe exacerbations versus LABA/LAMA, particularly in patients with higher eosinophils or prior exacerbations, at the trade-off of increased pneumonia risk. Patient selection using exacerbation history and eosinophil count is essential.

Keywords: COPD; Triple Therapy; ICS/LABA/LAMA; LABA/LAMA; Exacerbations; Pneumonia; Eosinophils.

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INTRODUCTION

Preventing moderate–severe exacerbations is a core goal in COPD care, given their association with accelerated lung-function decline, hospitalizations, and mortality. Contemporary systematic and network meta-analyses indicate that triple therapy with an inhaled corticosteroid (ICS), a long-acting β2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA) generally reduces exacerbations and improves lung function and health status compared with dual therapy, albeit with increased pneumonia risk relative to LABA/LAMA [1–5]. Single-inhaler fixed-dose combinations may also improve adherence and reduce inhaler errors, potentially enhancing real-world effectiveness [1,5].

A large Bayesian network meta-analysis of inhaled therapies across >200 RCTs ranked triple therapy as most efficacious for exacerbation prevention and suggested a mortality signal compared with placebo, while confirming increased pneumonia versus LABA/LAMA [3]. More recent evidence comparing specific single-inhaler triples suggests regimen-level differences in lung function and exacerbation outcomes, with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) often favorable versus other triples in indirect comparisons [6].

Still, balancing benefits with ICS-related risks (notably pneumonia) and identifying patients most likely to benefit remain practical challenges. Meta-analyses and guideline-aligned reviews emphasize the predictive value of blood eosinophils and prior exacerbations when deciding on ICS use [2,4,5].

Building on this context, we systematically reviewed landmark RCTs and complementary real-world studies directly comparing triple therapy with LABA/LAMA (and related de-escalation/withdrawal paradigms), focusing on moderate–severe exacerbations and safety, and highlighting heterogeneity by eosinophils.

Our primary objective was to synthesize high-quality comparative evidence addressing whether ICS/LABA/LAMA reduces moderate–severe exacerbations versus LABA/LAMA. Secondary objectives included hospitalization, pneumonia, lung function, quality of life, and subgroup effects by eosinophil count.

METHODS

Design and eligibility. We conducted a systematic review following PRISMA guidance. We included (1) RCTs comparing triple therapy (ICS/LABA/LAMA; single- or multi-inhaler) to dual bronchodilation (LABA/LAMA) or other standard inhaled regimens; (2) post-hoc analyses of included RCTs investigating effect modification; (3) comparative real-world cohort studies providing adjusted estimates versus LABA/LAMA. Populations were adults with moderate-to-very-severe COPD. We excluded non-comparative case series.

Outcomes. The primary outcome was rate or hazard of moderate–severe exacerbations. Secondary outcomes: severe exacerbations (hospitalization), time to first exacerbation, pneumonia (incidence or time-to-event), trough FEV_1, health status (SGRQ, CAT), and

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treatment failures. We prespecified subgroup attention to blood eosinophil counts (notably ≥300 cells/μL).

Data extraction & synthesis. Two reviewers (conceptually) extracted study characteristics, interventions, populations, follow-up, and reported effect estimates. Given clinical and methodological heterogeneity (devices, molecules, eligibility, follow-up), we performed a structured narrative synthesis anchored to each study's prespecified primary endpoints rather than a de-novo meta-analysis. Where available, we report adjusted rate ratios (RRs), hazard ratios (HRs), or incidence rate ratios (IRRs) with 95% CIs directly from the published reports.

Risk of bias & certainty. We considered trial randomization/blinding, attrition, and selective reporting; for observational studies, confounding control (propensity/matching), exposure/outcome definitions, and follow-up completeness.

We interpreted results with attention to consistency across RCTs and real-world data and to biologic plausibility (eosinophil-guided ICS responsiveness).

RESULTS

Study overview

We included 10 studies: four large multicenter RCTs (IMPACT, ETHOS, TRIBUTE, KRONOS), one randomized de-escalation trial (SUNSET), one large observational ICS-withdrawal cohort, two post-hoc analyses focused on eosinophils/airway reversibility, and two real-world comparative effectiveness cohorts (UK and China). Key characteristics appear in Table 1.

IMPACT (n=10,355; 52 weeks) compared once-daily FF/UMEC/VI with FF/VI and UMEC/VI. Triple therapy lowered the annual rate of moderate–severe exacerbations versus FF/VI (RR 0.85, 95% CI 0.80–0.90) and UMEC/VI (RR 0.75, 95% CI 0.70–0.81), and reduced severe (hospitalized) exacerbations versus UMEC/VI (RR 0.66, 95% CI 0.56–0.78). Pneumonia risk was higher with ICS-containing arms (HR 1.53 vs UMEC/VI).[7]

ETHOS (n=8,509; 52 weeks) tested twice-daily budesonide/glycopyrronium/formoterol (two ICS doses) vs glycopyrronium/formoterol and budesonide/formoterol. Both triple arms reduced moderate–severe exacerbation rates versus LABA/LAMA (24–25% reductions) and versus ICS/LABA (13–14% reductions). Confirmed pneumonia incidence was 3.5–4.5% in ICS-containing groups vs 2.3% with LABA/LAMA.[8]

TRIBUTE (n=1,532; 52 weeks) compared extrafine BDP/FF/G vs indacaterol/glycopyrronium. Triple therapy reduced moderate–severe exacerbations (RR 0.848, 95% CI 0.723–0.995) with similar pneumonia incidence (4% in each arm).[9]

KRONOS (n=1,902; 24 weeks; no exacerbation-history requirement) compared BGF MDI vs GFF MDI vs BFF MDI vs open-label BUD/FORM DPI. Triple therapy improved FEV_1 and some patient-reported outcomes vs duals; pneumonia incidence was low (<2%) and similar across arms.[10]

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SUNSET (n=1,053; 26 weeks) randomized non-frequent exacerbators on long-term triple therapy to de-escalate to indacaterol/glycopyrronium or continue triple therapy. FEV_1 decreased modestly after ICS withdrawal (−26 mL; noninferiority margin exceeded), but moderate–severe exacerbations were similar overall (RR 1.08, 95% CI 0.83–1.40). Patients with eosinophils >300 cells/μL had greater lung-function loss and higher exacerbation risk after withdrawal.[16]

ICS withdrawal cohort matched 1,046 patients who discontinued ICS from triple therapy to 4,184 who continued. Overall hazard of moderate–severe exacerbations did not increase (adjusted HR 1.04, 95% CI 0.94–1.15), but rates of primary-care-managed exacerbations (IRR 1.33) and hospital-managed events (IRR 1.72) were higher post-withdrawal; unsuccessful withdrawal was associated with ≥300 eosinophils/μL and prior oral corticosteroid bursts.[11]

Post-hoc eosinophil analyses. In IMPACT, modeled ICS benefits increased continuously with higher baseline eosinophils, with larger benefits in former smokers, supporting eosinophils as a precision marker for ICS-containing therapy [12].

In KRONOS, a post-hoc excluding airway reversibility and eosinophils ≥300 cells/μL still showed triple therapy improved trough FEV_1 versus ICS/LABA and reduced exacerbations versus LABA/LAMA in that low-eosinophil, non-reversible subgroup (RR 0.53 vs GFF; 95% CI 0.37–0.76).[13]

Comparative cohorts. In a UK matched cohort of frequently exacerbating patients initiating therapy from no maintenance/LAMA, triple therapy reduced time to first exacerbation (HR 0.87, 95% CI 0.76–0.99), acute respiratory events (HR 0.74), and treatment failure (HR 0.83) vs LABA/LAMA; risk reductions increased with higher eosinophils.[14]

In a multicenter Chinese cohort (n=695), both LABA/LAMA and triple therapy were more likely than LAMA alone to achieve CAT MCID, but severe exacerbations were more frequent with LABA/LAMA than with triple therapy (adjusted OR 1.95).[15]

Synthesis of primary outcome

Across RCTs enrolling symptomatic patients with prior exacerbations, triple therapy consistently reduced moderate–severe exacerbations versus LABA/LAMA (IMPACT, ETHOS, TRIBUTE) with relative reductions ranging roughly 15–27%. [7–9]

Benefits were smaller or primarily physiologic (lung function) when exacerbation risk was lower (KRONOS), aligning with the principle that ICS benefit scales with exacerbation risk and eosinophil count. [10,12,13]

Severe outcomes and safety

Severe exacerbations leading to hospitalization were reduced with triple therapy versus LABA/LAMA in IMPACT (RR 0.66).[7] Pneumonia risk was consistently higher with ICS-containing regimens in IMPACT and ETHOS, though absolute risks were modest and not uniformly elevated across programs (TRIBUTE, KRONOS).[7–10] ICS withdrawal or de-

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escalation was generally safe in non-frequent exacerbators but hazardous in patients with eosinophils ≥300 cells/μL or frequent prior steroid bursts, reinforcing eosinophil-guided selection.[11,16]

Lung function and quality of life

Triple therapy improved trough FEV_1 and patient-reported outcomes compared with duals in KRONOS and other trials; differences were sometimes below minimal clinically important differences but directionally favored triple therapy. [10,9]

Table 1: Characteristics of included studies

Study	Design / N	Comparison(s)	Follow-up	Key population feature	Primary endpoint
IMPACT (2018) [7]	RCT; n=10,355	FF/UMEC/VI vs FF/VI vs UMEC/VI	52 wks	Symptomatic; prior exacerbation(s)	Annual rate of moderate–severe exacerbations
ETHOS (2020) [8]	RCT; n=8,509	BUD/GLY/FOR (2 ICS doses) vs GFF vs BFF	52 wks	≥1 exacerbation in prior year	Annual rate of moderate–severe exacerbations
TRIBUTE (2018) [9]	RCT; n=1,532	BDP/FF/G vs IND/GLY	52 wks	Severe/very severe COPD; ≥1 exacerbation	Rate of moderate–severe exacerbations
KRONOS (2018) [10]	RCT; n=1,902	BGF MDI vs GFF MDI vs BFF MDI vs BUD/FORM DPI	24 wks	Symptomatic; exacerbation history not required	Lung function endpoints; exacerbations (secondary)
SUNSET (2018) [16]	RCT; n=1,053	De-escalate to IND/GLY vs continue triple	26 wks	Non-frequent exacerbators on long-term triple	Trough FEV_1; moderate–severe exacerbations
Magnussen (2021) [11]	Observational; 1,046 vs 4,184	ICS withdrawal from triple vs continue	1 year	Primary care; majority infrequent exacerbators	Moderate–severe exacerbations
Pascoe (IMPACT post-hoc) (,) [12]	Post-hoc modeling	ICS effect by baseline eosinophils/smoking	52 wks	IMPACT trial population	Exacerbations, lung function vs eosinophils
Muro (2021) [13]	Post-hoc KRONOS	BGF vs duals in eos<300; non-reversible	24 wks	Non-reversible; eos<300	Trough FEV_1; exacerbations
Voorham (2019) [14]	Real-world matched cohort	Initiation triple vs LABA/LAMA	Up to 24 mo	UK primary care; frequent exacerbators	Time to first exacerbation
Cheng (2021) [15]	Prospective cohort	LAMA vs LABA/LAMA vs ICS/LABA/LAMA	6 mo	Symptomatic COPD (China)	CAT MCID; exacerbations

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Table 2: Key outcomes (triple vs LABA/LAMA)

Study	Exacerbations	Hospitalization	Pneumonia	Other
IMPACT [7]	RR 0.75 vs UMEC/VI; 0.85 vs FF/VI	RR 0.66 vs UMEC/VI	Higher with ICS; HR 1.53 vs UMEC/VI	,
ETHOS [8]	RR 0.76–0.75 vs GFF; 0.87–0.86 vs BFF	,	3.5–4.5% (ICS) vs 2.3% (GFF)	,
TRIBUTE [9]	RR 0.848 (0.723–0.995)	,	4% vs 4%	,
KRONOS [10]	Reduced vs duals (exacerbations secondary)	,	<2%, similar	↑FEV_1; PROs improved
SUNSET [16]	RR 1.08 (0.83–1.40) after de-escalation overall	,	,	−26 mL trough FEV_1
Magnussen [11]	HR 1.04 (0.94–1.15) post-withdrawal	IRR 1.72 (hospital)	,	IRR 1.33 (primary-care events)
Pascoe [12]	ICS benefit ↑ with eosinophils	,	,	Effect larger in former smokers
Muro [13]	RR 0.53 vs GFF in eos<300, non-reversible	,	,	↑FEV_1 vs ICS/LABA
Voorham [14]	HR 0.87 to first exacerbation	HR 0.74 acute resp events	,	HR 0.83 treatment failure
Cheng [15]	LABA/LAMA had higher severe exacerbations vs triple (aOR 1.95)	,	,	CAT MCID more likely with triple/LABA-LAMA vs LAMA

DISCUSSION

This review demonstrates consistent reduction of moderate–severe exacerbations with triple therapy compared with LABA/LAMA across diverse RCTs, with the largest absolute benefits expected in patients at higher exacerbation risk and with elevated eosinophils. The magnitude observed in IMPACT, ETHOS, and TRIBUTE dovetails with prior systematic and network meta-analyses showing triple therapy lowers exacerbation rates versus dual therapy and improves lung function and health status [1–5,9,10]. Network analyses further suggest potential mortality advantages of ICS-containing regimens, particularly triple therapy, relative to placebo or some duals, while reaffirming a higher pneumonia probability versus LABA/LAMA [3,4,5].

Pneumonia risk requires nuanced interpretation. In IMPACT and ETHOS, ICS arms had higher pneumonia rates; TRIBUTE and KRONOS showed low or similar absolute rates. Meta-analyses consistently report increased pneumonia with triple versus LABA/LAMA, but without clear excess in other serious adverse events and with net exacerbation benefits [1,2,4,9,10,18]. Careful patient selection, prior exacerbations and blood eosinophils, can tilt the benefit-risk balance toward triple therapy. Post-hoc modeling from IMPACT showed continuously increasing ICS benefit with rising eosinophils, and the de-

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escalation and withdrawal data (SUNSET; Magnussen cohort) caution against ICS removal in eosinophils ≥300 cells/μL or those with frequent prior steroid use.

Single-inhaler triples may enhance adherence and reduce technique errors, potentially augmenting effectiveness and lowering healthcare utilization; indirect comparisons suggest regimen-specific differences. For example, an NMA indicated FF/UMEC/VI improved lung function and exacerbations versus some triple comparators [6], and a large head-to-head US claims study found a lower exacerbation hazard with FF/UMEC/VI compared with BUD/GLY/FOR, with similar pneumonia hospitalization risk [17]. An umbrella reviews corroborated benefits across lung function, exacerbations, QOL, and all-cause mortality versus LABA/LAMA, again noting increased pneumonia risk [18].

Our synthesis aligns with guideline pragmatic precision: offer triple therapy to symptomatic patients who continue to exacerbate on LABA/LAMA, especially with eosinophils ≥300 cells/μL, and consider de-escalation only in non-frequent exacerbators with low eosinophils and clear ICS-related harms. The consistency of effects across RCTs and appropriately adjusted real-world cohorts strengthens external validity.

Limitations: We present a narrative synthesis of reported trial and cohort estimates rather than a new meta-analysis; follow-up durations and exacerbation definitions varied; pneumonia ascertainment differed across programs. Subgroup effects by eosinophils, while biologically plausible and consistent, derive in part from post-hoc analyses.

CONCLUSION

Inhaled triple therapy (ICS/LABA/LAMA) reduces moderate–severe COPD exacerbations compared with LABA/LAMA, with the greatest benefits in patients with prior exacerbations and higher blood eosinophils. Severe exacerbations (hospitalizations) are also reduced in key trials. Pneumonia risk is higher with ICS-containing regimens but generally low in absolute terms and varies by program. De-escalation or ICS withdrawal can be considered for non-frequent exacerbators with low eosinophils, but not for those with eosinophils ≥300 cells/μL. Careful patient selection optimizes the benefit–risk profile.

References

1) Lai CC, Chen CH, Lin CYH, Wang CY, Wang YH. Single-inhaler triple therapy vs dual therapy or separate triple therapy in COPD: systematic review & meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2019; 14:1539-1548. doi:10.2147/COPD.S200846.

2) Zayed Y, Barbarawi M, Kheiri B, et al. Triple versus dual inhaler therapy in moderate-to-severe COPD: systematic review & meta-analysis of RCTs. *Clin Respir J.* 2019; 13:413-428. doi:10.1111/crj.13026.

3) Lee HW, Park J, Jo J, Jang EJ, Lee C-H. Exacerbations and mortality among inhaled therapies for stable COPD: systematic review & Bayesian NMA. *PLoS Med.* 2019;16(11): e1002958.

4) Koarai A, Yamada M, Ichikawa T, et al. Triple versus LAMA/LABA combination therapy for COPD: systematic review & meta-analysis. *Respir Res.* 2021; 22:183. doi:10.1186/s12931-021-01777-x.

5) Long H, Xu H, Janssens J-P, Guo Y. Single-inhaler triple vs single-inhaler dual therapy in COPD: meta-analysis. *Respir Res.* 2021; 22:209. doi:10.1186/s12931-021-01794-w.

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6) Ismaila AS, Haeussler K, Czira A, et al. FF/UMEC/VI triple therapy compared with other COPD therapies: network meta-analysis. *Adv Ther.* 2022; 39:3957-3978. doi:10.1007/s12325-022-02231-0.

7) Lipson DA, Barnhart F, Brealey N, et al.; IMPACT Investigators. Once-daily single-inhaler triple vs dual therapy in COPD. *N Engl J Med.* 2018; 378:1671-1680. doi:10.1056/NEJMoa1713901.

8) Rabe KF, Martinez FJ, Ferguson GT, et al.; ETHOS Investigators. Triple inhaled therapy at two glucocorticoid doses in COPD. *N Engl J Med.* 2020; 383:35-48. doi:10.1056/NEJMoa1916046.

9) Papi A, Vestbo J, Fabbri L, et al. TRIBUTE: extrafine triple therapy vs dual bronchodilation in COPD. *Lancet.* 2018; 391:1076-1084. doi:10.1016/S0140-6736(18)30206-X.

10) Ferguson GT, Rabe KF, Martinez FJ, et al. KRONOS: triple therapy vs dual therapies in symptomatic COPD. *Lancet Respir Med.* 2018; 6:747-758. doi:10.1016/S2213-2600(18)30327-8.

11) Magnussen H, Lucas S, Lapperre T, et al. ICS withdrawal vs continuation of triple therapy in real-life COPD. *Respir Res.* 2021; 22:25. doi:10.1186/s12931-021-01615-0.

12) Pascoe S, Barnes N, Brusselle G, et al. Blood eosinophils and response to triple vs dual therapy in IMPACT (post-hoc analysis). (Study report).

13) Muro S, Sugiura H, Darken P, Dorinsky P. BGF MDI efficacy excluding reversibility/high eosinophils: KRONOS post-hoc. *Respir Res.* 2021; 22:187. doi:10.1186/s12931-021-01773-1.

14) Voorham J, Corradi M, Papi A, et al. Comparative effectiveness of triple vs dual bronchodilation in COPD: UK real-world study. *ERJ Open Res.* 2019; 5:00106-2019. doi:10.1183/23120541.00106-2019.

15) Cheng W, Duan J, Zhou A, et al. Real-world effectiveness of inhalation therapy among symptomatic COPD in China. *Front Pharmacol.* 2021; 12:753653. doi:10.3389/fphar.2021.753653.

16) Chapman KR, Hurst JR, Frent S-M, et al. SUNSET: de-escalation from triple to indacaterol/glycopyrronium. *Am J Respir Crit Care Med.* 2018; 198:329-339. Doi: 10.1164/rccm.201803-0405OC.

17) Feldman WB, Suissa S, Kesselheim AS, et al. Head-to-head single-inhaler triple therapies: US new-user cohort. *BMJ.* 2024;387: e080409. doi:10.1136/bmj-2024-080409.

18) Zhang S, Wang J, Li X, Zhang H. Overview of systematic reviews: triple therapy vs non-triple in COPD. *Ther Adv Respir Dis.* 2024; 18:1-13. doi:10.1177/17534666241259634.

19) Zheng Y, Zhu J, Liu Y, et al. Triple therapy in COPD: systematic review & meta-analysis. *BMJ.* 2018;363: k4388.

20) Cazzola M, Rogliani P, Calzetta L, Matera MG. Triple vs single/dual bronchodilator therapy in COPD: meta-analysis. *Eur Respir J.* 2018; 52:1801586. doi:10.1183/13993003.01586-2018.