Therapeutics Initiative
Better prescribing. Better health.

THERAPEUTICS LETTER 153
February - March 2025

Triple therapy for COPD

Understanding evidence is complicated

PLAIN LANGUAGE SUMMARY

Questions and answers about COPD treatment

What is COPD?

COPD stands for chronic obstructive pulmonary disease. It is a lung condition that makes it hard to breathe, mostly caused by smoking. It can get worse over time and cause serious illness and death.

How is COPD usually treated?

Doctors prescribe inhalers to help open the airways so it's easier to breathe. There are two main types of inhalers:

- **Dual therapy**: Contains two types of long-acting medications to relax the airways.
- **Triple therapy**: Adds a third medication (a steroid) meant to reduce bronchial swelling.

What does the research say about triple therapy?

Some medical guidelines suggest triple therapy for "high risk" patients. "High risk" patients have had at least 2 moderate, or at least 1 severe episode of COPD in the last year. Severe episodes result in a visit to Emergency or a hospital admission. Sometimes triple therapy is prescribed if dual therapy isn't helping the patient feel better. But for first treatment for those who have just found out they have COPD, there isn't good evidence for triple therapy. It doesn't seem to reduce flare-ups and harms include a greater chance of pneumonia and even death.

Should blood tests be used to decide on triple therapy?

Doctors may order a test for blood eosinophils (a type of white blood cell) to decide if steroids might help. Studies have not shown that this testing helps.

What should be the focus of treatment for COPD?

For people with COPD, the most important steps are:

- Those who smoke should try to stop smoking.
- The patient and doctor should make a shared treatment decision after discussing benefits and harms.
- Include a discussion of the vaccinations that may lower the risk of getting an infection.
- Know how to use your inhaler properly to get the best results.

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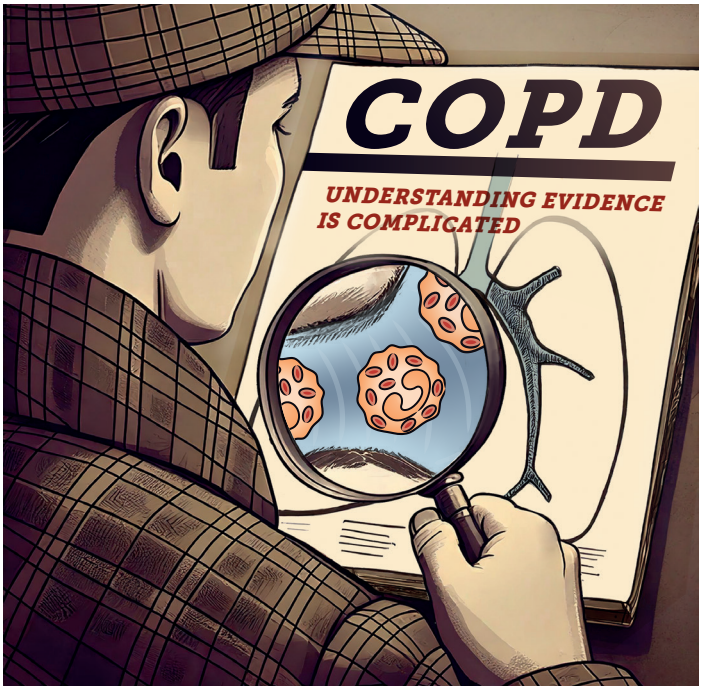

ABSTRACT

Background: Recent Canadian and international guidelines for management of chronic obstructive pulmonary disease (COPD) recommend single inhaler triple therapy (long-acting muscarinic antagonist/long-acting beta agonist/inhaled corticosteroid) as first-line treatment or as escalation from dual therapy for *"high risk"* patients who experienced at least 1 severe or 2 moderate exacerbations during the previous year. While they differ as to other eligibility criteria for triple therapy, these new recommendations could increase inappropriate prescriptions. In British Columbia, single-inhaler triple therapy is increasing rapidly.

Aims: This *Therapeutics Letter* critically appraises available evidence about triple therapy for *"high risk"* COPD patients.

Findings: No randomized controlled trial (RCT) has evaluated first-line triple therapy in people newly diagnosed with COPD. Three RCTs enrolled *"high risk"* patients (N=20,396) at a mean of 8 years after COPD diagnosis. Most were already using ICS and many had a history of asthma. Results cannot be extrapolated to treatment-naïve patients treated initially with triple therapy. We found unconvincing the RCT evidence that triple therapy reduces exacerbations. Like the US FDA's Advisory Committee, we could not confirm that triple therapy reduces mortality. Furthermore, retrospective real-world data indicate that triple therapy achieves no significant reduction in exacerbations, but increases pneumonia and total mortality.

Conclusions: Current evidence does not support first-line triple therapy in treatment-naïve COPD patients, nor routinely adding ICS for people already using a LAMA/LABA inhaler. Clinicians should prioritize smoking cessation, immunization, and inhaler technique over pharmacological intensification, and ensure evidence-informed shared decision-making.

Keywords: Adrenergic beta-Agonists; Bronchodilator Agents; Chronic Obstructive Pulmonary Disease; Combination Drug Therapy; Drug-Related Side Effects and Adverse Reactions; Inhaled Corticosteroids; Muscarinic Antagonists; Shared Decision Making; Smoking Cessation.

Multiple experts and primary care clinicians reviewed the draft of this Therapeutics Letter for factual accuracy, and to ensure it is relevant to clinicians.

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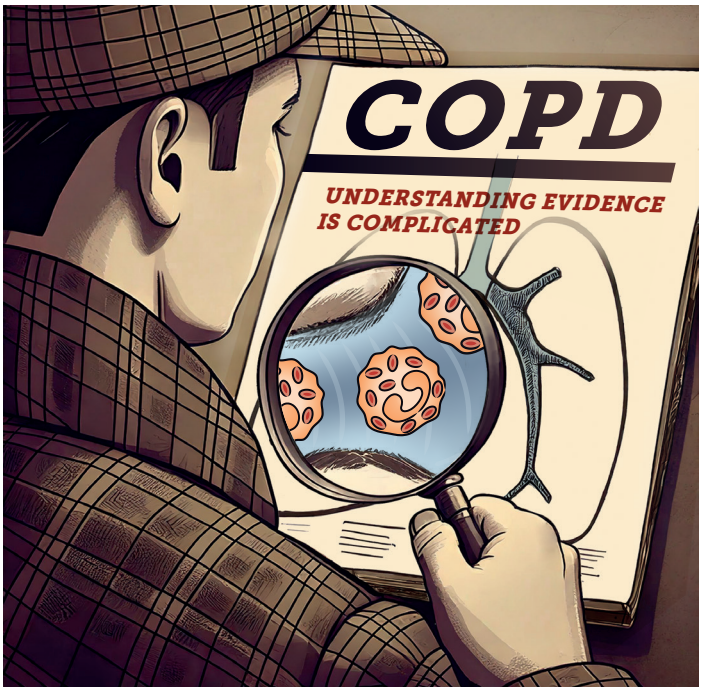

Vignette: *A 63-year-old smoker complains that he's short of breath on exertion, and has a frequent productive cough. A friend loaned him a salbutamol puffer, and he thinks it helps his breathing a little. At simple spirometry, his post-bronchodilator FEV1/FVC ratio of <0.7 confirmed non-reversible airflow obstruction. He was never asthmatic, and a recent blood count showed eosinophils of 100/µL (normal 0-500/µL or in some laboratories 0-700/µL). His agreement to cut back on smoking makes your day, and you arrange to discuss immunizations and physical activity. But you heard that a recent guideline recommended triple inhaler therapy.* ***Should you prescribe it?***

Summary and conclusions

- **First-line triple therapy in treatment-naïve COPD patients, including people deemed at *"high risk"* of exacerbation, has not been studied in RCTs.**
- **Independent of blood eosinophil count, there is insufficient evidence that escalation to triple therapy – compared with dual bronchodilator therapy - reduces mortality or moderate or severe exacerbations of COPD.**

Therapeutics Letter 145 recommended minimizing inhaled corticosteroids (ICS) for chronic obstructive pulmonary disease (COPD).[1] After extensive review, including by external academic experts, we finalized it in late 2022. In early 2023 we distributed it to a randomized "early" group of primary care prescribers registered for the *Portrait* program. In December 2023 we posted the *Letter* and distributed it to prescribers randomized to "late" delivery of the *Portrait*.

After a detailed critical appraisal of clinical trial evidence available in 2018, we had concluded in early 2019 that **for most COPD patients**, the risk of serious harms from ICS outweighs the limited known benefits for symptoms or exacerbations. We found no reduction of mortality from ICS.[2] Like others, we recognized the potential overlap of COPD with asthma – sometimes reflected by an elevated blood eosinophil count.

As a practical recommendation for primary care, we concluded: **"It is reasonable to try stopping ICS in clinically stable patients with infrequent exacerbations. For patients with eosinophils above 300/µL in a complete blood count, first taper ICS over a few months."**

Therapeutics Letter 145 pointed out that during 2017-2021, 27% of British Columbians who initiated inhaler drug therapy for COPD **started with an inhaler containing ICS**. It did not discuss the addition of ICS ("triple therapy") after an inadequate clinical response to dual therapy with a long-acting muscarinic antagonist (LAMA) and a long-acting beta agonist (LABA).

Once posted, a Canadian respirologist commented that our conclusions differed from recommendations of a new Canadian Thoracic Society (CTS) guideline e-published in September 2023.[1,3]

This *Letter* considers additional new evidence from randomized controlled trials (RCTs) of single-inhaler, triple therapy for COPD patients.[4] It reviews evidence relevant to recent guideline recommendations to initiate triple therapy in treatment-naïve patients, or to add ICS to dual bronchodilator therapy in patients considered at *"high risk"* of exacerbation. We explain why our conclusions still differ from guidelines updated by the CTS in 2023 and in November 2024 by the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2025). **Guidelines assign the term *"high risk"* to patients who within the last year have experienced at least 2 moderate, or at least 1 severe exacerbation of COPD.** A "moderate exacerbation" implies antibiotic or oral corticosteroid treatment, whereas "severe exacerbation" requires an emergency department visit or hospitalization. We italicise *"high risk"* within quotations, to remind readers that this categorization can only be applied retrospectively.

Triple therapy single-inhalers approved in Canada

Two triple therapy inhalers are approved in Canada to reduce exacerbations and airflow obstruction in patients with COPD not adequately treated by ICS/LABA or LAMA/LABA combinations:[5-8]

- Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol)
- Breztri Aerosphere (budesonide/glycopyrrolate/formoterol fumarate)

Current annual costs in BC (excluding dispensing fees) are $1,810 for Trelegy Ellipta and $1,670 for Breztri Aerosphere.[9]

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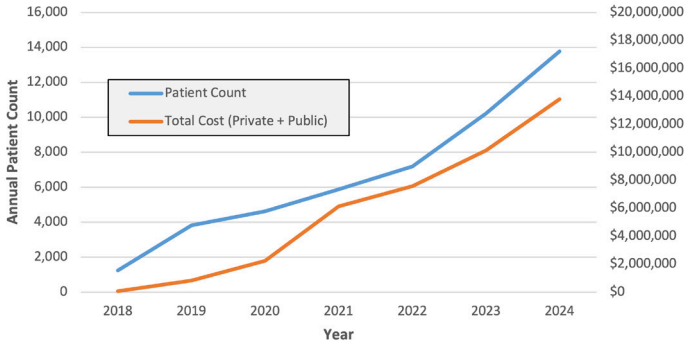
For people who experience persistent dyspnea and are at *"high risk"* of exacerbation despite maximal LAMA/LABA therapy, the 2025 BC and 2023 CTS guidelines recommend adding ICS as "step-up" to triple therapy.[2,10] The GOLD 2025 update, published in November 2024, recommends adding ICS only if eosinophils are ≥100/uL, **but adds that evidence "strongly favours use" only with eosinophils ≥300/µL.**[11] For patient convenience, CTS and GOLD recommend a single inhaler. All guidelines emphasize the crucial importance of smoking cessation, appropriate immunizations, maintaining physical fitness, demonstrating and rehearsing effective inhaler technique.

The CTS 2023 guideline added a new recommendation **for triple therapy as initial treatment for COPD patients at *"high risk"* of exacerbation** regardless of eosinophil count. Depending on how prescribers interpret *"high risk,"* adopting new guideline recommendations could substantially increase prescription of LABA/LABA/ICS as initial therapy. But is that preferable to reserving triple therapy for people in whom benefits are most likely to exceed harms, notably severe pneumonia?

Since their introduction in 2018, dispensing of triple therapy inhalers for people diagnosed with COPD in BC has increased steadily.[12] (Figure) This is probably not limited to people with *"high risk"* COPD. Combined costs for both triple inhalers (without dispensing fees or markups) reached almost $14 million in 2024 for just under 14,000 people. Of this, PharmaCare paid $6.65 million from public funds.

Figure: Single-inhaler triple therapy for COPD in BC (2018-2024)



Annual users and total cost (public plus private) of triple therapy single-inhalers (*Trelegy Ellipta* and *Breztri Aerosphere*) used for COPD in BC. Between 2019 and 2024, usage of these inhalers grew by 23% per year. This may reflect a shift from multi-device triple therapy to single-inhalers.

Recent guideline recommendations for triple therapy

The GOLD 2025 update, published in November 2024, reiterates: "There is no high-quality evidence such as randomized controlled trials to support initial pharmacological treatment strategies in newly diagnosed patients." Its new "practical recommendation" for patients defined as *"high risk"* is to **consider a patient's blood eosinophil count when deciding whether to initiate ICS treatment.**[11] Despite the caveat that "there are no direct data concerning initiation of triple therapy in newly diagnosed patients," GOLD 2025 recommends **considering first-line triple therapy** for patients with eosinophils ≥300/µL. In *"high risk"* patients already using LAMA/LABA therapy, it recommends escalation to triple therapy if eosinophils are ≥100/µL, but to azithromycin or roflumilast when eosinophils are <100/µL.

However, no RCT has evaluated using blood eosinophil count as a factor when deciding whether to add ICS treatment in patients at any level of severity, including COPD defined as *"high risk."*

In contrast, the Canadian guideline (CTS) recommends first-line triple therapy **for patients with a high symptom burden and severe health impairment** at *"high risk"* of exacerbations, regardless of eosinophil count. For people with persisting dyspnea at *"high"* or *"low"* risk of exacerbation despite dual LAMA/LABA therapy, CTS recommends escalation to triple therapy.[2]

3 RCTs of triple therapy

Three 52-week double-blind RCTs evaluated single-inhaler triple therapy versus single-inhaler dual therapy (LAMA/LABA or ICS/LABA) in COPD patients with a moderate to high symptom burden and history of moderate or severe exacerbations in the 12 months prior to study enrolment.[13-14] (Table)

Table: Double-blind RCTs of single-inhaler triple therapy versus dual therapy

Study, duration	Patient characteristics at baseline	Triple therapy	Dual bronchodilator (LAMA/LABA or ICS/LABA)	Prespecified primary outcome
IMPACT 2018[13] 52-week DBRCT	N=10,355 with symptomatic COPD. Exacerbations in previous year: ≥2 moderate (47%), ≥1 severe (26%). Past asthma diagnosis included. **At baseline, 40% on triple therapy, 70% on ICS.**	**Trelegy Ellipta once daily** (fluticasone 100 mcg + umeclidinium 62.5 mcg + vilanterol 25 mcg)	**LAMA/LABA once daily** (umeclidinium 62.5 mcg + vilanterol 25 mcg) **OR** **ICS/LABA once daily** (fluticasone furoate 100 mcg + vilanterol 25 mcg)	Annual rate of moderate or severe exacerbations
ETHOS 2020[14] 52-week DBRCT	N=8,509 with symptomatic COPD. Exacerbations in previous year: ≥2 moderate or severe (56%), ≥1 severe (21%). Past asthma diagnosis included. **At baseline, 40% on triple therapy, 80% on ICS.**	**Breztri Aerosphere twice daily** (budesonide 320 mcg or 160 mcg + glycopyrrolate 18 mcg + formoterol 9.6 mcg)	**LAMA/LABA twice daily** (glycopyrrolate 18 mcg + formoterol 9.6 mcg) **OR** **ICS/LABA twice daily** (budesonide 320 mcg + formoterol 9.6 mcg)	Annual rate of moderate or severe exacerbations
TRIBUTE 2018[15] 52-week DBRCT	N=1,532 with symptomatic COPD. Exacerbations in previous year: 1 moderate or severe (81%), ≥2 moderate or severe (19%). Past asthma diagnosis included. **At baseline, 0% on triple therapy** (exclusion criterion), **65% on ICS.**	**Trimbow** (not marketed in Canada) **ICS/LAMA/LABA twice daily** (beclomethasone 87 mcg + glycopyrronium 9 mcg + formoterol 5 mcg)	**LAMA/LABA once daily** (glycopyrronium 43 mcg + indacaterol 85 mcg)	Annual rate of moderate or severe exacerbations

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Does RCT evidence support first-line triple therapy?

No RCT has evaluated initiation of single-inhaler triple therapy in newly diagnosed or treatment-naïve COPD patients at high risk of exacerbations. The 3 RCTs described in the Table enrolled patients with a mean duration of 8 years since diagnosis of COPD. Their primary outcome was the incidence of moderate or severe exacerbations. At baseline, almost all patients (92-100%) were already receiving inhaler therapy, including 65-80% treated with an inhaler containing ICS (double or triple therapy). In the 2 largest trials, IMPACT and ETHOS, 40% of participants were already using triple therapy when randomized to continue triple therapy or step down to dual therapy. **Results of these RCTs cannot be extrapolated to naïve patients for whom triple therapy is considered for first-line treatment**.

Does RCT evidence support 'step up' from dual bronchodilator to triple therapy?

Exacerbations: Compared with LAMA/LABA dual therapy, IMPACT, ETHOS, and TRIBUTE reported that triple therapy achieved 15-25% relative risk reductions in annual moderate or severe exacerbations. Over 1 year, this translates to the following estimated absolute risk reductions (ARR) for exacerbation, and numbers needed to treat (NNT):[16]

- ETHOS: ARR 2.9%, 95% CI -0.1%-5.9% (not statistically significant);
- IMPACT: ARR 3.3%, 95% CI 0.7%-6.0%, NNT 30;
- TRIBUTE: ARR 9%, 95% CI 4%-14%, NNT 11.

However, a major study design flaw undermines internal and external validity of the 2 largest RCTs: IMPACT and ETHOS (combined N=18,864). IMPACT and ETHOS **included patients with a history of asthma**, and at baseline 70% and 80% of all participants, respectively, were using inhalers that included ICS.

For two important reasons, the observed reductions in exacerbations do not provide compelling evidence for triple therapy. First, the abrupt discontinuation of inhaled corticosteroids in control group patients in IMPACT and ETHOS may have caused adverse withdrawal effects. Second - and possibly related to having stopped ICS - dual therapy patients were more likely than triple therapy patients to be lost to follow-up. Excluding enrolled participants from the analysis in RCTs often results in biased estimates of treatment effects.[17] These factors limit generalizing the results of IMPACT and ETHOS to real world practice.

Mortality: CTS 2023 and GOLD 2025 guidelines contend that triple therapy, compared with LAMA/LABA **reduces mortality as well as exacerbations** in people with moderate to severe COPD and a history of exacerbations. The original and secondary publications of IMPACT and ETHOS reported that triple therapy reduced mortality, compared with LAMA/LABA.[13,14,18,19] The much smaller TRIBUTE RCT reported 16/764 (2.1%) deaths in the triple therapy arm, versus 21/768 (2.7%) with dual therapy (difference not significant).[15] Combining results from the 3 RCTs yields a pooled mortality estimate that favours triple therapy in people with prior exacerbations: absolute risk reduction 0.99% (95% CI 0.42%-1.56%), NNT 101 (95% CI 64-238) for 1 year.[4]

Is the apparent mortality benefit real?

In both IMPACT and ETHOS, excess deaths and exacerbations in the LAMA/LABA group – compared with triple therapy - **occurred during the first 90 days of follow-up.**[20,21] This includes the 30-day interval when biological effects of abrupt corticosteroid withdrawal would be maximal. During the remaining 9 months of follow-up, no benefit of triple therapy was observed.[4,20,21] Thus, the assumed benefit of triple versus dual inhaler therapy is likely due to abrupt ICS withdrawal in the LAMA/LABA group. **This is one reason why the US FDA Advisory Committee specifically rejected a claim that triple therapy reduces mortality,[22,23] and why Canadian triple inhaler monographs[5,6] and Health Canada's regulatory decisions[7,8] also do not suggest a mortality benefit.**

Retrospective real-world observational study

A recent high-quality observational study evaluated the real-world effectiveness of single-inhaler triple therapy versus single-inhaler LAMA/LABA therapy amongst nearly 31,000 primary care COPD patients age >40 in the United Kingdom.[24] From September 15, 2017 (when a triple inhaler first became available in the UK) through 2020, investigators compared 4,106 new users of triple therapy with 29,702 people who were prescribed LAMA/LABA. Patients were naïve to inhaled corticosteroids. During the prior year, 58% had used LAMA, LABA or both; 42% had used no long-acting bronchodilator; 35% had used a systemic corticosteroid. Patients were followed in the UK Clinical Practice Research Datalink database for up to 1 year, with a mean continuous treatment of 6 months in each group. Investigators used adjustment by propensity score weighting to render comparable the two treatment arms, and reduce the effects of confounding inherent to observational studies.

Compared with single-inhaler LAMA/LABA, single-inhaler triple therapy including inhaled corticosteroid had a similar risk of the primary outcome, a first moderate or severe exacerbation, adjusted HR 1.08 (95% CI 1.00–1.16). This finding, based on patients not previously treated with an ICS, avoiding the confounding effects of abrupt ICS withdrawal, differs from the reductions in moderate or severe exacerbations reported in IMPACT and ETHOS. **Triple therapy increased all cause mortality: adjusted HR 1.53 (95% CI 1.30-1.79), and increased pneumonia requiring hospitalization: adjusted HR 1.50 (95% CI 1.29-1.75).**

Vignette resolution: *Pharmacological treatment is less urgent for your patient than stopping smoking and other non-drug measures. You decide to proceed gradually, using shared decision making and evidence-informed consent, to guide your inhaler prescribing. As usual in your practice, you will review smoking status, physical activity, immunizations, and inhaler technique at least annually.*

Data acknowledgement

The BC Ministry of Health approved access to and use of BC data. The following data sets were used in this Letter: PharmaNet, Client Roster. All inferences, opinions, and conclusions drawn in this publication are those of the authors, and do not reflect the opinions or policies of the Data Stewards.

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