Plain Language Summary of Publication

Journal of Comparative Effectiveness Research

Rational use of inhaled corticosteroids for the treatment of COPD: a plain language summary

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Summary

What is this summary about?

Inhaled corticosteroids (ICS) are a type of medication delivered via an inhaler device that are commonly used in the treatment of asthma. ICS can also be used to treat **chronic obstructive pulmonary disease** (COPD), a progressive respiratory condition in which the lungs become worse over time. However, **unlike in asthma, ICS are only effective in a small proportion of people with COPD**.

ICS can cause significant side effects in people with COPD, including **pneumonia**. Because of this, guidelines written by COPD experts recommend that ICS should largely be prescribed to people with COPD whose symptoms flare up frequently and become difficult to manage (episodes known as **exacerbations**).

How to say (double click on the sound icon to play the sound)

Bronchodilators: bron-ko-dye-LAY-ters
Corticosteroids: kor-ti-ko-STEH-royds
Eosinophil: ee-oh-SIN-oh-fill
Exacerbations: ex-ah-sur-BAY-shuns
Glaucoma: gloor-KOH-muh
Neutrophil: NOOT-roh-fill
Osteoporosis: os-tee-oh-poor-OH-sis
Pneumonia: new-MOH-nee-uh
Tuberculosis: tew-berk-you-LOW-sis

Despite this guidance, records collected from routine clinical practice suggest that many healthcare professionals prescribe ICS to people with COPD who do not have frequent exacerbations, putting them at unnecessary risk of side effects.

The over-prescription of ICS in COPD may partly be due to the recent introduction of single-inhaler combination therapies, which combine ICS with other medicines (bronchodilators). This **'one inhaler for all' approach** is a concerning trend as it **goes against global COPD treatment guidelines, which recommend ICS use in only a small proportion of people**.

This is a plain language summary of a review article originally published in the journal *NPJ Primary Care Respiratory Medicine*. In this review, we investigate the benefits and risks of ICS use in COPD. Using data from both randomized controlled trials (RCTs) and observational studies, we explain which people benefit from ICS use, and why health regulatory bodies have concluded that ICS do not help people with COPD to live longer. Lastly, **we provide practical guidance for doctors and people with COPD regarding when ICS should be prescribed and when they should be withdrawn**.

An animated video describing this plain language summary is available online. Scan this QR code to watch the video.

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Who is this article for?

The aim of this summary is to inform primary care physicians who are not respiratory specialists, other healthcare professionals, and patients and their caregivers about the risks and benefits of ICS as a treatment for COPD.

Glossary of terms used in this summary

Inhaled corticosteroids: Medicines containing corticosteroids (drugs such as fluticasone, budesonide, beclomethasone, mometasone) that are inhaled to treat inflammation in the airways

Chronic obstructive pulmonary disease: Lung condition associated with long-term respiratory symptoms (shortness of breath, cough and production of mucus). This is due to structural changes within the airways, most often caused by exposure to cigarette smoke or other harmful air particles. Because of these airway changes, people with COPD have difficulty breathing out the air from their lungs

Pneumonia: Inflammation of the lungs, usually caused by an infection. People often recover within several weeks, but sometimes pneumonia can lead to serious illness and hospitalization

Exacerbation: Acute episode of significant worsening of COPD symptoms, such as shortness of breath, cough, and sputum production, lasting for less than 14 days, in the absence of other conditions that mimic COPD exacerbations (e.g., pneumonia, heart failure)

Where can I find the original article on which this summary is based?

You can read the original article published in the journal *NPJ Primary Care Respiratory Medicine* for free at:
https://www.nature.com/articles/s41533-023-00347-6

What is COPD and how is it managed?

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable lung disease that is associated with narrowing of the airways (reducing the amount of air exhaled from the lung) and chronic, often progressive, respiratory symptoms and reduced quality of life. COPD affects around 16% of men and 10% of women globally, and is more common in adults over 65 years of age.

The main treatment for COPD is inhaled **long-acting bronchodilator** (LABD) therapy delivered via handheld inhalers.

Long-acting bronchodilator: Inhaled medication that relaxes the muscles around the airways, causing them to widen; effects typically last for at least 12 hours. Two main types are used to treat asthma and COPD, often in combination: long-acting beta agonist (LABA) and long-acting muscarinic antagonist (LAMA)

Pharmacological treatments that have been approved by health regulatory authorities for the management of COPD

Short-acting bronchodilators (SABDs)

Used for quick symptom relief or in emergencies

- Short-acting beta agonists (SABAs)
  - E.g., salbutamol, levalbuterol, terbutaline
- Short-acting muscarinic antagonists (SAMAs)
  - E.g., ipratropium bromide, oxitropium bromide

Long-acting bronchodilators (LABDs)

Used for long-term management of COPD, often in combination

- Long-acting beta agonists (LABAs)
  - E.g., olodaterol, formoterol, indacaterol, salmeterol, vilanterol
- Long-acting muscarinic antagonists (LAMAs)
  - E.g., tiotropium, aclidinium bromide, umeclidinium, glycopyrronium

ICS-containing therapies

Combination inhalers containing budesonide, fluticasone, beclomethasone and mometasone; used as an add-on therapy for a small proportion of people with COPD who have:

- Eosinophilic inflammation
- History of frequent/repeated exacerbations
- Current or documented history of asthma

Other treatments

- Methylxanthines
  - E.g., aminophylline
- Mucolytics
  - E.g., carbocisteine, erdosteine, N-acetyl cysteine
- Phosphodiesterase inhibitors
  - E.g., roflumilast

Bronchodilators relax the muscles in the airways, causing them to widen. Global treatment guidelines for COPD recommend that most people receive two LABDs in combination (i.e., a LAMA plus LABA). This combination of medications helps to reduce respiratory symptoms and a person's risk of exacerbations, allowing them to be physically active without becoming too breathless.

Pharmacological: Therapy that involves the administration of drugs or medications. In COPD, use of long-acting bronchodilators is an example of pharmacological therapy, whereas physiotherapy is an example of non-pharmacological therapy

Quitting smoking is of foremost importance in reducing symptoms and disease progression. Other changes in lifestyle, namely regular exercise, certain breathing techniques and physiotherapy, can also help people control their symptoms and maintain their quality of life for longer.

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Vaccines that protect against COVID-19, **influenza**, **pertussis** and pneumonia can help to prevent COPD exacerbations or make them less severe. In addition, sometimes what appears to be a COPD exacerbation can in fact be a worsening of another disease or condition that a patient might have, such as anxiety or heart failure. Social distancing to avoid people with respiratory infections, as well as personal hygiene measures such as hand washing and the use of face masks can also reduce COPD exacerbation rates. During the COVID-19 pandemic, for example, one study found that exacerbation rates among people with COPD reduced by 50%.

Although people with COPD may experience similar symptoms (cough, breathlessness) to people with asthma, the two diseases are caused by different underlying changes in the lung and are therefore treated differently. Unlike for people with asthma, ICS are not effective at reducing inflammation in the airways of most people with COPD. Hence, treatment with ICS alone (monotherapy) is not effective in COPD and not recommended by treatment guidelines.

The addition of ICS to LABD combination therapy is most effective in less than one third of all people with COPD. This includes people who have frequent or severe exacerbations despite regular treatment with LABDs, especially in the presence of a specific type of inflammation caused by eosinophils (**eosinophilic inflammation**).

Influenza: A contagious respiratory illness caused by an influenza virus that infects the respiratory system (nose, throat and sometimes lungs)

Pertussis: A respiratory bacterial infection also known as whooping cough

Eosinophilic inflammation: Specific type of inflammation caused by eosinophils, a type of white blood cell associated with asthma and allergies

How do ICS work and why are they only effective in some people with COPD?

ICS are absorbed in the airways of the lung, where they reduce inflammation. However, ICS are only effective in reducing a particular type of inflammation, which is driven by high levels of eosinophils (a type of white blood cell). High levels of eosinophils are associated with asthma and allergies, and therefore ICS are very effective in treating asthma, even at low doses.

However, **in most people with COPD, airway inflammation is driven by neutrophils** (a different type of white blood cell) **and therefore ICS are not effective**. Only a small proportion of people with COPD have eosinophilic inflammation, and therefore measuring the level of eosinophils in the blood can help to predict which people with COPD will respond to ICS.

Global treatment guidelines written by a group of COPD experts (the Global Initiative for Chronic Obstructive Pulmonary Disease [GOLD]), recommend that people with a history of frequent or severe exacerbations begin treatment with dual bronchodilator therapy (LAMA/LABA). Addition of ICS to LAMA/LABA is recommended if people have frequent or severe exacerbations and a blood eosinophil level of 300 cells per microlitre of blood or higher.

Use of ICS can also be considered at lower eosinophil levels (100 cells per microlitre of blood or higher) if a patient's exacerbations are not well controlled by LAMA/LABA.

Practical guidance for the use of ICS in COPD

Use of ICS in people with frequent or severe exacerbations

Risks likely to outweigh benefits	ICS can be considered for people with persistent exacerbations despite LAMA/LABA therapy	Benefits likely to outweigh risks
Under 100 eosinophils per microlitre of blood	100–300 eosinophils per microlitre of blood	300 eosinophils per microlitre of blood or higher

Risk of pneumonia similar regardless of eosinophil level

Use of ICS for initial and follow-up treatment of COPD

1

Initial treatment

For people who have:

- Current or documented history of asthma
- Two or more moderate exacerbations (or one or more leading to hospitalization) in the previous year* AND blood eosinophil level of 300 cells per microlitre of blood or higher

2

Treatment adjustment, if exacerbations not controlled on LAMA/LABA

For people who have:

- Two or more moderate exacerbations (or one or more leading to hospitalization) in the previous year* AND blood eosinophil level of 300 cells per microlitre of blood or higher
- Two or more moderate exacerbations (or one or more leading to hospitalization) in the previous year* AND blood eosinophil level of between 100 and 300 cells per microlitre of blood, after careful risk-benefit assessment considering:
  - Recent pneumonia
  - Confirmed bacterial colonization of the lungs
  - Bronchiectasis (a different lung condition that requires other types of treatment)
  - Comorbidities, especially diabetes and osteoporosis or people at risk for these conditions

*Or since previous assessment if less than 12 months.

Withdrawal of ICS should be considered in people who do not fulfil guideline criteria for ICS use, as the risks of ICS use (e.g., pneumonia) in these people are likely to outweigh the benefits. For example, ICS should be withdrawn if a patient's eosinophils are low, they have not had an exacerbation in the previous year, and there is no clear history of asthma.

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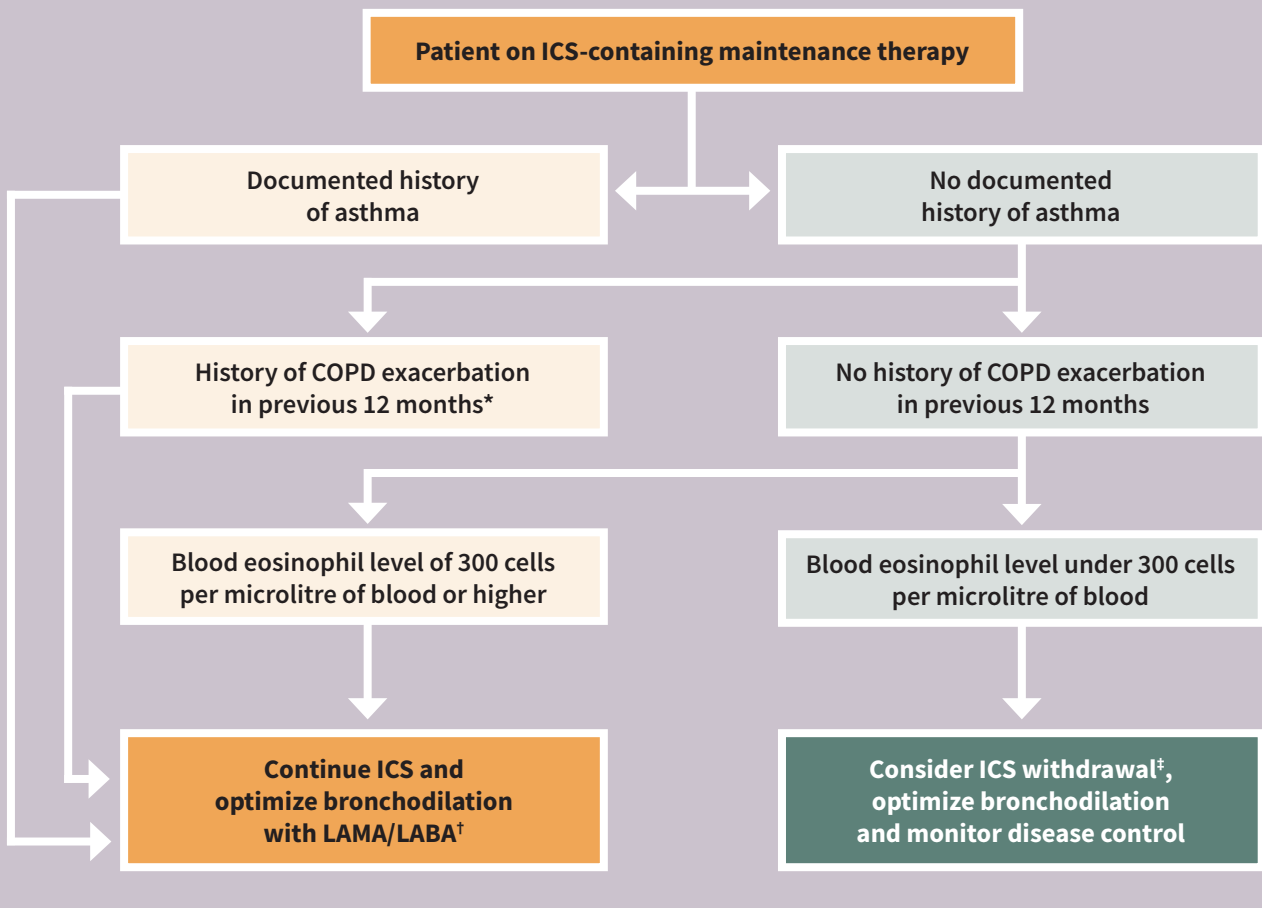
When to withdraw ICS from maintenance therapy



Adapted from the International Primary Care Respiratory Group (IPCRG) desktop helper for the appropriate use and withdrawal of ICS, 2020. Available at: https://www.ipcrg.org/sites/ipcrg/files/content/attachments/2020-06-02/IPCRG%20DH6%20ICS%20COPD%20Rev%20May20.pdf

*Or since previous assessment if less than 12 months.

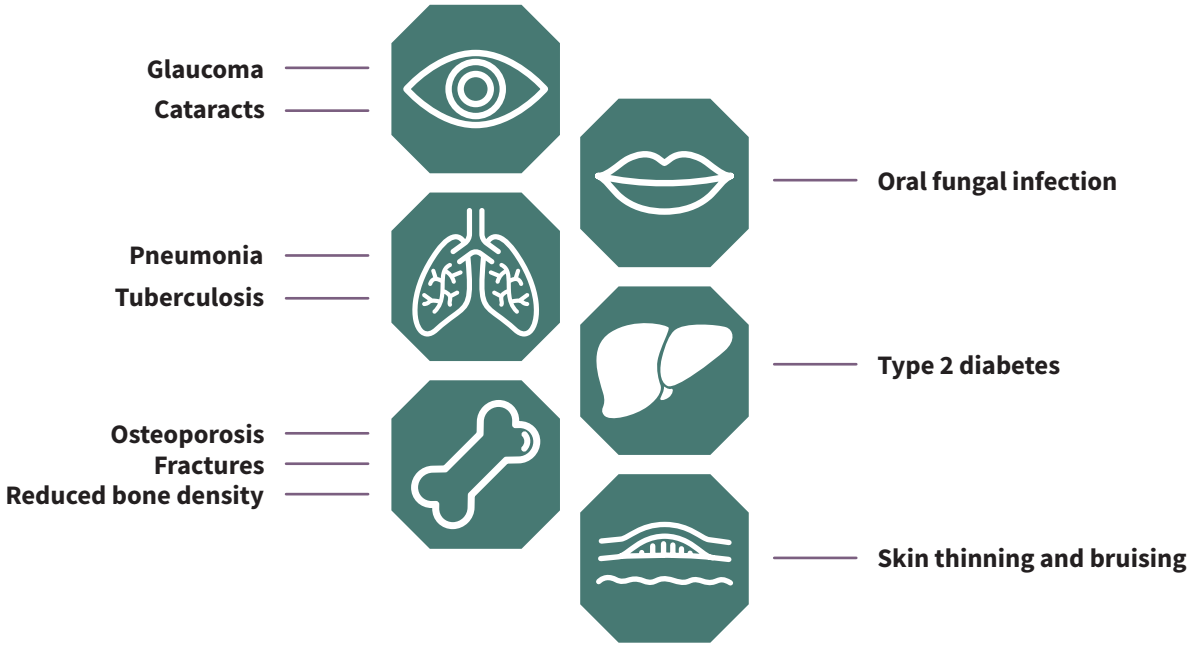
†For people with exacerbations despite triple therapy (LAMA/LABA + ICS), consider add-on therapy with roflumilast or macrolides.

‡If blood eosinophil level is 150–300 cells per microlitre of blood, reduce ICS dose/switch to an ICS with a better safety profile. If blood eosinophil level is under 150 cells per microlitre of blood, and there is no asthma history (or suspicion of current asthma) or exacerbation in the previous 12 months, consider withdrawal as the risks of ICS are likely to outweigh any benefits.

In summary, it is important to consider both exacerbation rates and blood eosinophil levels, as well as the presence of asthma, when prescribing ICS to people with COPD. If a patient does not have frequent or severe COPD exacerbations, they are unlikely to benefit from ICS unless they also have asthma.

What are the side effects of ICS use?

ICS-containing therapies have been associated with an increased risk of many unwanted side effects in people with COPD. In particular, the use of ICS in COPD can increase the risk of pneumonia.



Because of this, it is important to consider the expected benefits versus risks of treatment when prescribing ICS to people with COPD.

What have randomized controlled trials (RCTs) of ICS in COPD shown?

We looked at several key RCTs in people with COPD, called IMPACT, ETHOS, TRIBUTE and KRONOS. The findings from these RCTs suggest that ICS taken in combination with LABDs can benefit people with COPD. However, **due to the way these RCTs were carried out, the effectiveness of ICS is overestimated and not applicable to all people with COPD**. For instance:

- **Patient population**: The **people studied included 'ICS-sensitive' people** (i.e., those with a history of asthma, a history of exacerbations and/or high blood eosinophil levels), who represent only a small proportion of the general COPD population
- **Study design and interpretation**: Most of the people were taking ICS before the trials. When people who were benefitting from ICS treatment were randomly assigned to a non-ICS group during the trial, they experienced the detrimental effects of ICS withdrawal (i.e., early exacerbations and a higher risk of death). This skews the results in favor of the ICS group (i.e., people who either continued or initiated ICS at the start of the study)

Randomized controlled trial: Clinical study evaluating interventions under tightly controlled conditions, and among highly selective groups of people, in order to minimize factors that could bias or affect interpretation of any observed effects

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Positive and negative findings from key RCTs in people with COPD

LAMA/LABA versus LAMA/LABA/ICS

IMPACT	ETHOS	TRIBUTE	KRONOS
ICS addition: reduced mortality	ICS addition: reduced mortality	Mortality not examined in this study	Mortality not examined in this study
ICS addition: reduced exacerbations	ICS addition: reduced exacerbations	ICS addition: modestly reduced exacerbations	ICS addition: modestly reduced exacerbations
ICS addition: increased pneumonia risk	ICS addition: increased pneumonia risk	Similar pneumonia rates in both treatment groups	Similar pneumonia rates in both treatment groups

Positive treatment effects

Negative treatment effects

Similar treatment effects (or outcome not studied)

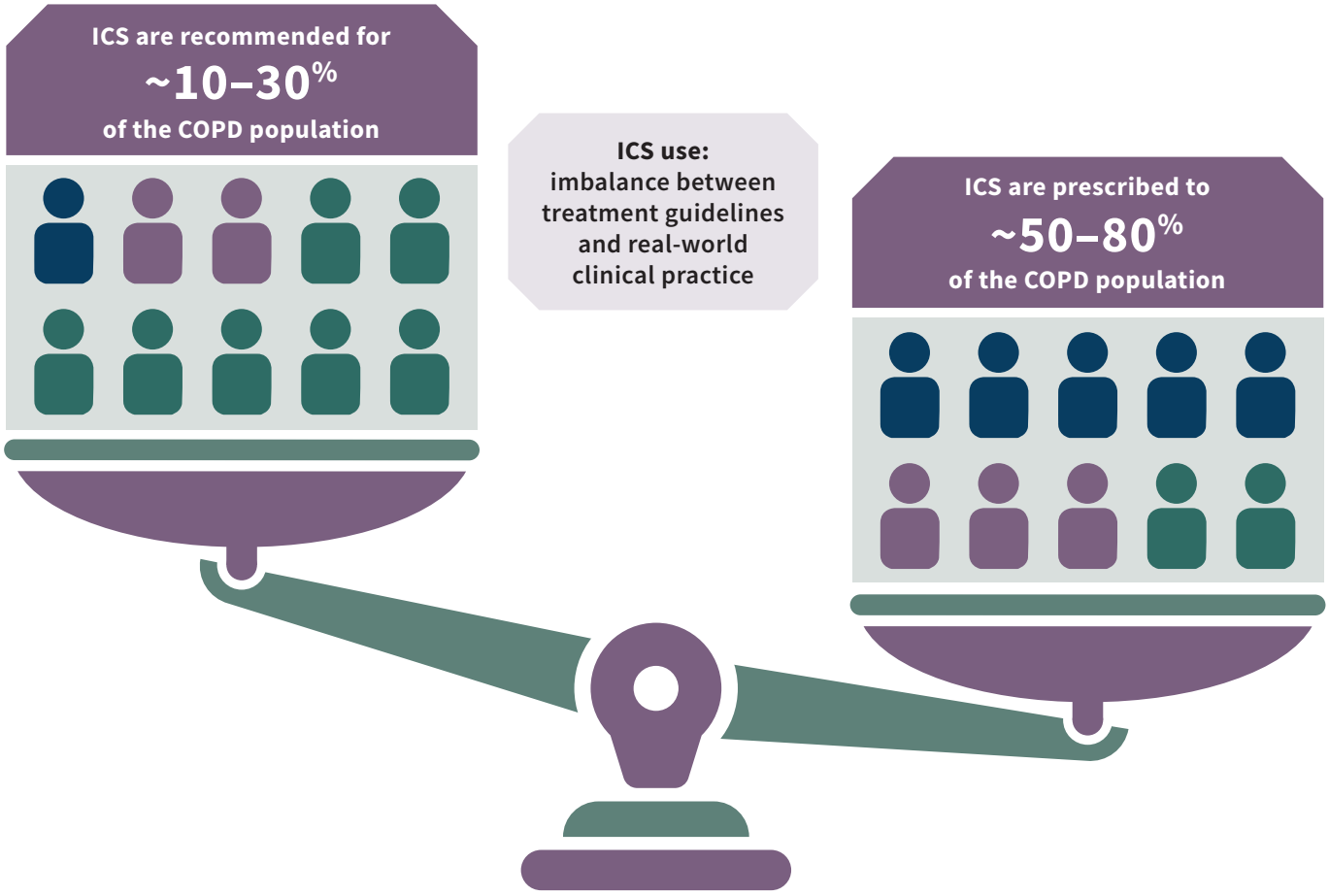
Key factors affecting clinical interpretation

- Selectively including 'ICS-sensitive' people
- Withdrawing ICS treatment for most people randomized to non-ICS treatment
- **No mortality differences observed among people without prior ICS use and during long-term (>90 days) follow-up**
- Difficult to generalize findings due to narrow target populations studied

The design of many of the RCTs investigating ICS in COPD, for instance, selectively including 'ICS-sensitive' people and withdrawing some people from ICS treatment at randomization, has led health regulatory authorities to conclude that ICS do not help people with COPD to live longer.

What have observational studies of ICS in COPD shown?

Global treatment guidelines recommend ICS for people with COPD who have frequent or severe exacerbations and high blood eosinophil levels. Analysis of data from over 200,000 people from Europe and the USA indicate that these people typically represent only ~10–30% of the overall COPD patient population. However, observational studies including over 8,000 people from routine clinical practice in Europe, the USA and South America show that ICS are prescribed to ~50–80% of people with COPD.



Observational studies are carried out in broader patient populations than clinical trials. Thus, they are more representative of the general real-world COPD population than RCTs and can provide useful information about the effectiveness of a given treatment in routine clinical practice.

Many observational studies comparing LAMA/LABA with LAMA/LABA + ICS or LABA + ICS found that the ICS-containing combinations were equally or less effective than LABDs in terms of reducing the frequency of exacerbations or improving mortality rates.

Only one observational study showed similar results to those of the RCTs discussed, and this was conducted in a similar patient population, i.e., frequent exacerbators (with 2 or more exacerbations in 1 year), which is not representative of the general COPD population.

Observational study: Clinical study examining the effects of an intervention (e.g., specific treatment) in routine clinical practice, usually conducted in a much broader patient population than in randomized controlled trials

Observational studies using data from routine clinical practice suggest that the benefits of ICS are largely limited to people with COPD who have frequent exacerbations, rather than to the COPD population as a whole.

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What do these results mean?

- Although recent RCTs suggest that adding ICS to LAMA/LABA or LABA therapy reduces exacerbations and increases survival in people with COPD, the populations involved in these studies were very specific and therefore do not represent most people with COPD
- Data from several observational studies, conducted in broader patient populations, suggest that for most patients with COPD, dual LABD (LAMA/LABA) therapy without the addition of ICS provides benefits without increasing the risk of side effects
- ICS use is associated with a risk of pneumonia and other side effects, so unnecessary use of ICS can increase treatment costs for healthcare services through, for example, hospitalization
- Therefore, ICS should be reserved for patients with COPD in whom the benefits of treatment are likely to outweigh the risks, namely people:
  - who experience 2 or more moderate exacerbations per year (or 1 or more leading to hospitalization); and
  - who have increased eosinophil levels (300 cells per microlitre of blood or higher); and/or
  - who have a history/current diagnosis of asthma
- As per the latest guidelines from GOLD, treatment can be escalated to triple therapy with LAMA/LABA + ICS for patients who continue to have exacerbations on LAMA/LABA and have an eosinophil level of 100 cells per microlitre of blood or higher. LABA + ICS is no longer recommended for use in COPD
- ICS withdrawal should be considered in people who do not meet these criteria, or those who develop pneumonia during ICS use

Where can readers find more information about this study?

The original article, 'Rational use of inhaled corticosteroids for the treatment of COPD', was published in *NPJ Primary Care Respiratory Medicine*. You can read the original article at the link below:

- https://www.nature.com/articles/s41533-023-00347-6

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