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Medical Guideline

COPD Guideline Abridged Version

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COPD is a major global cause of death, with over 3 million fatalities in 2012. It's preventable and treat-able but poses a significant public health challenge.

What is COPD?

Definition: COPD is a diverse lung disease marked by long-lasting respiratory symptoms like dyspnea, cough, and sputum production. It's caused by airway and/ or alveoli abnormalities, leading to ongoing airflow blockages that typically worsen over time.[1]

Causes and Risk Factors: COPD is influenced by gene-environment interactions throughout life, damaging lungs and affecting normal development. Tobacco smoke and pollution are key culprits, but other factors like abnormal lung development and genetic mutations, such as in the SERPINA1 gene causing α-1 antitrypsin deficiency, also play a role, albeit less common.

Diagnostic Criteria: The presence of non-reversible airflow obstruction confirmed by spirometry (FEV1/ FVC < 0.7 post-bronchodilation) in the right clinical context confirms COPD diagnosis. Some individuals may have respiratory symptoms and/or lung abnormalities without airflow obstruction, termed 'Pre-COPD'. 'PRISm' identifies those with normal ratio but abnormal spirometry. These individuals are at risk of developing COPD over time, though not all do.[2]

Clinical Presentation: Patients with COPD commonly experience dyspnea, activity limitations, and cough, sometimes with sputum. They may also have exacerbations, marked by worsened respiratory symptoms needing specific care

Diagnosis and Assessment

Key Points:

- Consider COPD in patients with dyspnea, chronic cough, sputum production, history of lower respiratory tract infections, or exposure to risk factors. Diagnosis requires spirometry showing FEV1/ FVC < 0.7 post-bronchodilation.
- Initial assessment aims to gauge airflow obstruction severity, disease impact on health, and risk of future events to guide treatment.
- Further assessment, like lung volume measurement or imaging, may be needed for persistent symptoms after initial treatment.
- COPD patients often have concurrent conditions like cardiovascular disease, skeletal muscle dysfunction, and depression, which should be actively addressed as they affect health status and mortality regardless of COPD severity.

Diagnosis: Consider COPD in patients with dyspnea, chronic cough, sputum production, or exposure to risk factors. Diagnosis requires spirometry showing FEV1/ FVC < 0.7 post-bronchodilation.[3]

Clinical Presentation: Chronic dyspnea is the hallmark symptom of COPD, often accompanied by cough and sputum production in some patients. These symptoms can fluctuate and may precede airflow obstruction by years. Even without chronic dyspnea or cough, airflow

Clinical Indicators for Considering a Diagnosis of COPD

Consider the diagnosis of COPD, and perform spirometry, if any of these clinical indicators are present: (these indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of the presence of COPD; in any case, spirometry is required to establish a diagnosis of COPD)

Dyspnea that is	Progressive over time Worse with exercise Persistent
Recurrent wheeze	
Chronic cough	May be intermittent and may be non-productive
Recurrent lower respiratory tract infections	
History of risk factors	Tobacco smoke (including popular local preparations) Smoke from home cooking and heating fuels Occupational dusts, vapors, fumes, gases and other chemicals Host factors (e.g., genetic factors, developmental abnormalities, low birthweight, prematurity, childhood respiratory infections etc.)

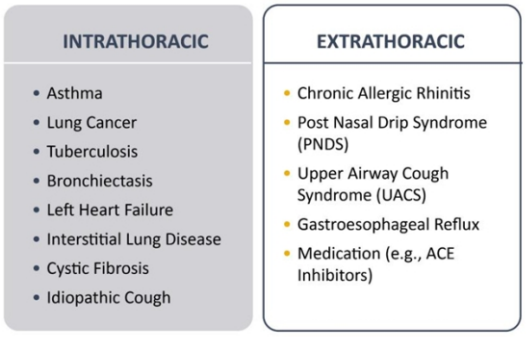
obstruction can be present, and vice versa. While COPD is defined by airflow obstruction, seeking medical help is typically driven by symptom impact on daily life. Patients may seek attention due to chronic symptoms or acute exacerbations.

Dyspnea: Dyspnea, a cardinal symptom of COPD, contributes significantly to disability and anxiety. Its prevalence is high across all stages of airflow obstruction, especially during exertion. Various factors, including impaired respiratory mechanics and comorbidities, contribute to its complexity

Chronic cough: Chronic cough, often the initial symptom of COPD, is sometimes dismissed by patients as a consequence of smoking or environmental exposure. It may start intermittently but can become constant throughout the day. In COPD, the cough may or may not produce sputum.

Sputum production: COPD patients often cough up small amounts of thick sputum. Chronic bronchitis, traditionally defined as regular sputum production for three months in consecutive years, doesn't fully capture the variability seen in COPD. Purulent sputum may suggest increased inflammation and possibly a bacterial exacerbation, though this association isn't always strong.

Other causes of COPD



Wheezing and chest tightness: In COPD, wheezes and chest tightness can vary day-to-day and throughout the day. Auscultation may reveal widespread wheezing, while chest tightness, often triggered by exertion, is muscular and diffuse. However, the absence or presence of these symptoms doesn't definitively diagnose or exclude COPD or asthma.

Fatigue: Fatigue is the subjective feeling of tiredness or exhaustion and is one of the most common and distressing symptoms experienced by people with COPD. People with COPD describe their fatigue as a feeling of "general tiredness" or as a feeling of being "drained of energy".

Additional clinical features in severe disease: Weight loss, muscle wasting, and loss of appetite are frequent in severe COPD and can indicate poor prognosis or other conditions like tuberculosis or lung cancer, warranting investigation. Ankle swelling may suggest cor pulmonale. Depression and anxiety, common in COPD, should be addressed in medical history as they impact health status and exacerbation risk, but are treatable.[4]

Medical History: A comprehensive medical history for a new patient with known or suspected COPD should cover:

- Exposure to risk factors like smoking and environmental pollutants.
- Past medical history, including early life events, respiratory infections, HIV, and tuberculosis.
- Family history of COPD or other respiratory diseases.
- Symptom development pattern, noting increased breathlessness and respiratory issues before seeking medical help.
- History of exacerbations or hospitalizations for respiratory issues.
- Presence of comorbidities like heart disease, osteoporosis, and mental health disorders.
- Impact of COPD on daily life, including activity limitations, work absence, and emotional well-being.
- Available social and family support.
- Opportunities for risk reduction, particularly smoking cessation.

Spirometry: Forced spirometry is crucial for diagnosing airflow obstruction in COPD due to its reproducibility and objectivity. It's noninvasive, affordable, and widely available, essential for healthcare providers managing COPD.A post-bronchodilator FEV1/FVC ratio < 0.7 is the GOLD standard for COPD diagnosis

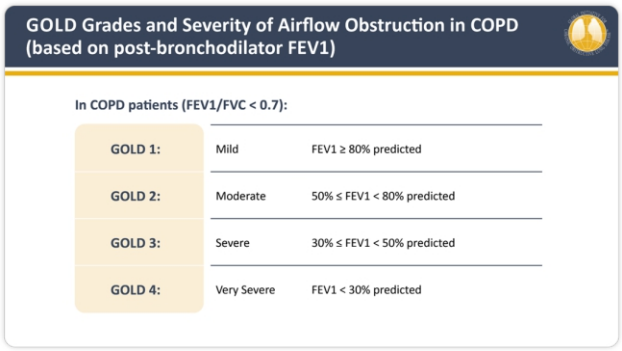
Initial assessment: Once the diagnosis of COPD has been confirmed by spirometry, in order to guide therapy COPD assessment must focus on determining the following five fundamental aspects:

- ► Severity of airflow obstruction
- ► Nature and magnitude of current symptoms
- ► Previous history of moderate and severe exacerbations
- ► Blood eosinophil count
- ► Presence and type of other diseases (multimorbidity)

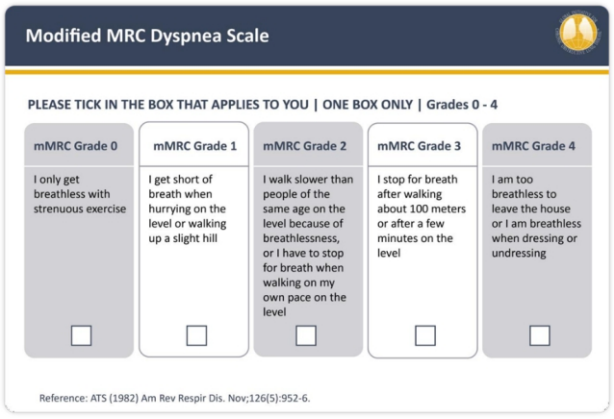
Severity of airflow obstruction: In the presence of FEV1/FVC ratio < 0.7 the assessment of airflow obstruction severity in COPD (note that this may be different from severity of the disease) is based on the post-bronchodilator value of FEV1 (% reference). The specific spir ometry cut points are proposed for purposes of simp-

licity.

Symptoms: Because there is only a weak correlation between the severity of airflow obstruction a formal assessment of symptoms using validated questionnaires is required.



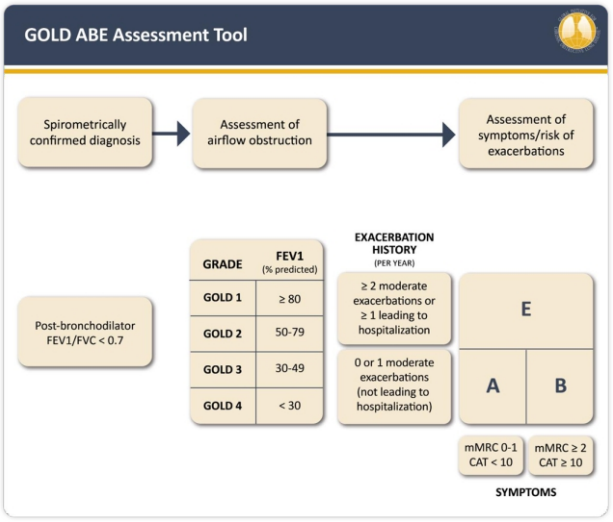
Dyspnea questionnaire: the modified Medical Research Council (mMRC) dyspnea scale: The mMRC scale was the first questionnaire developed to measure breathlessness, which is a key symptom in many patients with COPD, although often unrecognized.



Multidimensional questionnaires: COPD has impacts beyond dyspnea, necessitating multidimensional assessments. While comprehensive tools like the Chronic Respiratory Questionnaire (CRQ) and St. George's Respiratory Questionnaire (SGRQ) are vital for research, shorter measures like the COPD Assessment Test (CAT™) and Clinical COPD Questionnaire (CCQ©) are practical for clinical use. The CAT™, a globally applicable 8-item questionnaire, closely correlates with SGRQ and is extensively validated. SGRQ scores ≥ 25 indicate signi-ficant symptom burden, warranting regular treatment, while CAT™ scores ≥ 10 are indicative of symptom severity..

Blood eosinophil count: Blood eosinophil counts predict the effectiveness of adding ICS to regular bronchodilator treatment in preventing exacerbations, guiding ICS use as per GOLD recommendations

Multimorbidity: Common comorbidities include cardiovascular disease, metabolic syndrome, osteoporosis, depression, and anxiety, likely due to shared risk factors. COPD itself may increase the risk of other conditions like lung cancer. Extrapulmonary effects such as weight loss and skeletal muscle dysfunction contribute to exercise intolerance and poor health status but are modifiable through rehabilitation.



Combined initial COPD assessment: In 2011, GOLD introduced a combined assessment strategy for COPD severity and treatment, considering symptoms, airflow obstruction severity, and exacerbation history. This approach aimed to incorporate patient-reported outcomes and prioritize exacerbation prevention. In the 2023 update, GOLD proposed further evolution, merging groups C and D into a single group "E" to emphasize the clinical significance of exacerbations, highlighting the importance of exacerbation prevention irrespective of symptom severity.[5]

Prevention and management of COPD

Key points:

- Encouraging smoking cessation is paramount for all smokers.
- Legislative bans and counseling also aid quitting, but e-cigarettes lack evidence as cessation aids.
- Treatment goals focus on symptom reduction and preventing exacerbations, tailored to individual needs.
- Pharmacotherapy effectively manages symptoms, reduces exacerbations, and improves health status.
- Regular assessment of inhaler technique is crucial.
- COVID-19 vaccination is recommended for COPD patients, along with influenza and pneumococcal vaccinations.
- Pulmonary rehabilitation enhances exercise capacity and quality of life. Long-term oxygen therapy benefits those with severe resting hypoxemia,

while non-invasive ventilation aids severe chronic hypercapnia.

- Surgical or bronchoscopic interventions may be considered for advanced emphysema, and palliative care effectively manages symptoms in advanced stages.

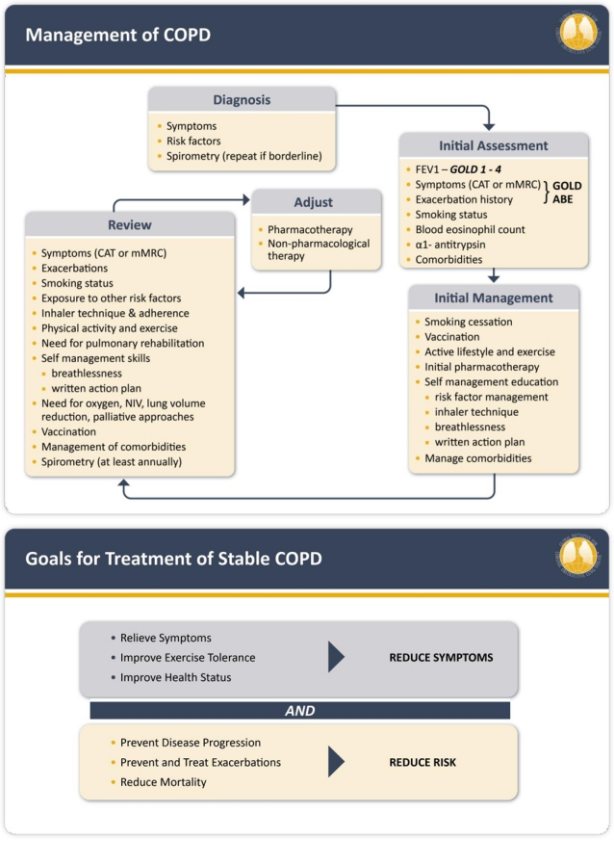
COPD Management

Introduction: COPD management aims to reduce symptoms and future risks. Patients need thorough assessments for personalized treatment plans. Both pharmacological and non-pharmacological therapies should be adjusted as necessary.

Identify and Reduce Exposure to Risk Factors

Smoking cessation: Smoking cessation is vital for all COPD patients, but many continue to smoke. Healthcare providers play a crucial role in encouraging and supporting quitting.

Vaccinations: People with COPD should receive all recommended vaccinations in line with the relevant local guidelines. [6]



Pharmacological Treatment of Stable COPD

We propose a personalized approach to initiating COPD treatment, considering symptom severity and exacerbation risk. Treatment escalation or de-escalation is guided by symptom dominance, exacerbation frequency, and therapy response. Patients are regularly assessed for symptom control, exacerbation frequency, and treatment efficacy, with attention to inhaler technique, adherence, smoking cessation, and risk factor exposure. Physical activity promotion and referral for pulmonary rehabilitation are encouraged, alongside consideration of oxygen therapy, non-invasive ventilation, and palliative care. Spirometry is repeated annually without interrupting bronchodilator therapy. [7]

Initial pharmacological management

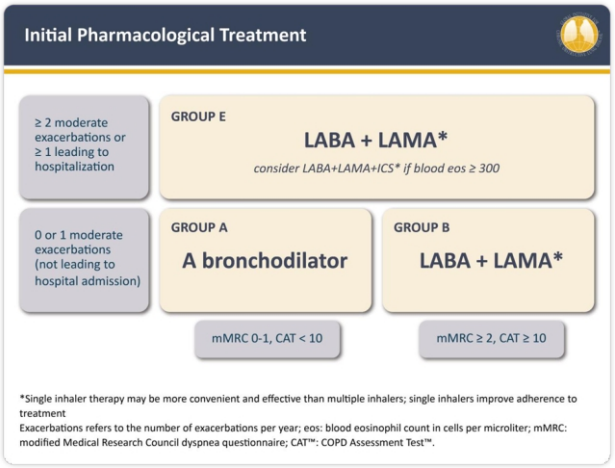
A proposal for the INITIATION of pharmacological management of COPD according to the individualized assessment of symptoms and exacerbation risk following the ABE scheme, and also accounting for blood eosinophil count.

Group A

- ► All Group A patients should be offered bronchodilator treatment based on its effect on breathlessness. This can be either a short- or a long-acting bronchodilator. If available and affordable a long-acting bronchodilator is the preferred choice except in patients with very occasional breathlessness.
- ► This should be continued if benefit is documented.

Group B

- ► Treatment should commence with a LABA+ LAMA combination for COPD patients.
- ► Studies show its superiority over LAMA alone for certain endpoints in patients with specific exacerbation history and symptom severity.
- ► If a LABA+LAMA isn't suitable, there's no preference between LABA or LAMA alone initially.



Group E

- Preferred Initial Therapy for Group E Patients: LABA+LAMA combination is recommended based on its efficacy in reducing COPD exacerbations.
- Use of LABA+ICS: Not encouraged in COPD.

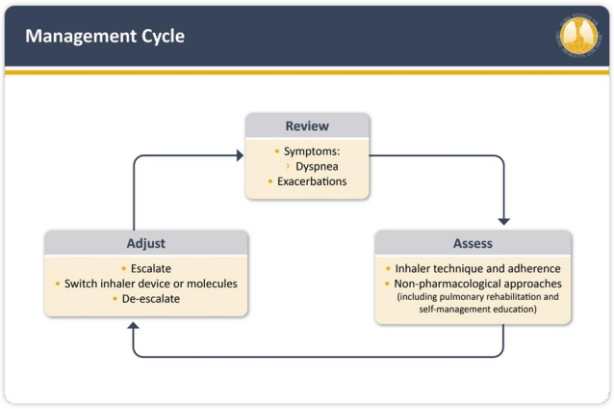
If needed, LABA+LAMA+ICS is preferred over LABA+ICS for better outcomes.

- Consideration for LABA+LAMA+ICS: In group E patients with blood eosinophil count ≥ 300 cells/µL, or in those with concomitant asthma.
- Rescue Medication: Short-acting bronchodilators should be prescribed for immediate symptom relief.
- Patient Reassessment: Regular reassessment is necessary to evaluate treatment goals and address any barriers to successful treatment.

► Review Review symptoms (dyspnea) and exacerbation risk (previous history, blood eosinophils).

► Assess inhaler technique and adherence, and the role of non-pharmacological approaches

► Adjust pharmacological treatment, including escalation or de-escalation. Switching inhaler device or molecules within the same class (e.g., using a different long-acting bronchodilator) may be considered as appropriate.



Follow-up pharmacological management: The follow-up treatment algorithm offers structured guidance for managing COPD patients on maintenance therapy, focusing on dyspnea and exacerbations. It provides escalation and de-escalation strategies based on efficacy and safety data, with close medical supervision advised.

Dyspnea: For patients experiencing persistent breathlessness or exercise limitation despite bronchodilator monotherapy, the recommendation is to use two long-acting bronchodilators.

Exacerbations:

► For patients with persistent exacerbations on bronchodilator monotherapy, escalation to LABA + LAMA is recommended.

► In patients who develop further exacerbations on LABA+LAMA therapy we suggest escalation to LABA+LAMA+ICS.

A beneficial response after the addition of ICS may be observed at blood eosinophil counts ≥ 100 cells/µL, with a greater magnitude of response more likely with higher eosinophil counts.(64)

► If patients treated with LABA+LAMA+ICS (or those with eos < 100 cells/µL) still have exacerbations the following options may be considered:

► Add roflumilast. This may be considered in patients with an FEV1 < 50% predicted and chronic bronchitis, particularly if they have experienced at least one hospitalization for an exacerbation in the previous year.

► Add a macrolide. The best available evidence exists for the use of azithromycin, especially in those who are not current smokers. Consideration to the development of resistant organisms should be factored into decision-making.

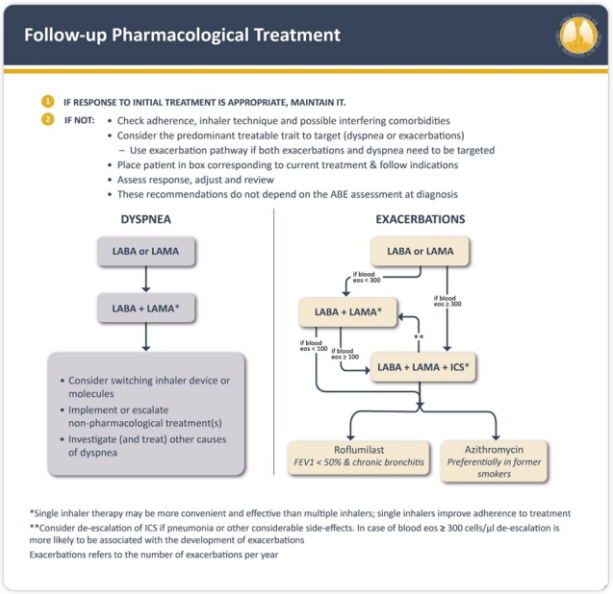
► Withdrawing ICS can be considered if pneumonia or other considerable side-effects develop. If blood eosinophils are ≥ 300 cells/µL de-escalation is more likely to be associated with the development of exacerbations. Carefully consider the dose of ICS used to reduce the potential of ICS related side effects that are more frequent at higher doses.

Patients under treatment with LABA+ICS

► If a patient with COPD and no features of asthma has been treated – for whatever reason – with LABA + ICS and is well controlled in terms of symptoms and exacerbations, continuation with LABA+ ICS is an option. However, if the patient has:

► Further exacerbations: treatment should be escalated to LABA+LAMA+ICS if the blood eosinophil count is ≥100 cells/µL or switched to LABA + LAMA if it is < 100 cells/µL.

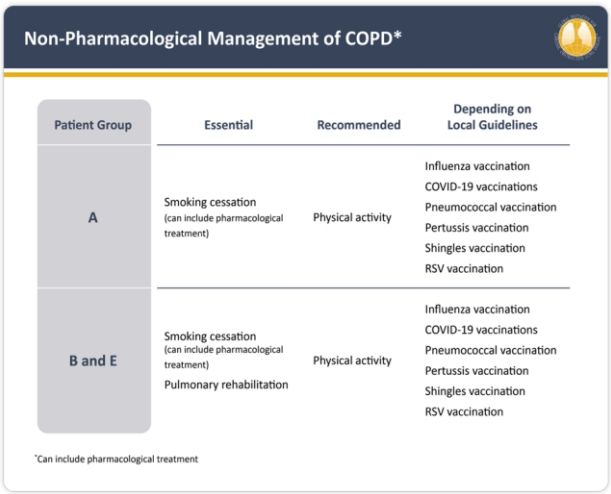
► Major symptoms: switching to LABA+LAMA should be considered.



Managing inhaled therapy: Appropriate use of inhaler devices is paramount for optimizing the benefit-risk ratio of inhaled therapy in COPD. This involves selecting the right device, providing thorough education, regularly assessing inhaler technique, and adjusting education and devices as needed. With a wide array of inhaled therapies and devices available, including various bronchodilators and corticosteroids, familiarity with their characteristics and proper usage is essential. Different inhaler devices, such as nebulizers, metered-dose inhalers (MDIs), breath-actuated MDIs (BAIs), soft mist inhalers (SMIs), and dry powder inhalers (DPIs), offer diverse options for delivery, each requiring specific techniques. [8]

Non-pharmacological treatment of stable COPD: Non-pharmacological treatments are integral to the comprehensive management of COPD and should complement pharmacotherapy. Upon diagnosis, patients should receive education about COPD, emphasizing smoking cessation, medication adherence, proper inhaler technique, physical activity promotion, vaccination, and referral to pulmonary rehabilitation.

Algorithms for initiating and following up on non-pharmacological treatments are provided based on the patient's GOLD A, B, E group at diagnosis. Recommendations for follow-up non-pharmacological treatments focus on treatable traits such as symptoms and exacerbations, ensuring a tailored approach to patient care.

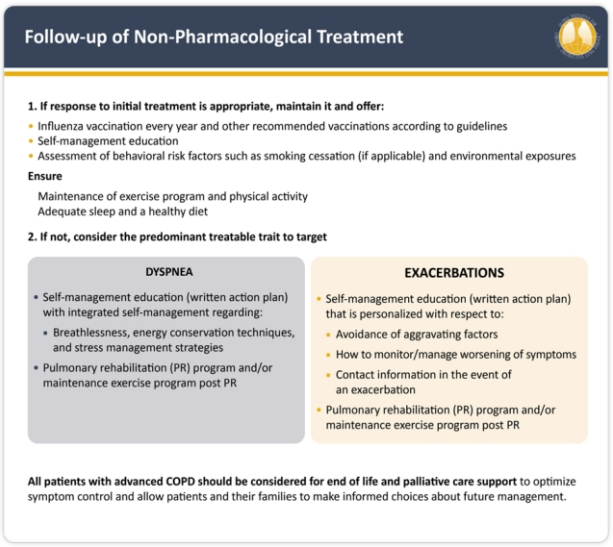


Oxygen therapy and ventilatory support

Oxygen therapy: Long-term oxygen therapy (>15 hours/day) improves survival in COPD patients with severe resting hypoxemia. Air travel is generally safe for most patients on long-term oxygen therapy, but maintaining adequate oxygen levels during flights is crucial, especially for those with moderate to severe hypoxemia. [9]

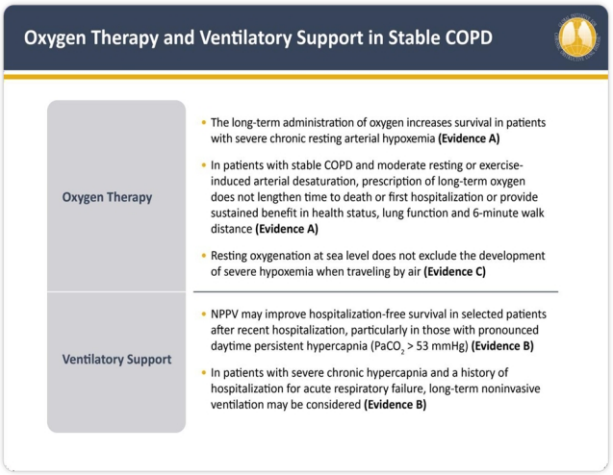
Long-term oxygen therapy (LTOT) is indicated for stable patients who have:

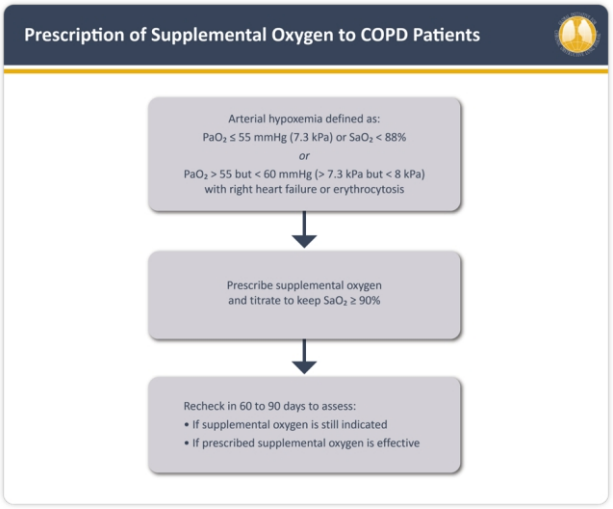
- PaO2 at or below 55 mmHg (7.3 kPa) or SaO2 at or below 88%, with or without hypercapnia confirmed twice over a three-week period; or
- PaO2 between 55 mmHg (7.3 kPa) and 60 mmHg (8.0 kPa), or SaO2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%).



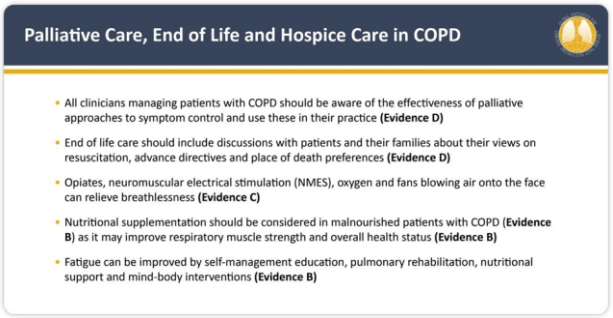
Ventilatory support: Once placed on LTOT the patient should be re-evaluated after 60 to 90 days with repeat arterial blood gas (ABG) or oxygen saturation measurements while inspiring room air and the level of oxygen flow that had been prescribed to determine if oxygen is still indicated or not.

Noninvasive ventilation (NIV) is occasionally used in patients with stable very severe COPD.NIV may be considered of some use in a selected group of patients, particularly in patients with both COPD and obstructive sleep apnea there are clear indications for continuous positive airway pressure (CPAP)





Supportive, Palliative, End-of-Life & Hospice Care



Pharmacological therapy: Previous studies like the TORCH and SUMMIT trials failed to demonstrate the efficacy of LABA+ICS combinations in reducing mortality in COPD patients compared to placebo, without requiring a history of previous exacerbations. Similarly, the UPLIFT trial, the largest LAMA treatment trial, did not show a mortality reduction compared to placebo, despite the majority of patients using ICS. However, recent evidence from the IMPACT and ETHOS trials suggests that fixed-dose inhaled triple combinations (LABA+LAMA+ICS) reduce all-cause mortality compared to dual inhaled long-acting bronchodilation therapy. These trials focused on symptomatic patients with a history of frequent or severe exacerbations.

Non-pharmacological therapy: Smoking cessation. From the Lung Health Study, a randomized clinical trial (RCT) that included asymptomatic or mildly symptomatic COPD patients treated with a 10-week smoking cessation intervention program and followed up to 14.5 years, the overall mortality rate was reduced in the smoking cessation intervention group compared to the usual care group.

Pulmonary rehabilitation (PR). A systematic review of RCTs reported a reduction in mortality for patients who had PR initiated during hospitalization or 4 weeks after discharge compared to those who did not have PR. These results have been corroborated by real-world evidence, from a large population-based cohort of 190,000 patients hospitalized for COPD, in whom initiation of PR within 90 days of discharge, while rare, was associated with a statistically significant reduced mortality.

Long term oxygen therapy (LTOT). Survival benefit of LTOT in COPD demonstrated in two studies in the early 1980s laid the foundation for long-term domiciliary management of hypoxemia. The Nocturnal Oxygen Therapy Trial (NOTT)(≥ 19 hours of continuous oxygen compared to ≤ 13 hours) and the Medical Research Council (MRC)(≥ 15 hours compared to no oxygen) two RCTs in COPD patients with resting PaO2 ≤ 55 mmHg or < 60 mmHg with cor pulmonale or secondary polycythemia showed a survival benefit. No significant benefit of LTOT was found in patients with moderate desaturation.

Non-invasive positive pressure ventilation (NPPV). Recent meta-analyses have shown positive results of long-term NPPV in patients with stable COPD. Although RCT results have being inconsistent on survival, larger trials with mortality as the primary outcome, enrolling patients with marked hypercapnia.

Lung transplantation and lung volume reduction surgery (LVRS). Because of the absence of randomized trials, observational data has been used to estimate the survival benefit of lung transplantation, relative to remaining "untransplanted." The survival benefit of transplantation varied by disease group, with a 2-year expected benefit in 2/5 of transplanted COPD patients.

LVRS has been shown to prolong survival compared to medical therapy in a very select group of patients with severe COPD, predominantly upper lobe emphysema, and low exercise capacity. Among patients with non-upper-lobe emphysema and high exercise capacity, mortality was higher in the surgery group than in the medical-therapy group. In summary, available data suggest that several pharmacological and non-pharmacological treatments may reduce mortality. Further analyses or studies may help to determine whether specific patient subgroups demonstrate a greater survival benefit.

Overview of the evidence: Pharmacotherapy

Pharmacotherapies for smoking cessation: Pharmacological treatments for smoking cessation include controller medications aimed at achieving long-term abstinence (nicotine patch, bupropion, and varenicline) and those that rapidly relieve acute withdrawal symptoms (short-acting nicotine).

Pharmacotherapy to treat stable COPD: Pharmacotherapy for COPD is currently focused on symptoms and exacerbations. FEV1 decline has been considered

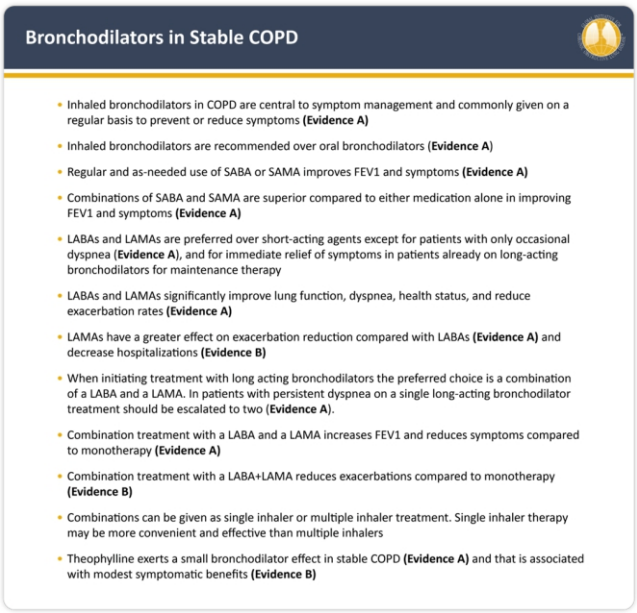
a surrogate for the natural course of the disease. In this context, studies have been performed to evaluate if pharmacotherapy may have an impact on the change of FEV1 over time. Individual clinical trials have not been sufficiently conclusive to show that pharmacotherapy can reduce the rate of FEV1 decline. However, a systematic review combining data from 9 studies demonstrated a reduction in the rate of FEV1 decline of 5.0 mL/year in active treatment arms compared with placebo arms. The difference between long-acting bronchodilator containing treatment arms and placebo arms was 4.9 mL/year. The difference between inhaled corticosteroid containing treatment arms and placebo arms was 7.3 mL/year. Although we need to be aware of the potential benefit of pharmacotherapy in reducing the rate of lung function decline, further research is needed to know which patients are likely to benefit.

The classes of medications commonly used and The choice within each class depends on the availability and cost of medication, and the clinical response balanced against side effects. Each treatment regimen needs to be individualized as the relationship between severity of symptoms, airflow obstruction, and severity of exacerbations can differ between patients.

Bronchodilators: Bronchodilators are medications that increase FEV1 and/or change other spirometric variables. Bronchodilators tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance.

Use of short acting bronchodilators on a regular basis is not generally recommended.

Beta2-Agonists: Beta2-agonists exert their effect by stimulating beta2-adrenergic receptors, leading to relaxation of airway smooth muscle and functional antagonism to bronchoconstriction.



Short-Acting Beta2-Agonists (SABA): SABAs have a duration of action of 4 to 6 hours and are used for immediate symptom relief and improvement in FEV1.

Long-Acting Beta2-Agonists (LABA): LABAs, such as formoterol, salmeterol, indacaterol, oladaterol, and vilanterol, have durations of action of 12 hours or more and provide sustained bronchodilation, improving lung function, symptoms, and exacerbation rates.

Adverse Effects: Adverse effects may include sinus tachycardia, somatic tremor, hypokalemia, and mild decreases in PaO2, but no association with loss of lung function or increased mortality in COPD patients has been reported.

Antimuscarinic Drugs

Antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors in airway smooth muscle. There are short-acting (SAMA) and long-acting (LAMA) antimuscarinic drugs available.

Short-Acting Antimuscarinic (SAMA):SAMAs, like ipratropium and oxitropium, provide small benefits over SABAs in lung function, health status, and oral steroid requirement.

Long-Acting Muscarinic Antagonists (LAMA): LAMAs, such as tiotropium, aclidinium, glycopyrronium bromide, umeclidinium, and revefenacin, improve symptoms, health status, and effectiveness of pulmonary rehabilitation, and reduce exacerbations and hospitalizations.

Adverse Effects: Adverse effects of antimuscarinic drugs are generally mild, including dry mouth, occasional urinary symptoms, and a bitter metallic taste with ipratropium.

Methylxanthines: Controversy surrounds the effects of xanthine derivatives in COPD, acting as non-selective phosphodiesterase inhibitors with disputed non-bronchodilator actions. Theophylline, the most common methylxanthine, metabolizes through cytochrome P450, with unclear impacts on gas trapping or respiratory muscles. Combining theophylline with salmeterol may improve FEV1 and breathlessness. Yet, recent large trials found no benefit from oral theophylline, either alone or with prednisolone, in reducing exacerbations in severe COPD.

Adverse effects: Toxicity of xanthine derivatives is dose-dependent, posing a challenge due to their narrow therapeutic range. Methylxanthines inhibit various phosphodiesterase enzyme subsets, leading to a wide range of toxic effects including cardiac arrhythmias and seizures, even at therapeutic levels. Additionally, interactions with several medications, including antibiotics and antidepressants, further complicate their use.

Combination bronchodilator therapy: Combining bronchodilators with different mechanisms and dura-

tions of action can enhance bronchodilation with lower side-effect risks compared to increasing the dose of a single bronchodilator. Combinations like SABAs and SAMAs improve FEV1 and symptoms more than either alone. Formoterol and tiotropium separately inhaled have a greater impact on FEV1 than either alone. Various LABA and LAMA combinations in single inhalers improve lung function and patient-reported outcomes compared to monotherapies. LABA+LAMA combinations effectively improve symptoms and health status in COPD patients, even at lower doses. Studies suggest LABA+LAMA combinations are more effective than monotherapy in preventing exacerbations, especially in patients with a history of exacerbations. However, effectiveness varies based on exacerbation risk and blood eosinophil concentrations.

Anti-inflammatory agents: To date, exacerbations (e.g., exacerbation rate, patients with at least one exacerbation, time-to-first exacerbation) represent the main clinically relevant end-point used for efficacy assessment of drugs with anti-inflammatory effects.

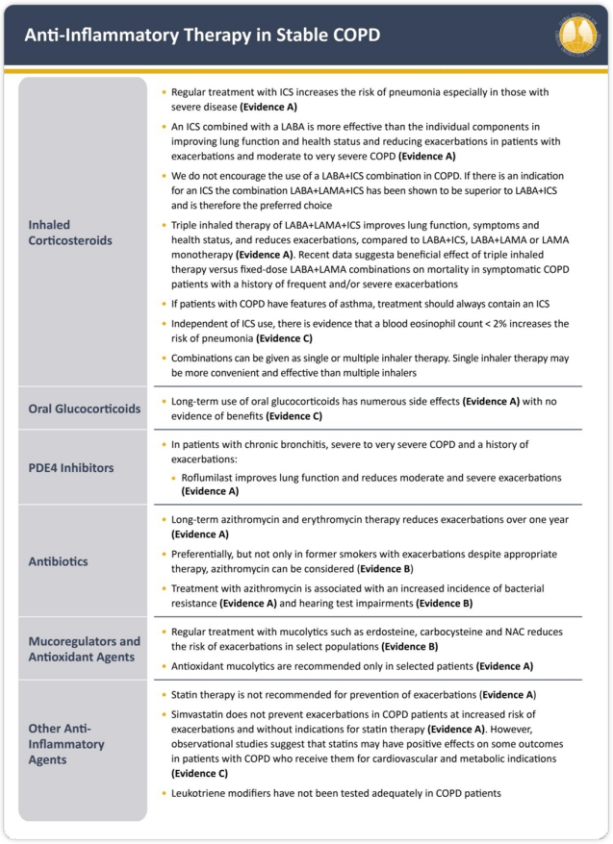
Inhaled corticosteroids (ICS)

General considerations: In vitro findings indicate limited responsiveness of COPD-associated inflammation to corticosteroids, but certain drugs like beta2-agonists, theophylline, or macrolides may enhance corticosteroid sensitivity in COPD, with unclear clinical significance. Long-term safety and dose-response relationships of ICS in COPD remain uncertain and require further study. Both current and ex-smokers with COPD derive lung function and exacerbation rate benefits from ICS use, though effectiveness may be reduced in heavy or current smokers compared to light or ex-smokers.

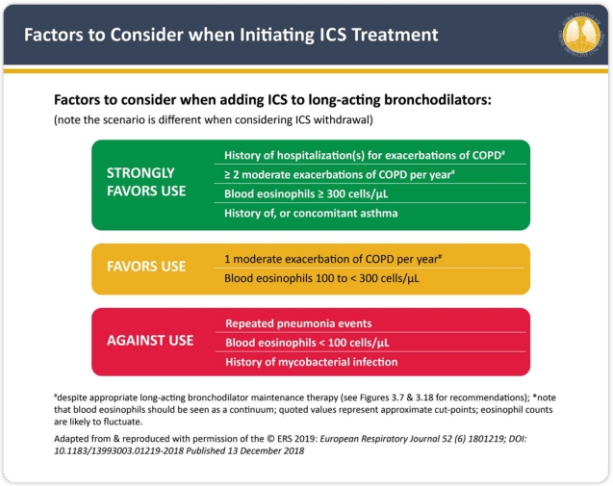
Efficacy of ICS (alone): Regular treatment with inhaled corticosteroids alone does not significantly alter the long-term decline of lung function or mortality in COPD patients, as evidenced by various studies and meta-analyses. While some trials showed trends toward increased mortality with certain ICS formulations, others did not observe such effects.

ICS in combination with long-acting bronchodilator therapy: Combining an inhaled corticosteroid (ICS) with a long-acting beta-agonist (LABA) in moderate to severe COPD patients reduces exacerbations and improves lung function and health status. However, trials focusing on mortality as the primary outcome have not shown significant benefits. Pragmatic trials reveal challenges in interpreting findings due to variations in treatment regimens and regional medical practices.[10]

Blood eosinophil count: Several studies highlight the predictive value of blood eosinophil counts in determining the efficacy of inhaled corticosteroids (ICS) in preventing exacerbations in COPD patients. A threshold of < 100 cells/μL indicates minimal to no benefit from ICS therapy, while ≥ 300 cells/μL suggests the highest likelihood of treatment benefit. Other factors like smoking status, ethnicity, and geographical location may influence the relationship between eosinophil count and ICS effectiveness.



Adverse effects: High-quality evidence from randomized controlled trials indicates that inhaled corticosteroid (ICS) use is associated with adverse effects such as oral candidiasis, hoarse voice, skin bruising, and pneumonia, particularly in patients with specific risk factors. However, studies in patients with moderate COPD suggest that ICS use alone or in combination



with a LABA does not increase the risk of pneumonia. Inconsistent results have been reported regarding the risk of decreased bone density and fractures with ICS treatment.

Withdrawal of ICS: Results from withdrawal studies regarding the consequences of discontinuing inhaled corticosteroids (ICS) on lung function, symptoms, and exacerbations show mixed findings. While some studies indicate an increase in exacerbations and/or symptoms after ICS withdrawal, others do not. There is evidence for a modest decrease in FEV1 (approximately 40 mL) with ICS withdrawal, especially among patients with higher baseline circulating eosinophil numbers.

Triple therapy (LABA+LAMA+ICS)

The step up in inhaled treatment to LABA plus LAMA plus ICS (triple therapy) can occur by various approaches and has been shown to improve lung function, patient reported outcomes and reduce exacerbations when compared to LAMA alone, LABA+LAMA and LABA+ ICS.(61,63,64,276-283) A post-hoc analysis of one of the RCTs that evaluated the effects of LABA+ LAMA + ICS showed that triple therapy improved clinical outcomes versus dual therapy regardless of smoking status.

A post-hoc pooled analysis of three triple therapy clinical trials in COPD patients with severe airflow obstruction and a history of exacerbations showed a non-significant trend for lower mortality (assessed as a safety outcome) with triple inhaled therapy compared to non-ICS based treatments. Two large one-year randomized controlled trials (named IMPACT and ETHOS) provide new evidence on mortality reduction with fixed-dose inhaled triple combinations compared to dual bronchodilation.

Oral glucocorticoids: Oral glucocorticoids have numerous side effects, including steroid myopathy which can contribute to muscle weakness, decreased functionality, and respiratory failure in people with very severe COPD. Systemic glucocorticoids for treating acute exacerbations in hospitalized patients, or during emergency department visits, have been shown to reduce the rate of treatment failure, the rate of relapse and to improve lung function and breathlessness. Conversely, prospective studies on the long-term effects of oral glucocorticoids in stable COPD are limited. Therefore, while oral glucocorticoids play a role in the acute management of exacerbations, they have no role in the chronic daily treatment in COPD because of a lack of benefit balanced against a high rate of systemic complications.

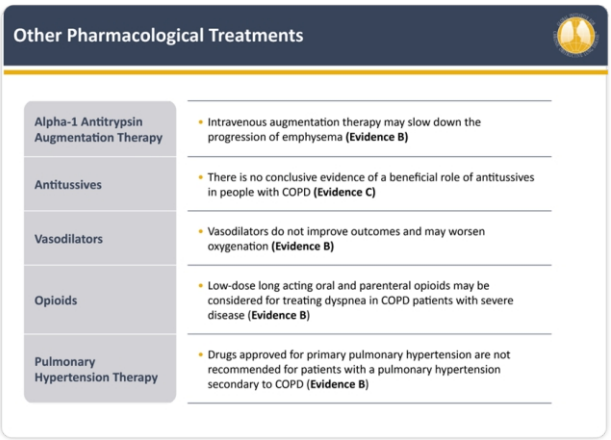
Phosphodiesterase-4 (PDE4) inhibitor: The principal action of PDE4 inhibitors is to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP. Roflumilast is a once daily oral medication with no direct bronchodilator activity. Roflumilast reduces moderate and severe exacerbations treated with systemic corticosteroids in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations. The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators and in patients who are not controlled on fixed-dose LABA + ICS combinations. The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation. There has been no study directly comparing roflumilast with an inhaled corticosteroid.

Adverse effects: Roflumilast has more adverse effects than inhaled medications for COPD. The most frequent are diarrhea, nausea, reduced appetite, weight loss, abdominal pain, sleep disturbance, and headache. Adverse effects have led to increased withdrawal rates from clinical trials. Adverse effects seem to occur early during treatment, are reversible, and diminish over time with continued treatment. In controlled studies an average unexplained weight loss of 2 kg has been seen and weight monitoring during treatment is advised, in addition to avoiding roflumilast treatment in underweight patients. Roflumilast should also be used with caution in patients with depression.

Antibiotics: Older studies initially showed no benefit of prophylactic, continuous antibiotic use or winter chemoprophylaxis on exacerbation frequency in COPD. However, recent research indicates that regular use of certain antibiotics, like azithromycin or erythromycin, can reduce exacerbation risk in susceptible patients. Azithromycin, though effective, is associated with bacterial resistance, QTc interval prolongation, and hearing test impairment, with diminished benefits observed in active smokers. Pulse therapy with moxifloxacin or long-term doxycycline did not show consistent benefits across all patients. In contrast, mucolytics like carbocysteine and N-acetylcysteine (NAC) may reduce exacerbations and modestly improve health status in COPD patients not on ICS, while erdosteine may have a significant effect on mild exacerbations irrespective of concurrent ICS treatment. However, due to varying study populations and treatments, precise identification of the target population for antioxidant agents remains uncertain.

Other drugs with potential to reduce exacerbations: Four large phase 3 studies investigated the efficacy of anti-IL-5 monoclonal antibody mepolizumab and anti-IL-5 receptor- antibody benralizumab in severe COPD patients with recurrent exacerbations and eosinophilic inflammation. While they showed a 15% to 20% reduction in severe exacerbation rates, the effect varied between studies and doses, with no significant impact on FEV1 or quality of life. A post-hoc analysis suggested potential benefit against oral corticosteroid-treated exacerbations in eosinophilic COPD patients. Additionally,

a trial with dupilumab, an anti-IL-4 receptor alpha monoclonal antibody, showed reduced exacerbations, improved FEV1, symptoms, and quality of life in COPD patients with chronic bronchitis and high baseline eosinophil counts, warranting further confirmation. However, nedocromil, leukotriene modifiers, and anti-TNF-alpha antibody (infliximab) did not show benefit and were associated with potential harm. Immunostimulants lacked sufficient evidence for support, while selective β1 receptor blocker metoprolol increased exacerbation risk.



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