Proactive Strategies for Mitigating Cardiopulmonary Risk in COPD

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KEY TAKEAWAYS

- Chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) are often found in the same patients.
- Patients with COPD have an elevated risk of cardiovascular events, and COPD exacerbations further increase the risk.
- All patients with COPD should be evaluated for CVD while also considering multimorbid COPD in those with known CVD.
- Treatment for both conditions, including prevention and rapid treatment for COPD exacerbations, leads to improved outcomes and lower mortality rates.
- Proactive implementation of maintenance therapies in COPD to prevent exacerbations and reduce the risk of early death should be a goal of COPD management.
- Comanagement of COPD and CVD is imperative and often requires collaboration and effective communication across specialties. Primary care practitioners are especially important in treating patients and coordinating care for both conditions.
- Certain patient care approaches should be prescribed for COPD and CVD: smoking cessation and support, up-to-date adult immunization, activity or exercise support, and dietary guidance. COPD and CVD rehabilitation programs can provide this education and support for patients.

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INTRODUCTION

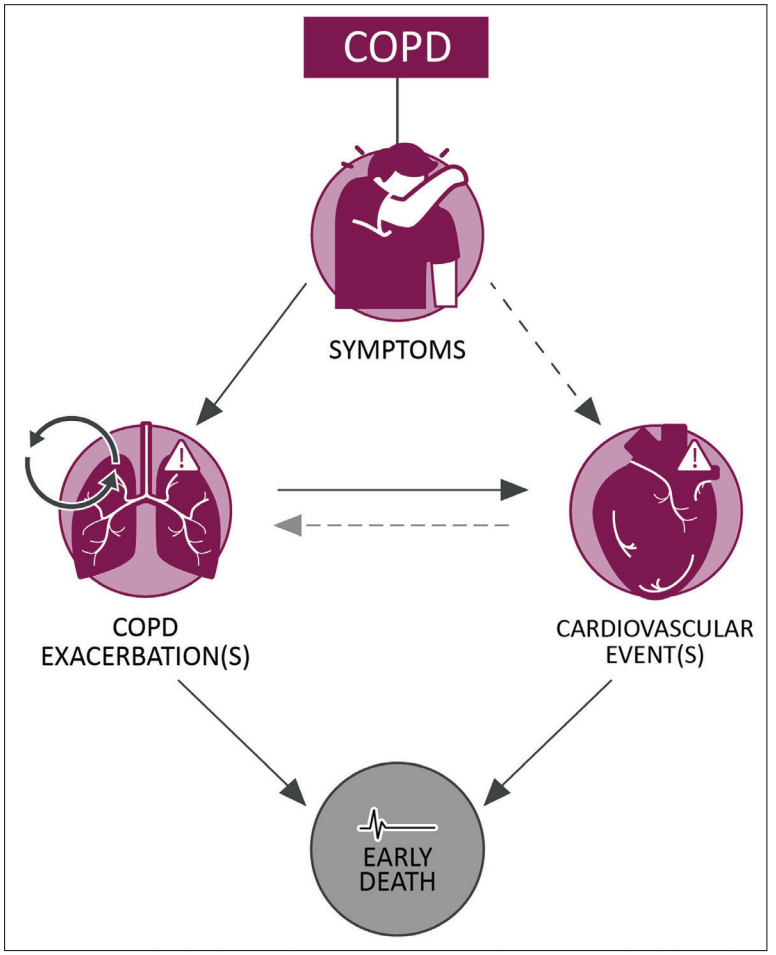
Chronic obstructive pulmonary disease (COPD) causes significant morbidity and mortality across the globe.[1,2] In the United States, COPD prevalence is estimated to be 4.3%, with 335,000 hospitalizations and 791,000 emergency department visits annually as of 2023.[1,3] COPD is often accompanied by cardiovascular disease (CVD) and COPD exacerbations, increasing the risk of both pulmonary and cardiovascular (CV) events (cardiopulmonary risk), and leading to potentially severe complications and/or early death (**FIGURE 1**).[4-7]

The association between COPD and CVD is becoming more widely recognized, and a new section in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2025 report addresses CV risk in COPD.[8] These risks include exacerbations that may be associated with myocardial infarction, stroke, heart failure decompensation, arrhythmias, and death from any of these events.[7] Unmet needs in the diagnosis and clinical care of patients with multi-morbid COPD and CVD remain.

Inhaled therapies are the mainstay of COPD therapy, yet prescribing and use remain suboptimal. Despite the safety and efficacy of inhaled bronchodilator maintenance therapy, it remains underutilized in the United States, with only about 36% of patients receiving maintenance therapy.[9] Moreover, there is evidence of both undertreatment and overtreatment relative to disease severity.[10] Further, many patients with COPD continue to experience symptoms and exacerbations despite receiving maintenance therapy.[11] Alarmingly, prescribed treatment adherence tends to be low—ranging from 30% to 50% within a few months.[12] Decreased adherence is associated with worse COPD outcomes, including a higher risk for exacerbations and increased long-term mortality.[12] This was highlighted in a recent meta-analysis that showed a 40% increased risk of COPD exacerbations with poor adherence to inhaled medication.[13]

Although coexistence of COPD and CVD is common, clinicians may focus on only one of these diseases—ignoring the importance of diagnosing and treating both conditions simultaneously.[7,8] This may be due to the failure to consider that symptoms such as dyspnea are common in both, as are risk factors such as smoking. Even patients with clinically stable COPD (not having exacerbations) have an increased prevalence of CVDs such as hypertension, coronary artery disease, heart failure, and arrhythmias, which are prominent

FIGURE 1. COPD-associated cardiopulmonary risk.[7]



Abbreviation: COPD, chronic obstructive pulmonary disease.

Arrow type and shade indicate strength of association: strong association, with substantial supporting data (dark grey solid), emerging association, with some supporting data (dark grey dotted), suspected association, with data yet to be generated (light grey dotted).

Source: Singh D, et al. Implications of cardiopulmonary risk for the management of COPD: a narrative review. *Adv Ther*. 2024;41(6):2151-2167. No changes were made to the figure prior to reprinting. Figure licensed under a Creative Commons Attribution-NonCommercial 4.0 International License. The license can be viewed at this link: https://creativecommons.org/licenses/by-nc/4.0/legalcode

causes of death in individuals with COPD.[8] Assessing CV risk using tools such as the Framingham or QRisk score may underestimate CVD risk in patients with COPD.[8] GOLD recommends evaluating for the presence of major CVD in any patient with COPD and treating appropriately.[8]

CASE STUDY

Mary is a 57-year-old mother of 3 who works outside the home as an elementary school secretary. She presents to her primary care clinic for help with increasing shortness of breath and frequent productive cough. She was diagnosed with COPD (GOLD group B) 3 years ago and has been taking long-acting beta$_2$-agonist (LABA) + inhaled corticosteroid (ICS) therapy for the past 6 months after previously experiencing multiple exacerbations on LABA-only treatment. She is a former smoker (26-pack-year history) who stopped smoking at the time of her COPD diagnosis and remains off cigarettes. She has been treated for hypertension for 5 years with a diuretic. She has good inhaler technique and says she uses all her medications most days.

Currently she has taken on more work at school but finds she often feels too tired to get going in the morning and is short of breath halfway up the stairs at school. On questioning, she reports episodes of "being so tired I have nausea when trying to go upstairs quickly or hurry down the school halls."

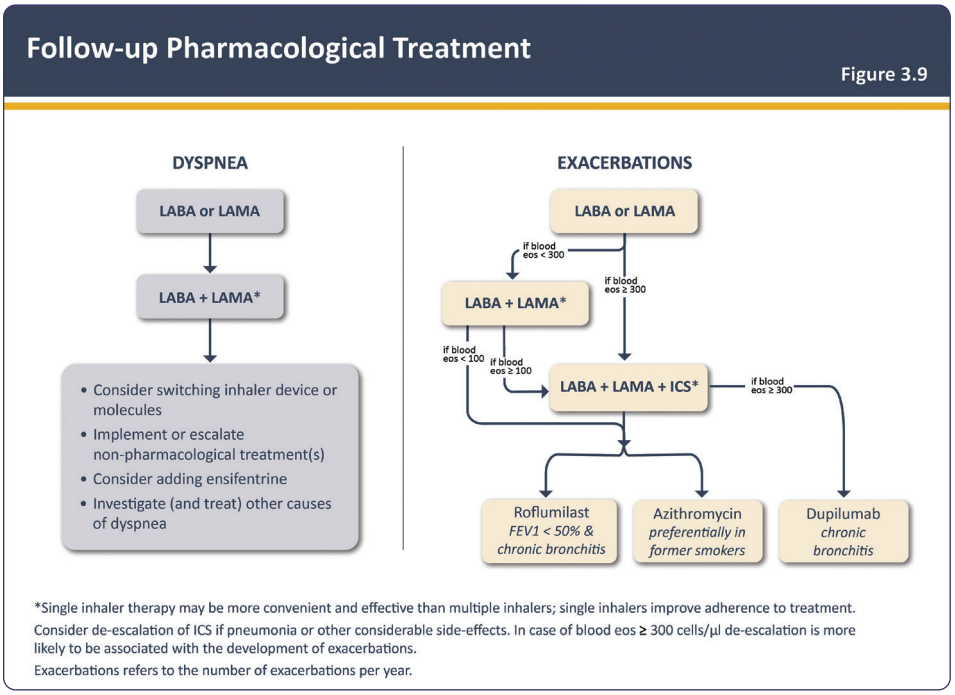
Clinical assessment: This patient is experiencing worsening dyspnea and frequent productive cough, but why? Questions for further investigation might include: Is her COPD progressing and causing more dyspnea? Are the increased dyspnea and perhaps the nausea variants of angina results of CVD that require evaluation and treatment?

COPD and CVD share several underlying mechanisms and risk factors such as hypoxemia, hyperinflation, systemic inflammation, age, smoking, physical inactivity, unhealthy diet, air pollution, genetics, and other health conditions such as diabetes, hypertension, hyperlipidemia, and infections.[14,15] These account for much of the multimorbidity of COPD and CVD and emphasize the need to evaluate individuals with COPD for CVD, as well as those with CVD for COPD. Patients with cardiopulmonary disease experience worse cardiac outcomes than those without. CV events are one of the most common causes of death in patients with COPD.[8,16,17] Assessment for CVD in those with known COPD is based on the patient's symptoms, personal risk factors, and available resources. These tests can vary from an electrocardiogram (ECG) and exercise-based stress test to imaging studies. Continued or repeated assessment of symptom levels may suggest additional or repeated evaluations over time. Additionally, patients with CVD and breathlessness should undergo spirometry to rule out COPD.

COPD-DRIVEN CARDIOPULMONARY RISK AND EXACERBATIONS

Although stable COPD is associated with multi morbid CVD, multiple dynamic and interacting pathophysiologic mecha-

FIGURE 2. GOLD 2025 escalation and de-escalation strategies for pharmacologic treatment for dyspnea and exacerbations.[8]



Abbreviations: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; LAMA, long-acting muscarinic antagonist.

nisms during and after a COPD exacerbation contribute to an increased risk of a range of cardiac events.[8,18] Major CV events are more likely after an acute COPD exacerbation, and CV risk can remain elevated for up to a year after a COPD exacerbation. Severe COPD exacerbations can double the risk of heart attack and increase risk of hospitalization and cardiopulmonary-related death.[19-24] Increased risk is related to worsening of systemic inflammation, abnormal pulmonary gas exchange, gas trapping, and lung hyperinflation.[8] In addition, reduced myocardial contractility (leading to pulmonary edema), pulmonary hypertension, and poor perfusion of systemic organs also worsen during COPD exacerbations.[8] This is highlighted in the results from the EXAcerbations of COPD and their OutcomeS in CardioVascular diseases (EXACOS-CV) study, a retrospective analysis of patients with newly diagnosed COPD.[25] In the US group studied, risk of death and CV events was highest within the first 30 days after an exacerbation and increased with subsequent exacerbations, remaining elevated for up to 2 years.[25]

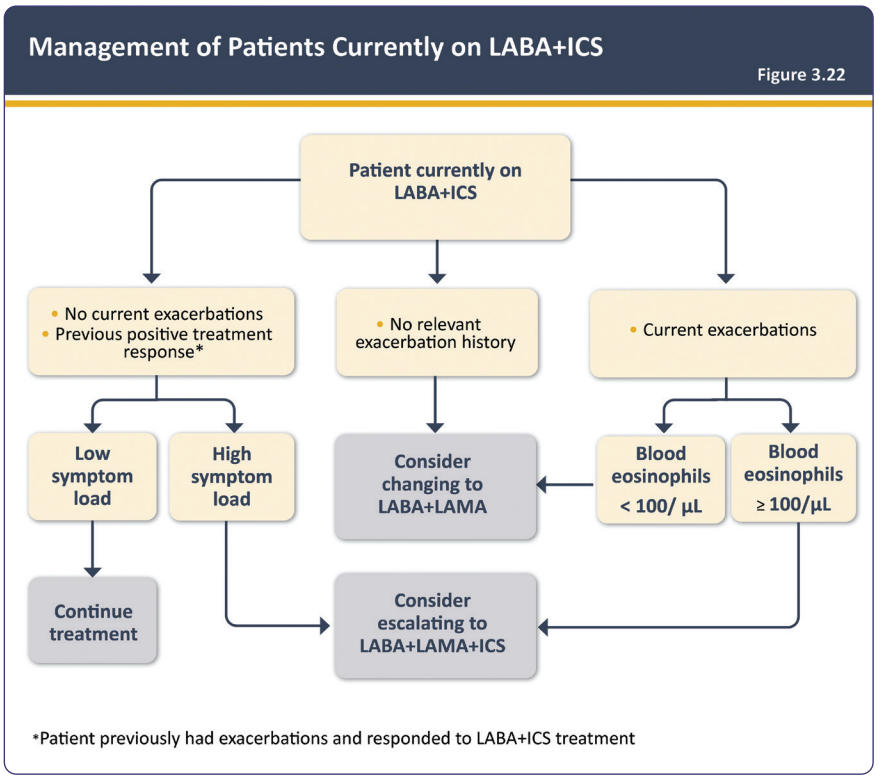
MANAGING COPD EXACERBATIONS AND CARDIOPULMONARY RISK

A COPD exacerbation is defined as "an event characterized by dyspnea and/or cough and sputum that worsen over <14 days" and is often associated with increased inflammation caused by airway infection, pollution, or other triggers.[8] Exacerbations are more common in some individuals with COPD, including those with poorer lung function and lower baseline oxygen saturations.[7] The goals for treating COPD exacerbations include minimizing the negative impact of the current event and preventing the development of future events.[8] For patients with persistent exacerbations on bronchodilator monotherapy, escalation to LABA + long-acting muscarinic antagonist [(LAMA) eosinophils <300 cells/µL] or LABA + LAMA + ICS (eosinophils ≥300 cells/µL) is recommended, and those with further exacerbations on LABA + LAMA therapy should be escalated to LABA + LAMA + ICS (**FIGURE 2**).[8] A beneficial response with ICS addition can be observed with blood eosinophils ≥100 cells/µL, with a greater magnitude of response expected with increasing eosinophil counts.[8]

Of note, some patients may be receiving LABA + ICS therapy, though this is not a recommended treatment for COPD.[8] If there is an indication for ICS use in COPD, LABA + LAMA + ICS has been demonstrated to be superior to LABA + ICS.[8] In such patients, clinicians should review relevant exacerbation history and adjust therapy to either LABA + LAMA + ICS or LABA + LAMA, depending on exacerbations and blood eosinophils (**FIGURE 3**).[8] Conversely, if there is no indication for ICS, patients receiving LABA + ICS should be switched to LABA + LAMA, which has been shown to be better than LABA monotherapy.[8]

Data from several trials suggest the benefit of triple therapy (LABA + LAMA + ICS), specifically for preventing COPD exacerbations in those at increased risk, leading to improvement in cardiopulmonary risk (**TABLE**).[26-32] Some studies indicate a reduction in cardiopulmonary events for patients receiving single-inhaler triple therapy.[27,33,34] Additional ongoing studies such as ATHLOS (NCT06067828) and THARROS (NCT06283966) are further evaluating the effects of triple therapy on cardiopulmonary outcomes in COPD. Real-world data suggest that prompt initiation of triple therapy within 30 days after a COPD exacerbation may

FIGURE 3. GOLD 2025 algorithm for adjusting therapy in patients with COPD currently receiving LABA + ICS.[8]



Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta2-agonist; LAMA, long-acting muscarinic antagonist.

further reduce the risk of future exacerbations compared with delayed intervention (>30 days).[35-37]

The GOLD 2025 report recommends proactive management of COPD exacerbations and cardiopulmonary risk, starting with appropriately identifying and treating COPD exacerbations, along with routine measurement of CV markers such as troponin and brain-natriuretic peptides during exacerbations when appropriate and possible.[8] Preventing COPD exacerbations and reducing cardiopulmonary risk through the use of effective therapies is critical to optimize patient outcomes.[8]

Guideline-directed cardiopulmonary therapies should be implemented at every opportunity; preventing exacerbations and intensively treating traditional CV risk factors should be a key focus in COPD management. Practical strategies for implementing effective treatments to address exacerbation and cardiopulmonary risk in COPD begin with the basics of smoking cessation and support, daily activity plans, dietary guidance, and completion of recommended adult immunizations for pneumococcal disease, COVID-19, pertussis, and herpes zoster.[8] COPD care will depend on history of exacerbations and oxygen status. An important and underused resource for both respiratory and CV support is COPD rehabilitation emphasizing education, activity, breathing exercises, medication adherence, and diet, which reduces the risk of repeat severe exacerbations.[38] As mentioned previously, dual bronchodilator therapy is the basis for all COPD management with the addition of ICS, roflumilast, and now biologic therapies when appropriate.[8]

Treatment for CVD depends on prior CVD history and current findings with select treatments for hypertension, cardiac failure, arrythmias, lipid abnormalities, and angina. These therapies are not contraindicated in individuals with COPD and in fact are central to the management of both CVD and COPD.[39]

CASE STUDY (CONTINUED)

Mary needs an updated evaluation of her COPD status, including pulse oximetry and spirometry or pulmonary function testing, to assess rapid progression of her COPD, which is causing greater dyspnea, worsening exacerbations, and possible CV events. Considering her previous positive response to ICS therapy, and based on exacerbation history, the patient would be a candidate for LABA + LAMA + ICS treatment.

In addition, her "nausea" with activity should be assessed as a potential angina variant. Considerations include an ECG and stress test. Like many people with COPD, Mary may not be a candidate for an exercise stress test, rather, requiring an imaging stress test. Such evaluations may include referral to a cardiologist, depending on the severity of symptoms, the primary care practitioner's comfort with ordering evaluations, and available local and health systems resources and guidance.

It is also appropriate to review her lipid profile and consider treating her abnormal lipids and blood pressure, updating her immunization status, and re-evaluating her inhaler technique.

Patients with COPD and CVD are often comanaged in primary care with specialty practitioners addressing more advanced therapies for COPD, CVD, and any other comorbidities such as diabetes, anxiety, or depression.

SUMMARY

COPD represents a substantial disease burden in the United States and is frequently associated with CVD, with cardio-

TABLE. Studies showing COPD exacerbation risk reduction with triple therapy (LAMA + LABA + ICS).

Study	Population	Treatment	Duration	Findings
ETHOS[27]	Moderate to very severe COPD and at least 1 exacerbation in the past year	Budesonide/ glycopyrrolate/ formoterol fumarate	52 weeks	Significant reduction in moderate or severe exacerbations vs LAMA + LABA and ICS + LABA
FULFIL[28]	Age ≥40 years, GOLD group D, and either ≥2 moderate COPD exacerbations or 1 severe COPD exacerbation within the past year	Fluticasone furoate/ umeclidinium/ vilanterol	24 weeks	Significant reduction in the rate of moderate or severe exacerbations vs ICS + LABA
IMPACT[26]	Age ≥40 years with symptomatic COPD and FEV_1 <50% predicted, ≥1 moderate or severe exacerbation in the past year, or FEV_1 50%-80% predicted and ≥2 moderate or ≥1 severe exacerbation in the past year	Fluticasone furoate/ umeclidinium/ vilanterol	52 weeks	Significant reduction in moderate or severe exacerbations vs LAMA + LABA and ICS + LABA
KRONOS[29]	Age 40-80 years, current or former smokers, and symptomatic for COPD despite receiving ≥2 inhaled maintenance therapies for ≥6 weeks	Budesonide/ glycopyrrolate/ formoterol fumarate	24 weeks	Significant reduction in the rate of moderate or severe exacerbations vs LAMA + LABA
TRILOGY[31] TRINITY[30] TRIBUTE[32]	TRILOGY and TRINITY: FEV_1 < 50%, ≥1 moderate-to-severe COPD exacerbation in the past year, and CAT score of ≥10 TRIBUTE: symptomatic COPD, severe or very severe airflow limitation, ≥1 moderate or severe exacerbation in the previous year, and receiving inhaled maintenance medication	Beclomethasone dipropionate/ glycopyrronium/ formoterol fumarate	52 weeks	Significant reduction in the rate of moderate or severe exacerbations compared to ICS + LABA, LAMA, or LAMA + LABA therapy

Abbreviations: CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting beta2-agonist; LAMA, long-acting muscarinic antagonist.

pulmonary risk increasing with exacerbations. Available and effective maintenance treatment often remains underused, putting many patients at continuing risk for symptoms, exacerbations, adverse outcomes, and comorbidities. Systemic inflammation, hyperinflation, and hypoxemia are associated with COPD and increase with exacerbation, resulting in sustained levels of greater respiratory and CV risk, even after the exacerbation resolves. Effective prevention and treatment of exacerbations, including timely optimization of therapies, are essential to mitigating cardiopulmonary risk in COPD. Multiple studies show reduction in the risk of exacerbations with triple therapy for appropriately selected patients. CVD assessment and targeted treatments should be pursued concomitantly to provide the greatest improvement in the patient's quality of life and outcomes. ●

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