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Mucus plugs in COPD and cardiovascular mortality: An emerging risk pathway and the therapeutic potential of mucolytic strategies

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A B S T R A C T

Airway mucus plugging is an underrecognized feature of COPD that is increasingly associated with adverse outcomes, including higher mortality rates. Computed tomography studies demonstrate that mucus plugs are prevalent, variable, and frequently persistent or dynamic over time. The presence of mucus plugs is independently linked to a worse prognosis, even after adjusting for cardiovascular and respiratory risk factors. Patients with mild COPD appear to be at particularly high risk, suggesting that mucus plugging may represent an early and potentially modifiable disease trait. Mucus plugging contributes to COPD progression through several mechanisms, including airflow obstruction, ventilation/perfusion mismatch, hypoxemia, airway inflammation, and increased susceptibility to infectious exacerbations. These exacerbations are strongly associated with acute cardiovascular events caused by systemic inflammation, endothelial dysfunction, and vascular stress. Additionally, chronic hypoxia and inflammatory signaling related to mucus dysfunction may independently increase cardiovascular risk. Within the "treatable traits" framework, mucus dysfunction is an important therapeutic target. Mucolytic and mucoactive therapies aim to improve mucus properties and clearance, which could reduce exacerbations and their systemic consequences. Some meta-analytic evidence suggests that, among thiol-based mucolytics, erdosteine is the most effective at reducing exacerbation frequency and duration. It also demonstrates antioxidant and anti-inflammatory effects that may influence systemic disease pathways. However, its comparative advantages over other agents remain uncertain. This narrative review summarizes the current evidence regarding the epidemiology, pathophysiology, and clinical implications of mucus plugging in COPD, with a focus on the proposed mucus plug–exacerbation–cardiovascular event axis and the potential role of mucus-directed therapies.

1. Introduction

COPD affects an estimated 479 million people worldwide and is a leading cause of morbidity and mortality [1]. Although traditionally defined by airflow limitation, COPD is now recognized as a systemic disorder with substantial extrapulmonary consequences, particularly cardiovascular implications. Cardiovascular events account for approximately 35% of deaths among COPD patients, irrespective of the severity of airflow obstruction [2]. This cardiovascular burden persists even in patients with mild-to-moderate COPD, underscoring the need to move beyond spirometric severity as the sole determinant of risk. Although accumulating evidence supports associations between mucus plugging, COPD exacerbations, and adverse cardiovascular outcomes, direct evidence demonstrating a causal relationship between mucus plugs and cardiovascular disease or cardiovascular mortality is currently lacking.

Mucus dysfunction has emerged as a central but under-recognized feature of COPD pathobiology. Characterized by mucus hypersecretion, altered biophysical properties, and impaired clearance, it leads to persistent airway obstruction [3].

Recent computed tomography (CT) imaging studies in COPD patients have shown that mucus plugs are highly heterogeneous in both size and morphology, ranging from 2 to 50 mm in length [4]. Two distinct phenotypes have been identified: stubby plugs (≤11 mm), which account for approximately 64% of cases, and stringy plugs (>11 mm), representing the remaining 36%. These plugs are found predominantly in relatively large segmental and subsegmental airways (airway generations 6-9), rather than being confined to the small airways. Interestingly, mucus plugging appears to be inversely associated with emphysema severity, with emphysematous regions tending to exhibit fewer but larger plugs [4]. CT imaging studies further demonstrate that mucus plugs causing complete occlusion of medium-to large-airways are present in 25-67% of COPD patients and remain remarkably stable over time, persisting in 67% of patients after 1 year and in 73% after 5 years [2,3].

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Within the "treatable traits" framework, mucus plugging represents a distinct, potentially modifiable phenotype that informs personalized management strategies [2]. However, longitudinal data from the COPDGene study showed that mucus plugging is not a static phenomenon, but rather a highly dynamic process [5]. Over 5 years, mucus plugs may resolve, persist, or newly emerge, each trajectory carrying distinct prognostic implications for lung function decline. Approximately 27% of patients with mucus plugs at baseline experienced spontaneous resolution within five years, with FEV_1 decline rates comparable to those who never had mucus plugs (~37 mL/year) [5]. In contrast, persistent mucus plugs were associated with the greatest FEV_1 decline (~60 mL/year), while newly developed plugs were linked to accelerated decline (~55 mL/year).

Notably, up to 30% of patients with CT-detected mucus plugs report no cough or sputum production, suggesting that clinical symptoms alone may underestimate the prevalence of this pathology [6]. These "silent" plugs are more prevalent in older adults, women, and Black patients, and are associated with worse structural and functional outcomes, highlighting a substantial burden that is not captured by symptom-based assessment.

2. Epidemiology of mucus plugging and mortality

The landmark COPDGene study provided key evidence linking mucus plugs to mortality in COPD patients [2]. Mucus plugs were present in 40.7% of the 4363 participants followed for a median of 9.5 years. The presence of mucus plugs in one to two lung segments was associated with a 15% increased risk of death (adjusted hazard ratio [aHR], 1.15; 95% confidence interval [CI], 1.02-1.29), while involvement of three or more segments was associated with a 24% increased risk (aHR, 1.24; 95% CI, 1.10-1.41) compared with patients without mucus plugging.

Mortality increased progressively with mucus plug burden, with rates of 34.0% in patients without plugs, 46.7% in those with plugs in one to two segments, and 54.1% in those with plugs in three or more segments [2]. These associations remained significant after adjusting for age, sex, race, body mass index, smoking history, lung function (FEV_1), and CT measures of emphysema and airway disease. Importantly, the relationship persisted even after accounting for coronary artery disease and chronic bronchitis, suggesting that mucus plugging provides independent prognostic information [2].

Recent validation using artificial intelligence (AI)-based automated quantification confirmed these findings, reporting hazard ratios of 1.18 for 1-2 obstructed segments and 1.27 for ≥3 obstructed segments [7]. Consistently, the 2026 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recognizes mucus plugging as being associated with greater airflow obstruction, lower oxygen saturation, reduced exercise tolerance, increased exacerbation risk, worse quality of life, and increased all-cause mortality [8].

3. Aim of the review

This narrative review synthesizes current evidence on the epidemiology, pathophysiology, and clinical implications of mucus plugging in COPD, with particular emphasis on the potential links between mucus plugging, COPD exacerbations, and cardiovascular outcomes.

4. Disproportionate impact in early-stage COPD

A critical subset analysis by Rogliani and Calzetta revealed that the mortality risk associated with mucus plugging is not uniform across COPD severity stages [9]. Using secondary data from the COPDGene cohort, this analysis demonstrated that patients with GOLD stage 1 (mild COPD) and ≥1 occluded lung segments had a significantly increased mortality risk (relative risk 1.48, 95% CI 1.10-1.86; $P < 0.01$) compared to those without occlusions (Fig. 1). The relative association between mucus plugging and mortality appeared more pronounced in GOLD stage 1 patients with ≥3 occluded segments (relative risk 1.89, 95% CI 1.43-2.36; $P < 0.001$).

Remarkably, no increased mortality risk was observed for patients with 1-2 occluded lung segments at GOLD stages 2-4, suggesting that mucus plugging may be particularly detrimental in early disease when other pathological processes are less advanced [9]. Number-needed-to-harm estimates suggested a potentially greater relative impact of extensive mucus plugging in early-stage disease; however, these findings should be interpreted cautiously and primarily as hypothesis-generating [9]. This finding suggests that mucus plugging in early COPD may represent a critical, potentially modifiable risk factor that warrants aggressive intervention.

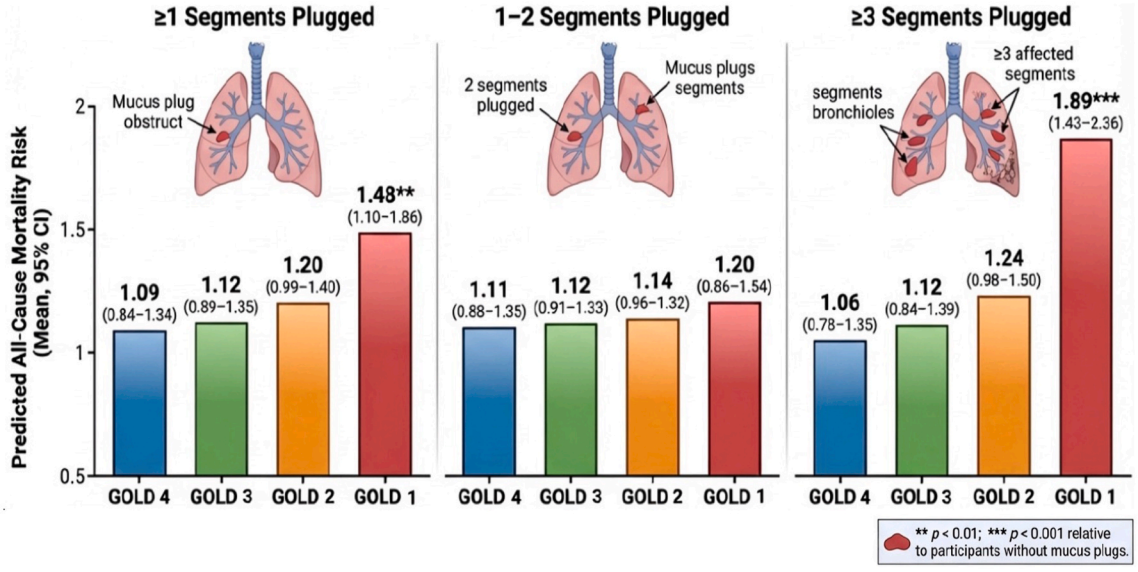

Fig. 1. – Predicted all-cause mortality risk by GOLD stage and number of segments with mucus plugs. Risk compared with participants without mucus plugs according to best-fit non-linear regression models. Data from Rogliani and Calzetta [9]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

5. Pathophysiological mechanisms of mucus plug formation

5.1. Mucus hyperconcentration and mucus plug formation

The formation of mucus plugs in COPD reflects a substantial disturbance in airway surface hydration (Fig. 2). Healthy airway epithelia maintain mucus at approximately 2% solids (98% water) through coordinated ion and fluid transport [8]. Normal airway surface hydration is maintained by ciliary mechanosensing of mucus layer concentration, regulated release of ATP by ciliated cells, and fine-tuning of ion transport rates through purinergic signaling [10].

In COPD, multiple mechanisms disrupt homeostasis, leading to mucus hyperconcentration (dehydration) [11]. Cigarette smoke causes abnormalities in cystic fibrosis transmembrane conductance regulator (CFTR)-mediated chloride secretion by reducing CFTR transcription and directly damaging the protein through oxidants [10]. Increased extracellular nucleotide and nucleoside metabolism decreases extracellular ATP and adenosine levels, suggesting defective purinoceptor regulation of airway surface hydration. These defects in epithelial ion and fluid transport are exacerbated by the hypersecretion of MUC5AC and MUC5B induced by cigarette smoke [9,10].

A key step in muco-obstructive disease pathogenesis is the osmotic compression of hyperconcentrated mucus onto the airway surface with formation of adherent mucus plugs, particularly in distal airways [11,12]. Relatively small changes in hydration status (from 2% to 8% solids) produce dramatic reductions in mucociliary transport [10]. Moderately hyperconcentrated mucus compresses cilia and slows mucus transport, whereas severe hyperconcentration flattens cilia and produces mucus stasis and adhesion [10].

5.2. Inflammatory and microbiome contributions

Once mucus plugs form, a bistable, positive-feedback "vicious cycle" is initiated [10]. These plugs create long diffusion distances for oxygen, producing hypoxic niches within adherent airway mucus and underlying epithelia [12]. Concentrated mucus plugs are proinflammatory, partly due to the release of interleukin (IL)-1α from hypoxic cells [12]. The hypoxic conditions locally created by mucus plugs promote airflow obstruction, inflammation, infection, and ultimately damage to the airway wall [11].

The composition of mucus plugs varies by inflammatory phenotype [13]. In eosinophilic airways, elevated MUC5AC and eosinophil-derived molecules, such as galectin-10 and eosinophil extracellular traps, cause highly viscoelastic plugs that are detectable as high-density regions on ultra-high-resolution CT scans [13]. In neutrophilic airways, where the phylum Proteobacteria and the genus *Haemophilus* are predominant, excessive neutrophil elastase impairs mucociliary clearance, induces neutrophil extracellular traps (NETs), and promotes mucus overproduction [13].

Mucus plugs serve as reservoirs for bacterial colonization, creating a complex interplay between the airway microbiome and inflammation [13]. The infectious component of mucoobstructive diseases may be initiated by anaerobic bacteria that proliferate in the nutrient-rich, hypoxic environment of mucus [12]. These anaerobes can alter the mucus, creating an environment conducive to the succession of classic airway pathogens, such as *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* [12]. This bacterial colonization has specifically been implicated as a potential link between COPD and cardiovascular events due to enhanced systemic inflammation [2].

6. Potential links between mucus plugging, exacerbations, and cardiovascular risk

6.1. Mucus plugs as predictors of COPD exacerbations

As previously mentioned, the COPDGene and ECLIPSE studies found that mucus plugs identified on chest CT scans are associated with an increased risk of moderate-to-severe and severe COPD exacerbations

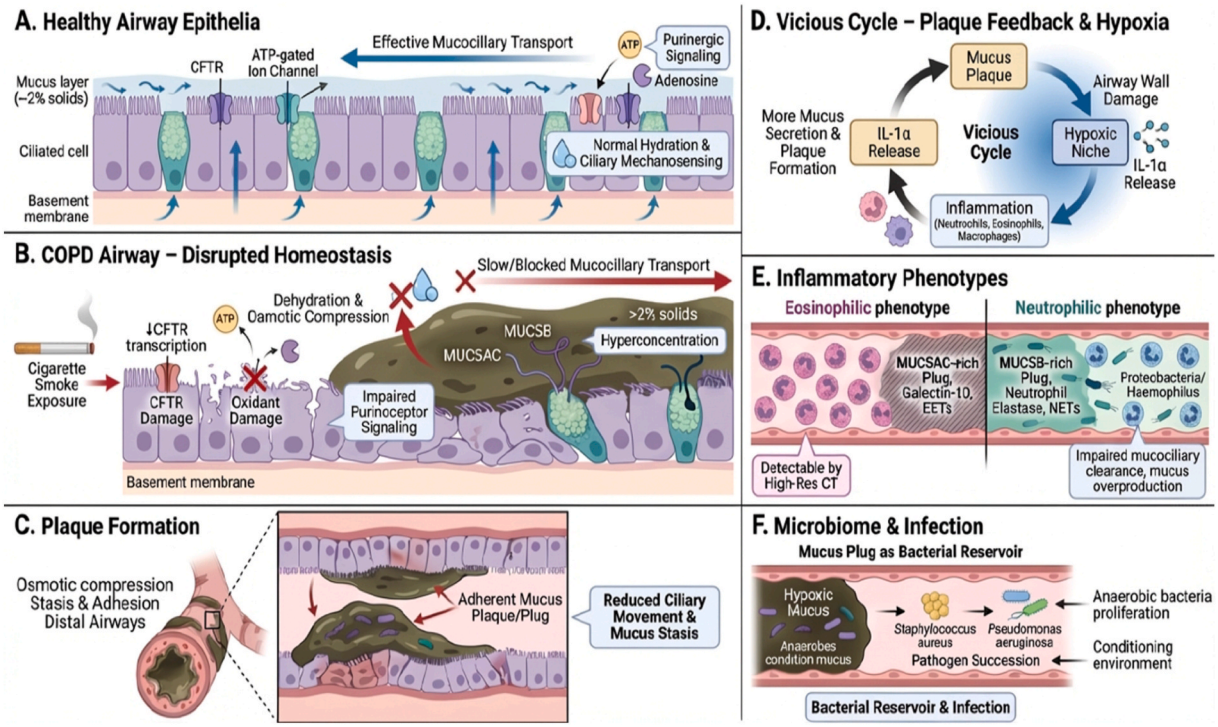

Fig. 2. Pathophysiological mechanisms of mucus plug formation. The figure illustrates these processes in COPD, highlighting disturbed airway hydration, ion transport defects induced by cigarette smoke, cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction, excessive mucin secretion, osmotic compression of mucus, impaired ciliary motion, and feedback amplification by inflammatory and microbiome factors. This includes the distinct features of eosinophilic and neutrophilic airways and their impact on mucus properties and bacterial colonization.

[2]. The risk increases as the number of plugged segments rises. This association was stronger for severe exacerbations requiring an emergency department visit or hospitalization. Patients with three or more mucus plugs had a 9% increased risk in COPDGene (aRR 1.09) and a 37% increased risk in ECLIPSE (aRR 1.37), compared to patients without mucus plugs [2]. Additionally, a Chinese cohort study's prospective data show that each one-point increase in airway mucus plug score was associated with an 8.3% higher risk of moderate-to-severe exacerbation (relative risk [RR] 1.08; 95% confidence interval [CI], 1.01-1.16) [14]. Patients with four or more plugged segments had a hazard ratio of 5.02 (95% CI, 1.84-13.75) for future exacerbations compared to those without mucus plugs.

6.2. Association between COPD exacerbations and cardiovascular events

COPD exacerbations are critical inflection points for cardiovascular risk. In the SUMMIT trial, which involved 16,485 patients with moderate COPD and cardiovascular disease or risk factors, exacerbations were associated with a significantly higher risk of subsequent cardiovascular events, such as cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic attack [15]. The hazard ratio for cardiovascular events was highest during the first 30 days after an exacerbation (HR 3.8, 95% CI 2.7–5.5) and remained elevated for up to one year. Cardiovascular risk was especially high following hospitalization for exacerbation, with a 30-day hazard ratio of 9.9 (95% CI 6.6-14.9), more than twice that of non-hospitalized exacerbations [15]. These findings suggest a dose-response relationship between exacerbation severity and cardiovascular risk, indicating that severe exacerbations are associated with the highest cardiovascular risk.

6.3. Potential mechanisms linking exacerbations to cardiovascular events

Several mechanisms may explain the association between COPD exacerbations and increased cardiovascular risk. Solid evidence indicates that mucus hyperconcentration causes local hypoxia, inflammation (via IL-1α/IL-1β pathways), bacterial colonization, and ventilation/perfusion (V/Q) mismatch [16]. A prospective study of 121 patients hospitalized for COPD exacerbations revealed impaired vascular function and increased systemic inflammation (CRP and IL-6) upon admission compared to patients with stable COPD [17]. Although vascular function improved within 14 days of discharge, it remained significantly lower than that of stable COPD patients, providing a mechanistic link that explains the enduring increase in cardiovascular risk following severe exacerbations.

Hypoxemia worsens during exacerbations due to an increased V/Q mismatch caused by mucus plugging and airway inflammation. Acute hypoxemia promotes a destructive “hypersecretory” neutrophil phenotype with an enhanced capacity for endothelial injury [18]. Neutrophil elastase release is augmented in COPD patients due to hypoxia, and plasma from COPD patients shows higher levels of hypoxia-upregulated neutrophil-derived proteins, protease activity, and vascular injury markers [18]. There is also documentation that chronic intermittent hypoxia, a condition that may be present in the frequent exacerbator phenotype, causes systemic inflammation, oxidative stress, endothelial dysfunction, and sympathetic activation, leading to cardiovascular disease [19].

6.4. Exacerbations as mediators of mucus plug-associated mortality

The association between mucus plugs and mortality was partially attenuated after adjustment for COPD exacerbations in statistical models, with the adjusted hazard ratio for patients with mucus plugs in three or more segments decreasing from 1.24 to 1.20 [2]. This finding suggests that exacerbations may account for part of the observed association between mucus plugging and mortality, potentially explaining approximately 16% of this relationship. Overall, the data support the hypothesis that exacerbations may partially mediate the association between mucus plugging and adverse outcomes, although this relationship remains incompletely understood.

The persistence of a significant association after adjustment for exacerbations suggests that additional mechanisms may also contribute to the relationship between mucus plugging and mortality. Potential contributors include chronic hypoxemia due to persistent V/Q mismatch, sustained systemic inflammation associated with bacterial colonization, and progressive decline in lung function [2,20].

7. Pathophysiological mechanisms linking mucus plugs to cardiovascular mortality

Complex pathophysiological mechanisms link mucosal plugs and cardiovascular mortality (Fig. 3).

7.1. Direct respiratory consequences

Complete airway occlusion by mucus can lead to a V/Q mismatch and respiratory failure, which is a common cause of death in COPD patients [2,6]. Mucus plugs and emphysema are independently associated with lower FEV_1 and peripheral oxygen saturation. The relationship between mucus plug score and lung function outcomes is strongest in smokers with limited emphysema [20]. These findings suggest that mucus plugging may be the dominant pathophysiological mechanism in certain COPD phenotypes, particularly in cases of mucus-dominant disease.

Mucus occlusion of multiple bronchi increases the risk of infection by reducing oxygen diffusion and causing local hypoxia, which promotes microbial growth [11]. *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* are detected in the sputum of 25%-50% of adults with COPD. Infection rates increase with disease severity [21]. Mucus plugs that occlude multiple bronchi may increase the risk of pneumonia and COPD exacerbations, creating a self-perpetuating cycle of infection, inflammation, and further mucus production [21].

7.2. Redox signaling and oxidative stress: a central mechanistic link

Redox signaling is a critical mechanism connecting mucus plug formation, airway inflammation, and cardiovascular dysfunction in COPD patients [22]. Oxidative stress is markedly increased in the lungs of COPD patients, as evidenced by elevated levels of 8-isoprostane, ethane, and hydrogen peroxide in breath condensate, sputum, and the systemic circulation [23]. This oxidative burden arises from both exogenous sources, such as cigarette smoke and air pollution, and endogenous sources, such as reactive oxygen species released from activated neutrophils, macrophages, and dysfunctional mitochondria [22].

Oxidative stress drives COPD pathogenesis through multiple pathways, including induction of chronic inflammation, cellular senescence, impaired autophagy, reduced DNA repair, increased autoimmunity, increased mucus secretion, and impaired anti-inflammatory response to corticosteroids [22]. The transcription factor Nrf2 activates antioxidant response elements and upregulates protective enzymes, such as glutathione peroxidase and heme oxygenase-1. However, Nrf2 is downregulated in COPD patients, which further compromises antioxidant defenses [24].

Importantly, oxidative stress extends beyond the lungs and drives cardiovascular dysfunction. Compared to controls, patients with COPD exhibit lower baseline antioxidant levels (e.g., vitamin C and superoxide dismutase activity) and higher markers of oxidative stress (e.g., thiobarbituric acid reactive species) [25]. This redox imbalance directly impairs vascular function. Patients with COPD display reduced brachial artery flow-mediated dilation and increased arterial stiffness (pulse wave velocity). Both conditions are acutely improved by oral antioxidant administration [24]. Oxidative damage to vascular endothelial

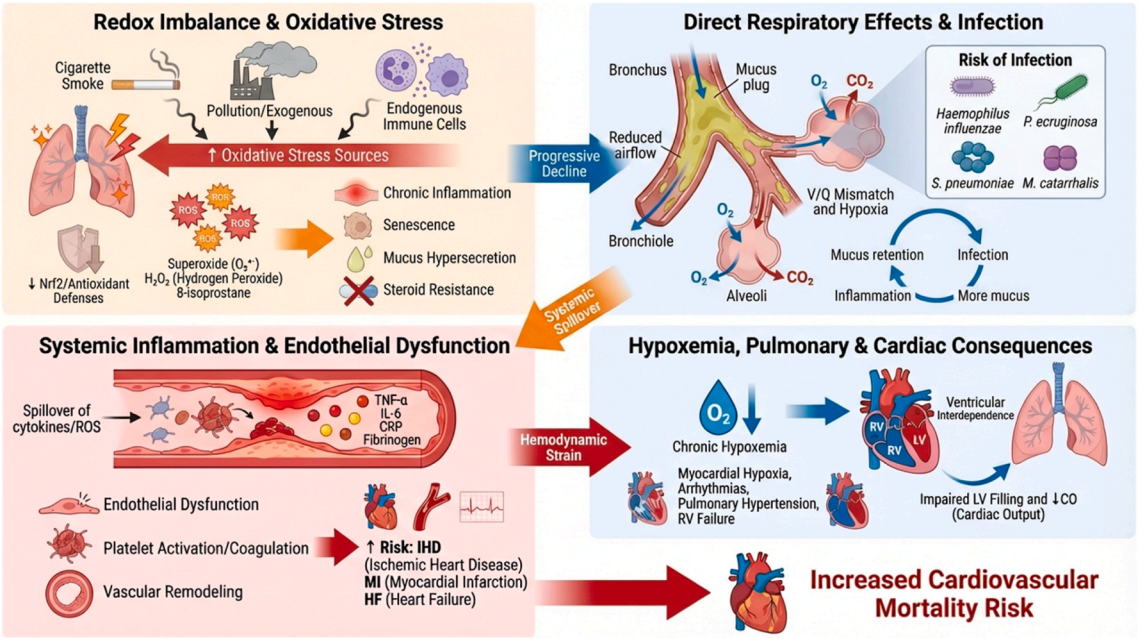

Fig. 3. Pathophysiological mechanisms linking mucus plugs to cardiovascular mortality. This figure illustrates the association between airway mucus plugging and cardiovascular risk, highlighting a graded relationship in which greater mucus plug burden is linked to less favorable cardiovascular outcomes.

cells alters the regulation of endothelial-derived vasoactive substances, particularly nitric oxide, which promotes vascular dysfunction, a key driver of cardiovascular disease [26].

The spillover of proinflammatory mediators and reactive oxygen species from the lungs into the systemic circulation triggers a chronic systemic inflammatory response that alters blood vessel structure via vascular remodeling and arterial stiffness, ultimately leading to atherosclerosis [27].

7.3. Systemic inflammation and endothelial dysfunction

Circulating inflammatory mediators from the lungs cause endothelial dysfunction, platelet activation, and coagulation disorders [28]. Key inflammatory biomarkers, such as TNF-α, IL-6, C-reactive protein, and fibrinogen, are elevated in COPD patients and are associated with a two-to fourfold increased risk of ischemic heart disease, myocardial infarction, and heart failure [29].

Mucus plugging amplifies this inflammatory cascade. Airway mucus obstruction triggers chronic airway inflammation, even in the absence of bacterial infection. This is likely due to mechanisms including hypoxic epithelial necrosis, retention of inhaled irritants or allergens, and immunomodulatory effects [30]. The presence of mucus plugs is associated with elevated blood eosinophils, suggesting Type 2 inflammation [31], though plugging may also be associated with other inflammatory phenotypes [32].

Small-airway mucus obstruction is characteristic of COPD even in patients who do not expectorate or who have an emphysematous phenotype [2]. Despite its weak correlation with sputum production, airflow obstruction is associated with changes in mucin gene expression, increases in goblet-cell number and size, mucus-filled occlusion of small airways, and expansion of submucosal glands [2]. This mucus dysfunction has deleterious consequences, including mucus stasis and airway infection, which in turn leads to inflammation and fibrosis that may contribute to a systemic inflammatory burden [2].

7.4. Hypoxia and cardiovascular stress

A V/Q mismatch resulting from mucus plugging causes arterial hypoxemia, which has direct cardiovascular consequences [33]. Chronic hypoxemia leads to myocardial hypoxia, which results in impaired contractility and an increased risk of arrhythmia. Additionally, hypoxemia induces pulmonary vasoconstriction, contributing to pulmonary hypertension and right heart failure. Through ventricular interdependence, these conditions can obstruct left ventricular filling and reduce cardiac output [34].

The disproportionate mortality risk in GOLD stage 1 patients with mucus plugging may reflect the fact that, despite having relatively preserved lung parenchyma, these patients have significant V/Q mismatch due to airway obstruction [9]. This creates a unique pathophysiological state in which hypoxemia and inflammation occur without the compensatory mechanisms that develop in more advanced disease.

8. Clinical implications and therapeutic strategies

8.1. Risk stratification

The presence and extent of mucus plugging on chest CT scans provide independent prognostic information in COPD patients, with increasing mortality observed across disease severity stages and mucus burden. Although the highest risk is observed in GOLD 4 patients [2], mucus plugging confers a disproportionate risk even in the early stages of the disease (GOLD 1) [2,9], which underscores the importance of early identification and intervention.

Traditional cardiovascular risk scores may underestimate risk in COPD patients, and incorporating mucus plug burden could improve risk stratification [35]. Furthermore, the frequent occurrence of “silent” mucus plugs in asymptomatic patients indicates that a chest CT scan is necessary for an accurate assessment because symptoms alone are insufficient [2].

8.2. Mucus as a treatable trait

Mucus hypersecretion represents a clinically relevant and potentially modifiable trait in COPD [3], although the strength of evidence supporting mucus-targeted interventions varies across therapeutic classes. Key treatment goals include reducing mucus production, modulating its biophysical properties, improving mucociliary clearance, and facilitating expectoration.

8.3. Current therapeutic approaches

In clinical practice, the management of mucus in COPD relies heavily on established therapies, even though mucus is increasingly recognized as a key therapeutic target.

First and foremost, smoking cessation is essential [8]. Beyond its general benefits, quitting smoking helps restore mucociliary function and reduce ongoing airway inflammation, both of which contribute to mucus accumulation.

Bronchodilator therapy, particularly with long-acting agents (LAMAs and LABAs), is central to COPD management. These drugs primarily improve airflow limitation and symptoms but may also indirectly reduce coughing and sputum production by improving airway patency and ventilation distribution [36]. In patients with more severe disease or frequent exacerbations, triple therapy (LABA/LAMA/ICS) is frequently used [8]. Optimizing bronchodilator therapy reduces COPD exacerbations and improves lung function, ventilation, and perfusion [37]. These physiological improvements may facilitate mucus clearance by improving airway caliber and expiratory flow, thereby potentially enhancing mucus transport and reducing V/Q mismatch [8]. Since mucus plugs are associated with an increased risk of exacerbations, which in turn are linked to acute cardiovascular events, optimizing bronchodilation may therefore confer downstream cardiovascular benefits through exacerbation prevention [38]. However, while improvements in gas exchange and reductions in exacerbation frequency may plausibly translate into fewer exacerbation-related cardiovascular events, direct evidence specifically linking mucus plug resolution to cardiovascular outcomes is currently limited and warrants further investigation.

Oral mucolytics are used as adjunct therapy in COPD patients with chronic bronchitis phenotype, particularly in those with persistent sputum production [8]. This includes patients who have difficulty expectorating sputum and those who experience frequent exacerbations [39]. The most widely used of these agents are thiol-based mucolytics such as N-acetylcysteine (NAC), erdosteine, and carbocysteine [8].

These compounds exert their primary mucolytic effect through their free thiol (sulfhydryl) groups, which can disrupt disulfide bonds within mucin polymers, thereby reducing mucus viscoelasticity and facilitating mucus clearance [40]. This represents the most consistently demonstrated mechanism across thiol-based mucolytics.

Beyond this classical mucolytic action, additional mucoregulatory effects have been described, although these are not uniformly demonstrated across all agents within the class. In particular, NAC has been shown in preclinical studies to modulate mucin biology, including downregulation of MUC5AC and MUC5B expression and reduction of goblet cell hyperplasia, supporting a potential mucoregulatory role beyond mucus thinning [41]. However, these findings derive primarily from experimental models, and their clinical relevance remains to be fully established.

Carbocysteine appears to exert mucoregulatory effects predominantly through modulation of mucus glycoprotein composition and improvement of mucus rheological properties, rather than through direct and consistent regulation of mucin gene expression or intracellular glutathione replenishment [40].

Erdosteine, a thiol-based prodrug, has been reported in experimental studies to exert antioxidant and anti-inflammatory effects through its active metabolite (Met I), with additional preclinical signals suggesting modulation of mucus-related inflammatory pathways, including NF-κB-associated signaling and regulators of protein stability such as USP7, a deubiquitinating enzyme that removes ubiquitin molecules from target proteins [42]. However, these mechanistic findings are mainly derived from experimental models, and whether they represent specific or clinically relevant advantages over other thiol mucolytics remains uncertain.

More generally, thiol compounds exhibit antioxidant and anti-inflammatory properties that may contribute to their effects on airway mucus biology, including modulation of oxidative stress and redox balance. In the case of NAC, this is primarily mediated through its role as a precursor of intracellular glutathione [40]. However, the extent to which these mechanistic effects translate into meaningful improvements in mucus plug resolution, exacerbation risk, or long-term clinical outcomes remains unclear.

Clinical studies and meta-analyses suggest that mucolytics improve symptom burden, reduce coughing at follow-up, and facilitate expectoration [43]. However, these effects are heterogeneous across studies, and the magnitude of benefit appears dependent on baseline exacerbation risk and background therapy, particularly ICS use.

Importantly, while these improvements in mucus clearance suggest potential benefits for resolving mucus plugs, this has not been directly evaluated using imaging-based endpoints such as CT-defined mucus plugs.

Among thiol-based mucolytic agents, comparative evidence suggesting differences in efficacy exists, but remains limited and largely indirect. A network meta-analysis has suggested potential differences in efficacy among NAC, erdosteine, and carbocysteine [44], with exploratory signals suggesting possible advantage for erdosteine. However, the authors themselves emphasize that these findings are based on indirect comparisons and heterogeneous study populations, and that direct head-to-head trials in comparable COPD populations are required to confirm any relative differences.

The RESTORE trial showed that administering 300 mg of erdosteine twice daily for 12 months reduced exacerbation rates and shortened exacerbation duration in patients with COPD [45]. The 2026 GOLD report highlights evidence suggesting that erdosteine may reduce exacerbations irrespective of concurrent ICS therapy [8]. In contrast, evidence for NAC and carbocysteine suggests a reduction in exacerbation risk predominantly in patients not receiving ICS therapy [46], a subgroup that likely represents a smaller proportion of the current COPD population, given the widespread use of ICS-containing regimens, often as part of triple therapy [47]. Notably, approximately 50% of participants in the PANTHEON trial evaluating NAC for exacerbation prevention were receiving concomitant ICS therapy [48], which may have influenced the observed treatment effect. Furthermore, the trial was conducted exclusively in a Chinese population and used a dosing regimen exceeding currently approved doses, which may limit the generalizability of its findings. In the RESTORE trial, a substantial proportion of participants (approximately 73%) received background ICS therapy [45], and the reduction in exacerbation risk was reported to be maintained irrespective of ICS use in exploratory analyses. While these findings are hypothesis-generating and subject to the limitations of subgroup analyses, they raise the possibility of an ICS-independent effect of erdosteine.

Beyond these class effects, erdosteine has been reported to influence bacterial adhesion and to enhance antibiotic activity in experimental settings, potentially through improved mucus rheology and penetration into bronchial secretions [49,50] (Fig. 4). In addition, experimental and clinical studies suggest that it may support mucociliary transport and help preserve the cough reflex, thereby facilitating sputum clearance [49]. However, similar mucoregulatory effects on mucus properties, mucociliary clearance, and airway secretion dynamics have also been described for other mucolytics, including NAC, although the magnitude and clinical relevance of these findings remain variable and not fully established. Overall, these effects may contribute to improved airway clearance during exacerbations, but their translation into robust clinical endpoints remains uncertain.

Concerning antibiotic co-administration, NAC has been reported to carry warnings about potential chemical incompatibilities with certain antibiotics, particularly tetracyclines, erythromycin, and ampicillin, when administered simultaneously or in close temporal proximity [51]. Additionally, in vitro studies suggest that high NAC concentrations may antagonize aminoglycoside activity, although the clinical relevance of these findings remains uncertain [52]. In contrast, erdosteine does not

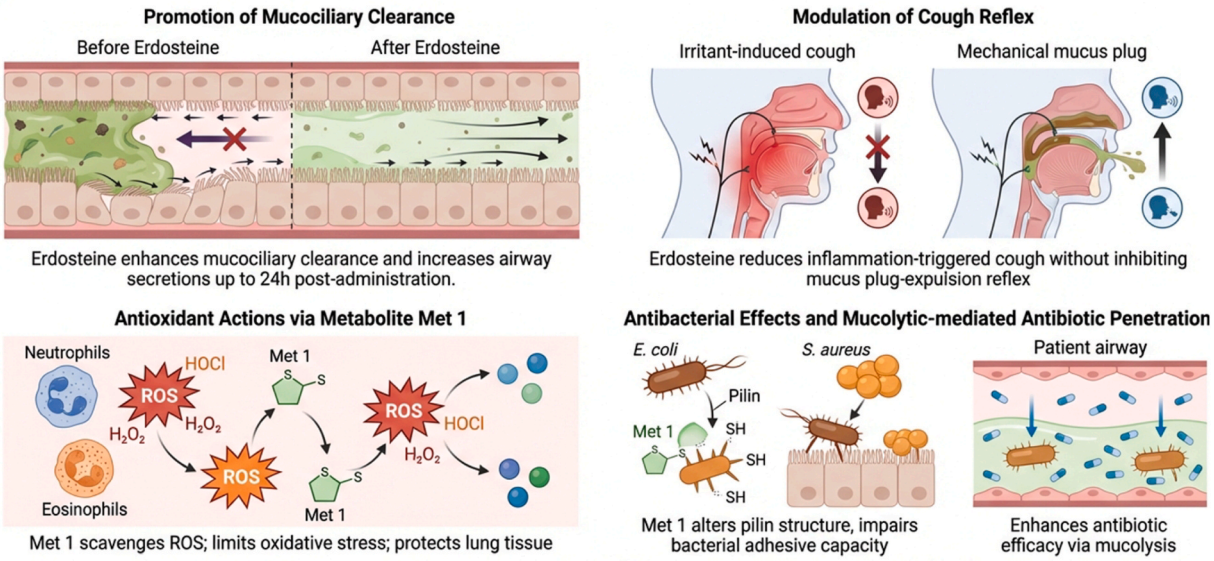

Fig. 4. – Mechanistic actions of erdosteine on mucus plugs and airway health. Erdosteine promotes mucociliary transport, preserves sputum-expelling cough reflex, exerts antioxidant protection via Met 1, reduces bacterial adhesion, and supports antibiotic activity, all contributing to effective mucus plug management and improved airway function.

appear to be associated with these chemical incompatibility issues, which may allow more straightforward co-administration with antibiotics without specific timing restrictions. This pharmacological characteristic may be of practical relevance in the context of acute exacerbations of COPD requiring antibiotic therapy [49].

Beyond drug–drug interaction considerations, clinical investigations have also reported that, compared with NAC, erdosteine may improve mucus properties and facilitate expectoration in patients with chronic bronchitis [53], supporting its role as a mucolytic agent in this clinical setting. However, whether these observed differences translate into meaningful advantages in clinically relevant outcomes remains to be fully established.

Preclinical studies have also described antiviral activity of erdosteine against respiratory viruses including SARS-CoV-2, respiratory syncytial virus (RSV), and influenza A virus (H1N1) [54]. Importantly, similar antioxidant and immunomodulatory effects, and in some cases antiviral signals, have also been reported for NAC and carbocysteine in experimental systems, although again with limited and heterogeneous clinical translation.

Since COPD exacerbations are frequently triggered by viral and bacterial respiratory infections [55], these mechanistic properties may contribute to the overall rationale for mucolytic therapy in exacerbation prevention. However, the extent to which differences in preclinical antimicrobial or antiviral activity between individual mucolytics translate into differential clinical efficacy remains uncertain.

Several other therapeutic strategies may influence mucus biology either indirectly or directly, although the level of evidence varies considerably across interventions.

Airway clearance techniques and pulmonary rehabilitation are recommended in patients with chronic sputum production. Airway clearance techniques (e.g., oscillatory PEP, active cycle of breathing) show modest improvements in sputum clearance and quality of life, although most evidence is extrapolated from bronchiectasis [56,57]. Pulmonary rehabilitation consistently improves exercise capacity and symptoms and reduces exacerbation risk [56].

Hypertonic saline inhalation is well established in bronchiectasis, where it improves mucus clearance and quality of life [58,59]. In COPD, however, evidence remains limited and inconsistent, with small studies failing to demonstrate consistent long-term clinical benefit [60].

Cystic fibrosis transmembrane conductance regulator (CFTR) modulation and epithelial ion transport targeting have been proposed as potential strategies to restore airway surface hydration [61]. CFTR dysfunction has been demonstrated in acquired forms in COPD airways [62]. However, CFTR potentiators have not yet shown established clinical efficacy in COPD, and their use remains investigational [63].

Although biologic therapies have demonstrated promising effects on mucus-related phenotypes in severe asthma [64], evidence supporting a similar role in COPD remains limited. Biologic agents targeting type 2 inflammation, including anti–IL-4/IL-13 and anti–IL-5 pathways, have shown clinical benefit in selected COPD populations with eosinophilic inflammatory signatures [65]. However, their effects on mucus hypersecretion, mucus plug formation, and mucus clearance have not been directly established. Any potential influence on mucus biology is likely indirect and mediated through attenuation of eosinophilic airway inflammation and modulation of airway remodeling processes.

Emerging protease-targeted therapies, including dipeptidyl peptidase 1 (DPP-1) inhibition, aim to reduce activation of neutrophil serine proteases such as neutrophil elastase, which are implicated in mucus hypersecretion and airway damage [66]. Early-phase and clinical trial programs (e.g., brensocatib) have shown promise in bronchiectasis [67], but data in COPD remain limited [68].

8.4. *Cardiovascular risk management*

Despite the high prevalence of cardiovascular disease in patients with COPD, cardiovascular risk factors remain poorly controlled in this population, necessitating heightened clinical attention [69]. All COPD patients should undergo a systematic evaluation for cardiovascular comorbidities, regardless of mucus plug presence. Once identified, these comorbidities must be treated according to established guidelines [8]. Clinicians and patients must remain vigilant for cardiovascular events following COPD exacerbations. The risk of cardiovascular events increases markedly within 30 days after an exacerbation and remains elevated for up to one year, especially after hospitalization [69].

This is particularly relevant when considering the role of mucus plugs. As previously mentioned, airway mucus plugs are independently associated with a higher frequency of moderate-to-severe exacerbations and may indicate an increased cardiovascular risk in a specific patient subgroup [70]. Given the established link between exacerbation frequency and cardiovascular events, patients with significant mucus

plugging may be at high risk and require closer cardiovascular monitoring [69].

9. Research priorities

Several key questions remain unanswered (Table). First, randomized trials are needed to evaluate whether interventions targeting mucus clearance can reduce CT-identified mucus plugs or alter their longitudinal trajectory and reduce cardiovascular events, particularly in early COPD.

Second, the optimal approach to cardiovascular risk assessment in COPD patients with mucus plugging needs definition. Integration of mucus plug burden, exacerbation history, and traditional cardiovascular risk factors may improve prediction models [69]. Third, biomarker-guided stratification strategies incorporating markers of systemic inflammation, endothelial dysfunction, and mucus burden may enable personalized treatment approaches [71].

Developing automated, AI-based quantification methods for mucus plugs could facilitate the incorporation of this parameter into clinical practice and research [7]. Enhanced phenotyping of COPD patients with V/Q abnormalities and mucus plugging could identify subgroups most likely to benefit from specific interventions [20]. Since silent mucus plugs are frequent and linked to poorer disease outcomes [6], routine CT assessment of mucus burden may be necessary, even in asymptomatic patients.

The mechanisms underlying the disproportionate mortality risk associated with mucus plugging in early-stage COPD require further investigation. Understanding why mucus plugs are particularly detrimental in GOLD Stage 1 disease could reveal new therapeutic targets and optimize the timing of interventions [9]. Additionally, the complex interplay between mucus plugging, airway microbiome alterations, exacerbation phenotypes, and cardiovascular outcomes warrants further investigation [13].

10. Conclusion

Airway mucus plugging is increasingly recognized as an important marker of adverse outcomes in COPD, including increased exacerbation frequency and mortality, and may have implications for cardiovascular risk. The relationship between mucus plugs and cardiovascular mortality involves multiple interconnected mechanisms operating through both exacerbation-dependent and -independent pathways [16–19,22,25–27]. Mucus plugs substantially increase the risk of COPD exacerbations [2], which are associated with higher mortality [2], and confer an increased risk of acute cardiovascular events via systemic inflammation, vascular dysfunction, and arterial stiffness.

In addition to acute events, mucus plugging may contribute to cardiovascular risk through several chronic mechanisms, including mucus hyperconcentration, mucus plug formation, persistent ventilation/perfusion mismatch, chronic hypoxemia, sustained systemic inflammation, endothelial dysfunction, and bacterial colonization. Longitudinal evidence suggests that mucus plugging is a dynamic and potentially reversible process [5]. Spontaneous resolution of mucus plugs has been associated with lung function decline rates comparable to those of patients who never exhibited mucus plugging. This suggests a more favorable disease trajectory. Conversely, patients with persistent or newly formed mucus plugs experience substantially greater lung function decline compared to those without.

These observations provide a strong rationale for therapeutic intervention. Mucolytic therapies have been associated with a reduced risk of exacerbations, supporting the concept that addressing mucus abnormalities could affect clinically relevant outcomes [43]. This is particularly important since increased mortality risk has been observed in patients with mild COPD (GOLD Stage 1) and significant mucus plugging [9], highlighting the potential benefit of early intervention aimed at clearing mucus to prevent both exacerbations and cardiovascular events. Among the available oral mucolytics, erdosteine is currently supported by the most substantial evidence in COPD patients [44].

Table
Research priorities aimed at improving both our understanding of the relationship between mucus plugs and increased cardiovascular mortality and the potential for therapeutic intervention in patients with COPD.

Research Focus	Key Objective
Mucus clearance trials	Test if targeting mucus reduces CT-identified mucus plugs or alters their longitudinal trajectory and reduces cardiovascular events in early COPD
Cardiovascular risk assessment	Integrate mucus burden with traditional risk factors for better prediction
Biomarker-guided treatment	Use inflammation, endothelial, and mucus markers for personalized therapy
AI quantification of mucus	Automate mucus plug measurement for clinical and research use
COPD phenotyping	Identify subgroups with V/Q defects and mucus plugging who benefit most
Mechanisms in early COPD	Explore why mucus plugs increase mortality and link to microbiome and exacerbations

Importantly, the potential reversibility of mucus plugging suggests that mucoactive therapies could favorably modify disease progression by promoting the resolution of mucus plugs. The recent documentation that mucus plugs are located in segmental and subsegmental airways in COPD provides a strong rationale for targeting mucus plugs with mucoactive treatment as a strategy, with the potential to favorably influence cardiovascular risk, although direct evidence for cardiovascular benefit is currently lacking [4]. However, no studies have yet directly evaluated whether such treatments can reduce CT-detected mucus plugs or alter their evolution over time. This represents a significant knowledge gap and an important target for future research.

Future studies should therefore focus on determining whether mucus-targeted interventions can reduce CT-defined mucus plugging, exacerbation frequency, and potentially cardiovascular events, clarifying how to best integrate assessment of mucus burden into comprehensive COPD management and cardiovascular risk prediction, and understanding why mucus plugging appears particularly detrimental in early-stage disease. Meanwhile, heightened clinical vigilance for cardiovascular events following COPD exacerbations remains essential, especially within the first 30 days.

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CRediT authorship contribution statement

Mario Cazzola: Conceptualization, Supervision, Validation, Writing – original draft. **Luigino Calzetta:** Validation, Writing – review & editing. **Vincenzo Parente:** Data curation. **Paola Rogliani:** Validation, Writing – review & editing. **Maria Gabriella Matera:** Conceptualization, Validation, Writing – review & editing.

Declaration of competing interest

Mario Cazzola, Luigino Calzetta, and Paola Rogliani were consultants for Edmond Pharma, which manufactures erdosteine. Mario Cazzola is a consultant for PIAM Farmaceutici, which markets erdosteine. Cazzola is the deputy editor, Calzetta is an associate editor, and Rogliani is an editorial board member of Respiratory Medicine. Neither Cazzola, Calzetta, nor Rogliani are involved in selecting peer reviewers for the manuscript or making any subsequent editorial decisions.

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