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The Effects of Long-Term Bronchodilators and Inhaled Corticosteroids in COPD Patients on the Risk of Cardiovascular Events: Literature Review

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Abstract

Chronic obstructive pulmonary disease (COPD) is a leading global cause of morbidity and mortality, manifesting as a systemic disorder marked by persistent inflammation, oxidative stress, and metabolic dysfunction that closely link it to cardiovascular diseases (CVD) such as ischemic heart disease, heart failure, arrhythmia, and stroke. Shared risk factors, overlapping pathophysiological mechanisms including endothelial dysfunction and autonomic imbalance, and the impact of COPD exacerbations synergistically elevate the risk of major adverse cardiovascular events (MACE), especially within critical post-exacerbation windows. Long-acting bronchodilators (LABA, LAMA) and inhaled corticosteroids (ICS) form the cornerstone of COPD management, with extensive evidence from randomized trials, meta-analyses, and real-world cohorts demonstrating their cardiovascular safety and, in some contexts, protective effects via inflammation suppression. Triple therapy (ICS/LAMA/LABA) is recommended as first-line for high-risk COPD phenotypes characterized by frequent exacerbations and cardiovascular comorbidity, showing superiority in reducing severe cardiopulmonary events and all-cause mortality. Despite concerns of transient cardiovascular risks during treatment initiation, robust cumulative data affirm the long-term safety profile of these inhaled therapies, underpinning individualized, phenotype-driven treatment strategies to mitigate COPD's cardiovascular burden and improve clinical outcomes.

Keyword: COPD; Cardiovascular events; Long-acting bronchodilators; LABA; LAMA; ICS; Triple therapy; Exacerbation

1. Introduction

COPD is a leading cause of morbidity and mortality worldwide, characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities (1). Chronic obstructive pulmonary disease (COPD) is not only a respiratory condition but a systemic disorder characterized by chronic inflammation, oxidative stress, and metabolic dysfunction (2). These biological disruptions link COPD closely with cardiovascular diseases such as ischemic heart disease, heart failure, arrhythmia, and stroke. There are several important links between COPD and CVD, including shared risk factors such as smoking, common pathobiological pathways, and the impact of abnormal lung physiology and COPD medications on CVD. Patients with COPD have up to a two-fold higher risk of major adverse cardiovascular events (MACE), and cardiovascular complications represent a leading cause of hospitalization and mortality in this population(3). Because the presence of one condition increases the risk of the other, clinicians should be vigilant when evaluating these patients (4). However, real-world data show that current clinical practice is suboptimal.

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Long-acting bronchodilators including LABA, LAMA, and their fixed-dose combinations have become the primary therapeutic modality for symptom control and exacerbation prevention (5). Inhaled corticosteroids (ICS), alone or as part of dual or triple therapy, are incorporated mainly for patients with frequent exacerbations or eosinophilic inflammation (6). Despite decades of use, questions remain about the cardiovascular safety of these medications, especially during long-term therapy.

Concerns have centered on β2-agonist–driven sympathetic stimulation, antimuscarinic effects on cardiac conduction, and the possibility of increased heart rate variability or arrhythmogenesis (7). In contrast, the ability of ICS to reduce airway and systemic inflammation suggests a potential cardioprotective effect (8). As treatment strategies for COPD evolve toward more intensive regimens especially with the growing use of triple therapy, rigorous assessment of cardiovascular safety has become an essential component of therapeutic decision-making. This review synthesizes contemporary evidence on the cardiovascular effects of long-term bronchodilators and ICS, combining biological rationale with RCTs, meta-analyses, and real-world cohort data.

2. Pathophysiological Links Between COPD and Cardiovascular Events

2.1. Systemic inflammation and endothelial dysfunction

Systemic inflammation plays a central role in linking COPD and cardiovascular events. COPD is characterized by persistently elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and acute phase reactants like C-reactive protein (CRP). These circulating inflammatory mediators contribute to endothelial dysfunction, which is a hallmark of cardiovascular disease pathogenesis (3). Li et al.(2022) also noted in his study that inflammatory mediators circulate from the lungs to the whole body, causing intravascular dysfunction, promoting the formation and rupture of atherosclerotic plaques, and ultimately leading to the occurrence and development of CVD (9).

β2-adrenergic receptors, widely expressed in cardiac tissue, mediate sympathetic nervous system signaling. Persistent β2-adrenergic receptor activation in COPD can lead to receptor desensitization, altered intracellular calcium handling, and myocardial remodeling, which contribute to impaired cardiac contractility and electrophysiological perturbations (10,11). Furthermore, hypoxemia and oxidative stress associated with COPD exacerbate autonomic nervous system imbalance by activating chemoreceptors and increasing sympathetic output, thereby worsening endothelial dysfunction and promoting vasoconstriction (12).

Vascular endothelial dysfunction refers to the imbalance between vasodilator and vasoconstrictor factors produced by endothelial cells, which is the main factor of atherosclerosis and occurs in the early stages of atherosclerosis (13). Endothelial dysfunction induced by systemic inflammation in COPD leads to impaired nitric oxide bioavailability, increased oxidative stress, and upregulation of adhesion molecules (14). These changes promote the formation and destabilization of atherosclerotic plaques, increasing the risk of thrombogenesis. This prothrombotic environment predisposes COPD patients to myocardial ischemia, atrial fibrillation, and stroke (3).

Acute COPD exacerbations further aggravate systemic inflammation, causing surges in inflammatory mediators temporally correlated with increases in cardiovascular complications (10,14). Recent meta-analyses and cohort studies support that endothelial vasodilatory dysfunction worsens and oxidative stress intensifies during exacerbations, accelerating vascular injury and acutely elevating cardiovascular risk (15). This highlights a continuous pathophysiological axis linking pulmonary and vascular inflammation in COPD patients.

Multiple studies have also elucidated that oxidative stress, endothelial dysfunction, and adhesion molecule activation synergistically destabilize plaques and promote atherosclerosis progression in COPD (3,9,14). Emerging evidence underscores the necessity of therapeutic strategies addressing not only pulmonary symptoms but also systemic inflammation and endothelial repair to reduce cardiovascular morbidity in this population

2.2. Autonomic imbalance and β2-adrenergic activation

Autonomic imbalance and β2-adrenergic activation represent critical pathophysiological mechanisms linking COPD to cardiovascular events beyond pharmacological effects. In COPD, chronic systemic inflammation and hypoxia contribute to alterations in autonomic nervous system regulation, resulting in an increased sympathetic tone and reduced parasympathetic (vagal) activity. This dysregulation favors heightened heart rate, increased myocardial oxygen consumption, and electrical instability, which predispose patients to arrhythmias such as atrial fibrillation and ventricular tachycardia (3,9).

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β2-agonists can acutely increase cardiac output and heart rate by stimulating sympathetic pathways. LAMA agents, on the other hand, inhibit parasympathetic tone, theoretically reducing vagal protection and increasing arrhythmogenic potential in susceptible individuals (16). Although these pathways offer a coherent biological rationale, the extent into clinically meaningful cardiovascular effects in real-world COPD populations remains a matter of ongoing investigation.

2.3. Exacerbation-related hypoxemia and cardiovascular instability

Exacerbation-related hypoxemia significantly contributes to cardiovascular instability in patients with chronic obstructive pulmonary disease (COPD), serving as a key pathophysiological link between pulmonary and cardiac complications. During acute exacerbations, impaired gas exchange leads to systemic hypoxemia, which triggers sympathetic nervous system activation, pulmonary vasoconstriction, and increased cardiac workload (3,9). Hypoxemia-induced sympathetic overdrive elevates heart rate and blood pressure, destabilizing hemodynamics and increasing myocardial oxygen demand, thereby precipitating ischemic episodes and arrhythmias in vulnerable COPD patients (14,15). Acute hypoxemia and hypercapnia increase sympathetic outflow and reduce vagal tone, creating electrophysiological conditions favorable to atrial and ventricular arrhythmias (17).

3. Effects of Long-Acting Bronchodilators on Cardiovascular Events

3.1. Evidence from large studies

Several large cohort studies have examined the cardiovascular safety of long-acting bronchodilators (LABA, LAMA) in COPD patients, revealing an increased short-term cardiovascular risk immediately after treatment initiation. A landmark nested case-control study involving over 280,000 COPD patients demonstrated a 1.5-fold increase in cardiovascular events—particularly arrhythmias and ischemic events—within the first 30 days of initiating LABA or LAMA therapy (18). However, this excess risk waned with chronic use, suggesting a vulnerable early initiation window rather than long-term toxicity. Importantly, while the risk is elevated shortly after initiation, it diminishes with continued use, suggesting an early therapy-related cardiovascular vulnerability (18). Similarly, Gershon et al. (2013) documented elevated cardiovascular events among older adults during initial bronchodilator therapy, while Wong et al. (2025) reported LAMA associated with higher atrial fibrillation incidence versus LABA (19,20). 2025 Hong Kong population-based cohort found that LAMA use was associated with a modestly higher risk of atrial fibrillation compared with LABA (adjusted HR ~1.14), while other outcomes including acute coronary syndrome and heart failure were not significantly different (20). These findings suggest transient hemodynamic stress contributes to short-term susceptibility in high-risk populations.

In the other hand, numerous longitudinal cohort studies report no excess cardiovascular risk during chronic bronchodilator use beyond this initial period, suggesting overall cardiovascular safety with maintenance therapy. The UPLIFT trial, which investigated tiotropium (LAMA) over five years, demonstrated no significant increase in cardiovascular events compared to placebo (21). Cohort studies from Taiwan also show that long-term LAMA or LABA monotherapy does not increase major adverse cardiovascular event rates and may be associated with reduced cardiovascular hospitalizations in some populations. Wang et al. (2019) confirmed no significant difference in cardiovascular risk between LABA and LAMA during long-term follow-up (18). Kim et al. (2024) Korean nationwide cohort confirmed long-term cardiovascular safety of LABA/LAMA monotherapy without increased MACE incidence compared to non-users (22). This cumulative evidence supports the safe use of inhaled bronchodilators as a foundation therapy in COPD without increasing cardiovascular morbidity.

3.2. Comparative safety of LABA/LAMA vs LABA/ICS combinations

Large population based analyses increasingly show that LABA/LAMA fixed-dose combinations offer a more favorable cardiovascular safety profile than LABA/ICS therapy in patients with COPD. In a nationwide cohort from Taiwan including 99,506 individuals (n=75,926), Chen et al. (2023) found that LABA/LAMA therapy was associated with a lower incidence of composite major adverse cardiovascular events (MACE) compared to LABA/ICS (25.22 vs 30.90 per 1000 person-years). The strongest effect was observed for dysrhythmia, where LABA/LAMA significantly decreased risk (23). Similar findings emerged in a large U.S. claims-based cohort by Samp et al. (2017), which reported a 21% reduction in

cardiovascular events among LABA/LAMA users compared to LABA/ICS (24). Suissa et al. (2019) demonstrated LABA/LAMA reduced severe pneumonia risk versus LABA/ICS in a UK CPRD cohort despite equivalent exacerbation prevention, linking lower hypoxia-mediated CV triggers (25).

Mechanistically, the cardiovascular advantage of LABA/LAMA therapy is plausible. Dual bronchodilation leverages the complementary actions of β2-agonism (which increases cAMP and relaxes airway smooth muscle) and M3-receptor antagonism (which reduces vagal bronchomotor tone), resulting in greater improvements in lung hyperinflation, dynamic airway collapse, and ventilatory efficiency (26,27). These changes reduce intrathoracic pressure swings and ventricular loading conditions, mitigating the hemodynamic stress that frequently contributes to post-exacerbation cardiovascular events—particularly within the high-risk 30-day window where MACE risk may increase more than threefold (28). In the other hand, LABA/ICS increases severe pneumonia risk, precipitating hypoxia-driven arrhythmias and heart failure, compounded by ICS-induced fluid retention and hypokalemia (25). LAMA's parasympathetic modulation provides additional cardioprotection against COPD-related atrial fibrillation (23), establishing LABA/LAMA as the preferred foundation therapy for COPD with cardiovascular comorbidity (24).

3.3. Meta-analysis of LAMA and LABA safety

Meta-analyses of randomized controlled trials provide high-level evidence confirming the cardiovascular safety of LABA/LAMA fixed-dose combinations in COPD. Calzetta et al. (2018) systematic review and meta-analysis of 43 RCTs (n=52,351 patients) found LABA/LAMA FDCs associated with neutral cardiovascular serious adverse events and no increased mortality risk compared to monotherapy (29). Chenx et al. (2019) Bayesian network meta-analysis demonstrated inhaled long-acting bronchodilators (LABA/LAMA) do not elevate cardiovascular adverse events overall, while Mammen et al. (2020) ATS guideline meta-analysis of 24 RCTs confirmed no differences in pneumonia or mortality versus monotherapy (30,31). Although Yang et al. (2023) reported higher MACE risk with LAMA/LABA versus LABA/ICS (RR 1.42, 95% CI 1.11-1.81) across 51 RCTs (n=91,021), though this finding requires cautious interpretation given trial heterogeneity and real-world cohort contradictions (32). These meta-analytic findings establish LABA/LAMA combinations as cardiovascular-safe foundation therapy for COPD, particularly when avoiding ICS-related pneumonia risks, aligning with cohort evidence favoring dual bronchodilation in cardiovascular comorbidity.

4. Effects of Inhaled Corticosteroids on Cardiovascular Events

4.1. ICS and cardiovascular outcomes in RCT-based meta-analysis

Chen et al. (2018) comprehensive meta-analysis of 31 RCTs involving 38,669 patients found ICS associated with no increased risk of composite cardiovascular events, heart failure, arrhythmias (RR 0.97), or myocardial infarction, confirming direct cardiovascular safety across diverse COPD populations https://pmc.ncbi.nlm.nih.gov/articles/PMC6079461/. Gadhvi et al. (2023) systematic review incorporating 15 RCTs reported non-significant protective effects on CVD events, particularly heart failure (OR 0.85) and stroke (OR 0.91) with follow-up exceeding 3 years, attributable to ICS suppression of COPD-driven systemic inflammation including IL-6 and CRP pathways that accelerate atherosclerosis (33). In contrast, ICS elevate pneumonia risk by 50-70% (RR 1.5-1.7) through impaired local pulmonary immunity, precipitating hypoxia-mediated arrhythmias, acute heart failure decompensation, and post-pneumonia MACE cascades (HR 3.2 within 30 days) (28,34). Inhaled corticosteroid use in COPD is known to increase the risk of pneumonia, yet this elevated pulmonary infection risk does not translate into excess cardiovascular harm. The systemic anti-inflammatory effects of ICS appear to counteract the hypoxia-driven cardiovascular instability typically triggered by pneumonia, resulting in an overall reduction in cardiovascular events despite higher pneumonia incidence (35).

4.2. ICS and cardioprotection via reduced systemic inflammation

COPD sustain systemic inflammation through chronic neutrophil activation, elevated IL-6, CRP, and fibrinogen, alongside endothelial dysfunction conditions that accelerate every stage of atherosclerosis, from plaque initiation to destabilization and rupture. Sin and Man (2004) showed that withdrawing inhaled corticosteroids (ICS) resulted in a rapid 70% rise in circulating CRP within four weeks, driven by unchecked cytokine release from alveolar macrophages. Reintroduction of fluticasone reversed this rise, effectively dampening the IL-6-CRP acute-phase signaling cascade that expands lipid cores and promotes plaque vulnerability (36). In support of this mechanism, Shin et al. (2020) found that higher cumulative ICS exposure was associated with reduced coronary heart disease incidence despite increased pneumonia risk, proposing that ICS protect against atherosclerosis by inhibiting IL-6 trans-signaling in vascular smooth muscle and suppressing CRP-mediated complement activation at plaque shoulders (35)

Mechanistic work further confirms that ICS directly modulate multiple inflammatory checkpoints that are upregulated in COPD-related atherosclerosis. The meta-analysis by Gadhvi et al. (2023), which reported a cardiovascular hazard reduction (HR 0.87), reflects the long-term attenuation of fibrinogen-driven platelet aggregation and suppression of IL-6–induced smooth muscle proliferation—processes central to plaque stabilization (33). Falk et al., (2008) further highlighted that ICS exhibit statin-like pleiotropic behavior by inhibiting NF-κB nuclear translocation in vascular endothelium, thereby preventing adhesion molecule upregulation and mitigating COPD's pro-thrombotic milieu (37). Together, these pathways explain how ICS maintain cardiovascular neutrality or even confer protection, despite their known pneumonia risk, by directly suppressing the systemic inflammatory architecture that drives atherothrombosis in COPD.

4.3. Real-world evidence supporting ICS benefit

Real-world observational evidence consistently shows that inhaled corticosteroids (ICS) provide meaningful cardiovascular benefits for patients with COPD, offering sustained cardioprotection even in the presence of an elevated pneumonia risk. In a nationwide Korean NHIS cohort, Shin et al. (2020) reported that patients with higher long-term ICS exposure experienced markedly fewer coronary heart disease events, and this association remained stable after accounting for comorbidities and episodes of pneumonia. The pattern followed a clear biological gradient, suggesting that the systemic anti-inflammatory effects of ICS extend beyond the airways and contribute to clinically relevant cardiovascular protection in everyday practice (35).

Further support comes from a subsequent, larger Korean NHIS study by the same group, which demonstrated that ICS use was linked to lower all-cause mortality when evaluated with rigorous time-dependent modelling to eliminate immortal-time bias. The protective effect appeared strongest among women, individuals who had never smoked, and those with pre-existing coronary disease (38). These real-world findings are consistent with the randomized evidence summarized by Chen et al. (2018), who concluded that ICS therapy is overall cardiovascularly neutral across standard composite cardiovascular outcomes (39). Together, these data reinforce the rationale for selective ICS use in COPD phenotypes at heightened cardiovascular risk, where the systemic anti-inflammatory benefits of therapy may outweigh the potential harms associated with pneumonia.

4.4. Triple Therapy (LABA/LAMA/ICS) and Cardiovascular Risk

Major phase 3 trials consistently show that triple therapy combining an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA), and a long-acting beta-agonist (LABA) offers a cardiovascular safety profile that is at least comparable—and in several analysis superior—to that of dual bronchodilation in patients with moderate-to-severe COPD. In the ETHOS programme, a post-hoc cardiovascular analysis by Martinez et al. (2025) evaluated budesonide/glycopyrrolate/formoterol against glycopyrrolate/formoterol in a large cohort of patients and reported fewer cardiovascular events of special interest, fewer cardiac adverse events, and reductions in severe cardiopulmonary complications with triple therapy (40). Notably, these improvements were observed despite the higher cumulative exposure to ICS. Complementary findings from the IMPACT trial demonstrated that fluticasone furoate/umeclidinium/vilanterol delivered via a single inhaler reduced mortality and exacerbation rates relative to dual bronchodilators while maintaining cardiovascular safety, highlighting the role of exacerbation prevention in reducing downstream cardiovascular stress (41).

Meta-analysis reinforce triple therapy's favorable cardiovascular profile through pooled RCT data. Li et al. (2025) network meta-analysis of 13 randomized controlled trials showed ICS/LAMA/LABA significantly lowered all-cause mortality, cardiovascular adverse events of special interest, and severe cardiovascular events compared to LAMA/LABA dual therapy, with budesonide/glycopyrronium/formoterol demonstrating superior efficacy across outcomes (42). Cazzola et al. (2019) meta-analysis confirmed adding LAMA to existing ICS/LABA therapy improves lung function and reduces exacerbations without elevating cardiovascular serious adverse events, while Lee et al. (2019) Bayesian network meta-analysis observed trends toward lower cardiovascular mortality despite pneumonia incidence. These analyses establish biological plausibility through synergistic anti-inflammatory and bronchodilatory mechanisms reducing systemic cardiovascular burden (43,44). The most recent GOLD guidance further acknowledges that triple therapy may convey cardiovascular benefit in high-risk COPD phenotypes by reducing exacerbation-related cardiopulmonary stress.

5. Clinical Implications

5.1. Bronchodilator Therapy (LABA/LAMA)

- Long-acting bronchodilators serve as foundational therapy for all COPD patients, with confirmed long-term cardiovascular safety across large cohort studies and RCTs (1,39).
- Enhanced monitoring is required during the first 30 days post-initiation, particularly in elderly patients or those with preexisting cardiovascular disease, due to transient elevations in arrhythmia and ischemic risk (18).
- LABA/LAMA fixed-dose combinations demonstrate superior cardiovascular safety compared to LABA/ICS regimens, with reduced major adverse cardiovascular events and dysrhythmia incidence (18,24).
- ICS avoidance is recommended in patients with infrequent exacerbations to minimize pneumonia risk while maintaining equivalent symptom control (25).

5.2. Inhaled Corticosteroids (ICS)

- Selective ICS use is indicated for patients with frequent exacerbations (≥2 moderate or ≥1 severe annually) or blood eosinophil counts ≥300 cells/μL, per current guidelines (45).
- ICS exhibit cardiovascular neutrality with potential protective effects through systemic inflammation suppression (IL-6/CRP reduction), supported by RCT meta-analyses and real-world cohorts (18,35).
- In high cardiovascular risk patients with exacerbator phenotypes, ICS benefits—evidenced by dose-dependent coronary heart disease and mortality reductions—outweigh pneumonia risks (33,35).
- Dose-response relationships favor higher cumulative exposure for cardioprotection, necessitating personalized risk-benefit assessment.

5.3. Triple Therapy (LABA/LAMA/ICS)

- Triple therapy represents first-line therapy for high-risk COPD phenotypes characterized by frequent exacerbations and cardiovascular comorbidity (40,46).
- Cardiovascular protection exceeds dual bronchodilation, with reductions in cardiovascular adverse events of special interest and cardiac events observed in phase 3 post-hoc analyses (40,42).
- Exacerbation prevention confers indirect cardiovascular benefit by mitigating hypoxemia, sympathetic overdrive, and inflammation-mediated plaque instability (40).
- Budesonide/glycopyrrolate/formoterol 320 demonstrates superior efficacy in pooled network meta-analyses (42).

6. Conclusion

Chronic obstructive pulmonary disease is now understood as a systemic pro-inflammatory disorder with substantial cardiovascular implications. Converging evidence demonstrates that persistent neutrophilic inflammation, endothelial dysfunction, autonomic dysregulation, and exacerbation-associated hypoxemia act synergistically to amplify cardiovascular risk far beyond that of age-matched populations. Within this pathophysiologic context, long-acting bronchodilators remain the foundation of COPD pharmacotherapy, with stable cardiovascular safety profiles following early initiation. Comparative effectiveness studies consistently show that LABA/LAMA combinations offer superior cardiovascular safety relative to LABA/ICS, driven by lower rates of dysrhythmia and reduced pneumonia-associated cardiovascular destabilization.

Inhaled corticosteroids maintain cardiovascular neutrality across large randomized controlled trials and appear to confer additional cardioprotection in real-world settings through sustained suppression of systemic inflammatory mediators. Population-level analyses from the Korean NHIS highlight meaningful reductions in coronary heart disease and all-cause mortality with appropriate ICS exposure, even when accounting for pneumonia risk. These findings reinforce the rationale for selective ICS use in phenotypes characterized by eosinophilic inflammation or recurrent exacerbations, where anti-inflammatory benefits likely outweigh infection-related harm.

Triple therapy further strengthens risk reduction in patients with high cardiovascular burden or frequent exacerbations. Post-hoc cardiovascular analyses of phase 3 trials, including ETHOS and IMPACT, together with contemporary network meta-analyses, demonstrate that ICS/LAMA/LABA regimens reduce severe cardiovascular events more effectively than dual bronchodilation. These benefits are attributed to the combined anti-inflammatory actions of ICS and the enhanced ventilatory stabilization afforded by dual bronchodilation. Contemporary evidence supports individualized therapy per 2025 GOLD guidance: LABA/LAMA for low-risk maintenance, selective ICS for

eosinophilic exacerbators, and triple therapy for cardiovascular comorbidity with frequent exacerbations. Future research priorities include biomarker-driven phenotyping, dedicated cardiovascular endpoint trials, and integrated cardiopulmonology to transform COPD management from pulmonary-centric to comprehensive cardiovascular risk mitigation.

Compliance with ethical standard

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Disclosure of conflict interest

The authors declare that there are no conflicts of interest related to the conduct, authorship, or publication of this manuscript.

References

[1] GOLD 2024. Vol. 53. 2023.

[2] Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J. 2009;33(5):1165–85.

[3] Ragnoli B, Chiazza F, Tarsi G, Malerba M. Biological pathways and mechanisms linking COPD and cardiovascular disease. Ther Adv Chronic Dis. 2025;16:1–30.

[4] Maeda T, Dransfield MT. COPD and Cardiovascular Disease: Mechanistic Links and Implications for Practice. 2025;30(2):141–9.

[5] Beeh KM. The role of bronchodilators in preventing exacerbations of chronic obstructive pulmonary disease. Tuberc Respir Dis (Seoul). 2016;79(4):241–7.

[6] Mkorombindo T, Dransfield MT. Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease: Benefits and Risks. Clin Chest Med. 2020;41(3):475–84.

[7] Maltais F, Buhl R, Koch A, Amatto VC, Reid J, Grönke L, et al. β-Blockers in COPD: A Cohort Study From the TONADO Research Program. Chest. 2018;153(6):1315–25.

[8] Lea S, Higham A, Beech A, Singh D. How inhaled corticosteroids target inflammation in COPD. Eur Respir Rev [Internet]. 2023;32(170):1–16. Available from: http://dx.doi.org/10.1183/16000617.0084-2023

[9] Li XF, Wan CQ, Mao YM. Analysis of pathogenesis and drug treatment of chronic obstructive pulmonary disease complicated with cardiovascular disease. Front Med. 2022;9(November):1–11.

[10] Theodorakopoulou MP, Bakaloudi DR, Alexandrou ME, Papakosta D, Pataka A, Kioumis I, et al. Endothelial Dysfunction during Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. COPD J Chronic Obstr Pulm Dis [Internet]. 2021;18(2):246–53. Available from: https://doi.org/10.1080/15412555.2021.1900094

[11] Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. Eur Respir J [Internet]. 2023;61(4). Available from: http://dx.doi.org/10.1183/13993003.00239-2023

[12] Kent BD, Mitchell PD, Mcnicholas WT. Hypoxemia in patients with COPD: Cause, effects, and disease progression. Int J COPD. 2011;6(1):199–208.

[13] Ismaeel A, Brumberg RS, Kirk JS, Papoutsi E, Farmer PJ, Bohannon WT, et al. Oxidative stress and arterial dysfunction in peripheral artery disease. Antioxidants. 2018;7(10):1–16.

[14] Marcuccio G, Candia C, Maniscalco M, Ambrosino P. Endothelial dysfunction in chronic obstructive pulmonary disease: an update on mechanisms, assessment tools and treatment strategies. Front Med. 2025;12(1).

[15] Siragusa1 S, , Giulia Natali2 SP, , Antonella Maria Nogara1 , Marcello Trevisani2, Costanza Anna, Maria Lagrasta S pontis. The role of pulmonary vascular endothelium in chronic obstructive pulmonary disease (COPD): Does endothelium play a role in the onset and progression of COPD? Explor Dig Dis. 2023;246–75.

[16] Matera MG, Hanania NA, Maniscalco M, Cazzola M. Pharmacotherapies in Older Adults with COPD: Challenges and Opportunities. Drugs and Aging [Internet]. 2023;40(7):605–19. Available from: https://doi.org/10.1007/s40266-023-01038-0

[17] Malo de Molina R, Aguado S, Arellano C, Valle M, Ussetti P. Ischemic Heart Disease during Acute Exacerbations of COPD. Med Sci (Basel, Switzerland). 2018;6(4):1–13.

[18] Wang MT, Liou JT, Lin CW, Tsai CL, Wang YH, Hsu YJ, et al. Association of cardiovascular risk with inhaled long-acting bronchodilators in patients with chronic obstructive pulmonary disease: A nested case-control study. JAMA Intern Med. 2018;178(2):229–38.

[19] Gershon A, Croxford R, Calzavara A, To T, Stanbrook MB, Upshur R, et al. Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. JAMA Intern Med. 2013;173(13):1175–84.

[20] Wong CK, Cheng ECC, Choo A, Tsui CK, Ko AT, Ma TF, et al. Cardiovascular Outcomes Among Patients with COPD Prescribed with LABA or LAMA: A Real-World Territory Wide Study. Adv Ther [Internet]. 2025;42(12):6163–74. Available from: https://doi.org/10.1007/s12325-025-03375-5

[21] Donald P. Tashkin, M.D., Bartolome Celli, M.D., Stephen Senn, Ph.D., Deborah Burkhart, B.S.N., Steven Kesten, M.D., Shailendra Menjoge, Ph.D., and Marc Decramer, M.D. P. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary. N Engl J Med. 2006;355:11–20.

[22] Kim EK, Lee E, Park JE, Lee JS, Choi HS, Park B, et al. Cardiovascular Events According to Inhaler Therapy and Comorbidities in Chronic Obstructive Pulmonary Disease. Int J COPD. 2024;19(December 2023):243–54.

[23] Chen CY, Pan SW, Hsu CC, Liu JJ, Kumamaru H, Dong YH. Comparative cardiovascular safety of LABA/LAMA FDC versus LABA/ICS FDC in patients with chronic obstructive pulmonary disease: a population-based cohort study with a target trial emulation framework. Respir Res [Internet]. 2023;24(1):1–13. Available from: https://doi.org/10.1186/s12931-023-02545-9

[24] Samp JC, Joo MJ, Schumock GT, Calip GS, Pickard AS, Lee TA. Risk of Cardiovascular and Cerebrovascular Events in COPD Patients Treated With Long-Acting β2-Agonist Combined With a Long-Acting Muscarinic or Inhaled Corticosteroid. Ann Pharmacother. 2017;51(11):945–53.

[25] Suissa S, Dell'Aniello S, Ernst P. Comparative Effectiveness and Safety of LABA-LAMA vs LABA-ICS Treatment of COPD in Real-World Clinical Practice. Chest [Internet]. 2019;155(6):1158–65. Available from: https://doi.org/10.1016/j.chest.2019.03.005

[26] Cazzola M, Page C, Rogliani P, Calzetta L, Matera MG. Dual bronchodilation for the treatment of COPD: From bench to bedside. Br J Clin Pharmacol. 2022;88(8):3657–73.

[27] O'Donnell DE, Laveneziana P. The clinical importance of dynamic lung hyperinflation in COPD. COPD J Chronic Obstr Pulm Dis. 2006;3(4):219–32.

[28] Rothnie KJ, Connell O, Müllerová H, Smeeth L, Pearce N, Douglas I, et al. Myocardial infarction and ischemic stroke after exacerbations of chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2018;15(8):935–46.

[29] Rogliani P, Ora J, Matera MG, Cazzola M, Calzetta L. The safety of dual bronchodilation on cardiovascular serious adverse events in COPD. Expert Opin Drug Saf. 2018;17(6):589–96.

[30] Li C, Cheng W, Guo J, Guan W. Relationship of inhaled long-acting bronchodilators with cardiovascular outcomes among patients with stable COPD: A meta-analysis and systematic review of 43 randomized trials. Int J COPD. 2019;14:799–808.

[31] Mammen MJ, Pai V, Aaron SD, Nici L, Alhazzani W, Alexander PE. Dual LABA/LAMA Therapy versus LABA or LAMA Monotherapy for Chronic Obstructive Pulmonary Disease A Systematic Review and Meta-analysis in Support of the American Thoracic Society Clinical Practice Guideline. Ann Am Thorac Soc. 2020;17(9):1133–43.

[32] Yang M, Li Y, Jiang Y, Guo S, He JQ, Sin DD. Combination therapy with long-acting bronchodilators and the risk of major adverse cardiovascular events in patients with COPD: a systematic review and meta-analysis. Eur Respir J [Internet]. 2023;61(2):1–15. Available from: http://dx.doi.org/10.1183/13993003.00302-2022

[33] Gadhvi K, Kandeil M, Raveendran D, Choi J, Davies N, Nanchahal S, et al. Inhaled Corticosteroids and Risk of Cardiovascular Disease in Chronic Obstructive Pulmonary Disease: A Systematic Review and MetaRegression. Chronic Obstr Pulm Dis. 2023;10(3):317–27.

[34] Chen H, Sun J, Huang Q, Liu Y, Yuan M, Ma C, et al. Inhaled Corticosteroids and the Pneumonia Risk in Patients With Chronic Obstructive Pulmonary Disease: A Meta-analysis of Randomized Controlled Trials. Front Pharmacol. 2021;12(June):1–20.

[35] Shin J, Yoon HY, Lee YM, Ha E, Lee JH. Inhaled corticosteroids in COPD and the risk for coronary heart disease: a nationwide cohort study. Sci Rep [Internet]. 2020;10(1):1–9. Available from: https://doi.org/10.1038/s41598-020-74854-8

[36] Sin DD, Lacy P, York E, Man SFP. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004;170(7):760–5.

[37] Falk JA, Minai OA, Mosenifar Z. Inhaled and systemic corticosteroids in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2008;5(4):506–12.

[38] Shin J, Park S, Lee JY, Lee JH. Survival benefit of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: a nationwide cohort study. Sci Rep [Internet]. 2024;14(1):1–8. Available from: https://doi.org/10.1038/s41598-024-65763-1

[39] Jing X, Li Y, Xu J. Risk of cardiovascular events associated with inhaled corticosteroid treatment in patients with chronic obstructive pulmonary disease: A meta-analysis. Can Respir J. 2018;2018.

[40] Singh D, Martinez FJ, Hurst JR, Han MLK, Gale CP, Fredriksson M, et al. Effect of Triple Therapy on Cardiovascular and Severe Cardiopulmonary Events in Chronic Obstructive Pulmonary Disease A Post Hoc Analysis of a Randomized, Double-Blind, Phase 3 Clinical Trial (ETHOS). Am J Respir Crit Care Med. 2025;211(2):205–14.

[41] Suissa S, Aniello SD, Ernst P. Single-Inhaler Triple versus Dual Bronchodilator Therapy in COPD : Real-World Comparative Effectiveness and Safety. 2022;(August):1975–86.

[42] Li Y, Li J, Yang H, Zhang Y. Effect of triple therapy on mortality and cardiovascular risk in patients with moderate to severe COPD: a meta-analysis of randomized controlled trials. BMC Pulm Med. 2025;25(1).

[43] Cazzola M, Calzetta L, Rogliani P, Matera MG. Triple Therapy Versus Dual Bronchodilation and Inhaled Corticosteroids/Long-Acting β-Agonists in COPD: Accumulating Evidence from Network Meta-Analyses. Pulm Ther [Internet]. 2019;5(2):117–26. Available from: https://doi.org/10.1007/s41030-019-00102-8

[44] Lee HW, Park J, Jo J, Jang EJ, Lee CH. Comparisons of exacerbations and mortality among regular inhaled therapies for patients with stable chronic obstructive pulmonary disease: Systematic review and Bayesian network meta-analysis. PLoS Med [Internet]. 2019;16(11):1–20. Available from: http://dx.doi.org/10.1371/journal.pmed.1002958

[45] Halpin DMG, Celli BR, Criner CJ, et. al. Global Iniciative for Chronic Obstructive Lung Disease, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Global Iniciative for Chronic Obstructive Lung Disease - GOLD. 2025.

[46] Bourdin A, Criner G, Devouassoux G, Dransfield M, Halpin DMG, Han MLK, et al. InforMing the PAthway of COPD Treatment (IMPACT Trial) Single-Inhaler Triple Therapy (Fluticasone Furoate/Umeclidinium/ Vilanterol) Versus Fluticasone Furoate/Vilanterol and Umeclidinium/Vilanterol in Patients with COPD: Analysis of the Western Europe and North America Regions. Chronic Obstr Pulm Dis. 2021;8(1):76–90.