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Review

The Intersection of Chronic Obstructive Pulmonary Disease and Cardiovascular Disease: Recent Insights in a Challenging Area

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) are 2 prevalent and interconnected health conditions that have a significant global impact. COPD is characterized by airflow obstruction and is caused by smoking and/or environmental factors. COPD is associated with chronic inflammation and structural changes in the airways and lung parenchyma. CVD encompasses various cardiac and vascular conditions and is a leading global cause of mortality, with risk factors that include diabetes, smoking, and dyslipidemia. CVDs discussed in this review, in relation to COPD, include hypertension, coronary artery disease and ischemic heart disease, heart failure, cardiac arrhythmias, and cerebrovascular disease. The interplay between COPD and CVD is evident, with shared risk factors and physiological mechanisms contributing to their frequent comorbidity. Therefore, an integrated approach to care involving primary care physicians, respirologists, and cardiologists is essential to effectively manage the dual burden of COPD and CVD.

This review outlines the shared risks and underlying mechanisms of these conditions, their diagnosis, and the clinical implications of dual COPD and CVD in a patient, including how COPD exacerbations significantly elevate the risk of cardiovascular (CV) events and mortality. Pharmacologic CVD and COPD therapies, as well as their CV and respiratory effects, are discussed. Key trials (Towards a Revolution in COPD Health [TORCH]; Study to Understand Mortality and Morbidity in COPD [SUMMIT]; InforMing the Pathway of COPD Treatment [IMPACT]; and Efficacy and Safety of Triple Therapy in Obstructive Lung Disease [ETHOS]) are discussed that demonstrate the effectiveness of triple bronchodilator therapy in reducing exacerbation rates, as well as all-cause and cardiovascular mortality in patients with COPD and CVD.

RÉSUMÉ

La bronchopneumopathie chronique obstructive (BPCO) et les maladies cardiovasculaires (MCV) sont deux problèmes de santé prévalents et interconnectés qui ont un impact mondial important. La BPCO se caractérise par une obstruction des voies aériennes et est causée par le tabagisme et/ou des facteurs environnementaux. La BPCO est associée à une inflammation chronique et à des modifications structurelles des voies respiratoires et du parenchyme pulmonaire. Les MCV englobent diverses affections cardiaques et vasculaires et constituent l'une des principales causes de mortalité dans le monde, avec des facteurs de risque tels que le diabète, le tabagisme et la dyslipidémie. Les MCV abordées dans cette revue de littérature, en relation avec la BPCO, comprennent l'hypertension, la maladie coronarienne et la cardiopathie ischémique, l'insuffisance cardiaque, les arythmies cardiaques et les maladies cérébrovasculaires. L'interaction entre la BPCO et les MCV est évidente, les facteurs de risque et les mécanismes physiologiques communs contribuant à leur fréquente comorbidité. Par conséquent, une approche intégrée des soins impliquant les médecins de soins primaires, les pneumologues et les cardiologues est essentielle pour gérer efficacement le fardeau partagé de la BPCO et des MCV.

Cette revue décrit les risques partagés et les mécanismes sous-jacents de ces pathologies, leur diagnostic et les implications cliniques de la double présence de BPCO et MCV chez le patient, y compris la façon dont les exacerbations de la BPCO augmentent de manière significative le risque d'événements cardiovasculaires (CV) et de mortalité. Les traitements pharmacologiques des MCV et de la BPCO, ainsi que leurs effets CV et respiratoires, sont abordés. Des essais clés (Towards a Revolution in COPD Health [TORCH]; Study to Understand Mortality and

Chronic obstructive pulmonary disease (COPD) and cardiovascular (CV) disease (CVD) together represent a complex and clinically significant medical challenge. COPD, characterized by chronic airflow limitation, inflammation, and structural changes in the airways and lung parenchyma, is a leading cause of morbidity and mortality worldwide.[1-15] In

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Overall, this review highlights the need for an integrated approach to patient management, involving collaboration among primary care physicians, respirologists, and cardiologists, to effectively address the dual burden of these diseases.

Morbidity in COPD [SUMMIT]; InforMing the Pathway of COPD Treatment [IMPACT]; et Efficacy and Safety of Triple Therapy in Obstructive Lung Disease [ETHOS]) sont évoqués, qui démontrent l'efficacité de la trithérapie bronchodilatatrice dans la réduction des taux d'exacerbation, ainsi que de la mortalité cardiovasculaire et toutes causes confondues, chez les patients atteints de BPCO et de MCV. Dans l'ensemble, cette revue souligne la nécessité d'une approche intégrée de la prise en charge des patients, impliquant une collaboration entre les médecins de soins primaires, les pneumologues et les cardiologues, afin de traiter efficacement la double problématique de ces pathologies.

parallel, CVD encompasses a spectrum of cardiac and vascular conditions, including hypertension, coronary artery disease (CAD) and/or ischemic heart disease (IHD), heart failure (HF), cardiac arrhythmias, and cerebrovascular disease. CVD continues to be a major contributor to the incidence of mortality globally.[1,3,7,13]

The prevalent coexistence of COPD and CVD underscores the interconnected nature of these conditions, which makes them a clinically significant medical challenge.[1-4,8] These 2 diseases share common risk factors and pathophysiological mechanisms that contribute to their being frequent comorbid conditions.[1-9,12] The recognition of this complex interplay between COPD and CVD requires a paradigm shift in clinical practice. An imperative in this regard is to adopt an integrated, multidisciplinary approach that bridges the domains of respirology and cardiology to provide holistic care for patients living with both COPD and CVD.[3,4,6,8,12]

This review provides an integrated overview of the relationship between COPD and multiple CVD conditions, spanning epidemiology, pathophysiology, diagnosis, and pharmacologic management. A comprehensive approach is presented, because previous reviews have focused on either specific CVDs and their impact in COPD patients, without highlighting treatment,[5,7,9] or COPD therapies, without detailing their implications for treating specific CVDs.[6,13] In addition, the importance of triple bronchodilator therapy in the management of patients with COPD,[1,4,8,12] including reduction in the incidence of exacerbations, improvement in quality of life (QoL), reduced mortality and lower cardiovascular risk, is often underrecognized by CV specialists. By highlighting these emerging therapies and diagnostic advancements, this review underscores the need for integrated-care models that facilitate early detection, coordinated treatment, and ongoing management of multimorbidity in COPD patients. This holistic approach addresses critical knowledge and practice gaps in COPD care, providing clinicians with updated strategies to better assess and manage patients who have concurrent CV risks.

Consequences of Comorbid COPD and CVD

Increased risks

The systemic effects of COPD extend beyond the lungs, and they include systemic inflammation and endothelial dysfunction.[1,2,4,6-9] Patients with COPD face an elevated risk of developing CVD—that is, the prevalence of CVD may reach 70% in this patient population (maximally adjusted risk estimate, 1.71; 95% confidence interval [CI], 1.61-1.81).[7] In fact, a meta-analysis of 27 studies demonstrated that patients with COPD have a 2-5-fold increased risk of having a CVD, even after adjustment for age, smoking, and other risk factors (odds ratio [OR], 2.46; 95% CI, 2.02-3.00; $P < 0.0001$).[3,16-21] In addition, those with COPD experience worse outcomes when CVD is present.[1-10] As highlighted in the 2023 Canadian Thoracic Society guideline for COPD management, an acute exacerbation of COPD increases the risk of CV events, including the incidence of acute coronary syndrome and stroke within 1 month of the exacerbation and for up to 1 year following it.[11] This risk is 10-fold higher following a severe exacerbation.[16] In contrast, the presence of CVD in a patient with COPD increases the risk of COPD hospitalizations, mortality, and a decreased QoL.[1-10,12,13] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recognizes that CVD is responsible for more than half of the hospitalizations and deaths of COPD patients.[19] Other estimates demonstrate that up to one-third of COPD patients die as a result of CVD, and up to 40% of those with a CV history die.[4] In summary, the presence of comorbid COPD and CVD portends a worse prognosis and a higher mortality rate, compared to those for patients who have either condition in isolation.[1-8,12,13,19]

Prevalence and Outcomes of COPD and Common Cardiac Comorbidities

HF

Nearly one third of patients with HF have a diagnosis of COPD.[25] This high prevalence is contextualized by the HF OR of 2.57 (95% CI, 1.90-3.47) in those with COPD.[20] In a retrospective matched cohort study of 45,966 patients, the prevalence of HF among patients with COPD ranged from 7% to 42%, an incidence that is significantly higher than that in the non-COPD population.[19,21] Additional studies cite the prevalence as being as high as 75% in hospitalized COPD patients who require mechanical ventilation.[19,22-24]

An important point to note is that HF worsens patient prognosis in those hospitalized due to COPD, and COPD

worsens patient prognosis in those hospitalized with HF.[19] A retrospective cohort study demonstrated a mortality incidence of 39% among patients with coexisting COPD and HF.[19,26] The high incidence of mortality associated with HF, which can be increased further by comorbid COPD, highlights the importance of providing guideline-directed HF therapy to this patient population.

No evidence indicates that HF treatment strategies that differ from current guidelines should be pursued as a result of a diagnosis of COPD. As discussed later, several of the therapies recommended for the treatment of HF could be expected to have a favourable pulmonary benefit in a patient with COPD. Unfortunately, the reduced use of beta (β)-blockers in the population with HF and/or COPD has been well established, despite the fact that multiple large analyses have confirmed that β1-selective blockers have been found to be safe for use in patients with COPD and CVD.[3,8,27] In addition, dual bronchodilator therapy for treatment of COPD has been shown to improve cardiac function, and it may be particularly beneficial in HF patients with COPD and hyperinflation.[28] When COPD and HF occur in the same patient, elucidating the cause of dyspnea can be difficult. The approach to this diagnostic challenge is discussed later.

IHD

In COPD patients, IHD and CAD have ORs of 2.28 (95% CI, 1.76-2.96) and 1.86 (95% CI, 1.51-2.30), respectively.[20] The prevalence of these diseases in stable COPD patients can range from 7% to 33% (rate ratio, 1.25; 95% CI, 1.19-1.31).[19,29-32] Adding to this, a cross-sectional multicentre study found that IHD occurred in 17%-22% of those hospitalized for COPD exacerbations, and that the presence of IHD predicted an increased likelihood of mortality (hazard ratio [HR], 1.29; 95% CI, 1.04-1.61; $P < 0.01$).[19,32] A systematic analysis of the Global Burden of Disease Study demonstrated that the occurrence of CAD and/or IHD is the most common cause of early mortality in COPD patients.[19] In fact, the presence of COPD nearly doubles the risk of myocardial infarction (MI), and those with CAD and/or IHD and COPD have a significantly decreased exercise capacity and more-severe dyspnea.[19] Having CAD and/or IHD doubles a COPD patient's risk of hospitalization and increases their risk of 3-month mortality.[19] Unfortunately, the underdiagnosis of COPD in IHD approximates 80% and encompasses patients who are in the early or moderate stages, in which better preventative and therapeutic options would be expected to provide a benefit.[33]

Cardiac arrhythmias

Cardiac arrhythmias have an OR of 1.94 (95% CI, 1.55-2.43) in a COPD population,[20] and they are present in 5%-15% of stable COPD cases, and in 20%-30% of severe COPD cases.[7,19,20] However, these estimates are confounded by asymptomatic and paroxysmal atrial fibrillation (AF), as well as self-reporting.[19]

AF is the most common cardiac arrhythmia, and its prevalence is higher in patients with COPD (an up to 1.8-fold increase).[34] AF is particularly common during COPD exacerbations, and it must be differentiated from multifocal atrial tachycardia, which may also be present in the setting of hypoxia.[35] The prevalence of AF among patients hospitalized with COPD is as high as 22%, and it is associated with an increase in in-hospital mortality and hospital length-of-stay ($P < 0.001$).[36] A 2021 meta-analysis assessing the relationship between COPD and arrhythmia risks found that COPD is significantly associated with the risk of AF (risk ratio [RR], 1.99; 95% CI, 1.46-2.70), ventricular arrhythmias (RR, 2.01; 95% CI, 1.42-2.85), and sudden cardiac death (RR, 1.68; 95% CI, 1.28-2.21).[27] In addition, COPD is associated with a decrease in the efficacy of catheter ablation for AF and an increase in recurrence following electrical cardioversion.[37,38]

Non-dihydropyridine calcium-channel blockers (CCBs) and cardioselective β-blockers are effective and safe in providing rate control in a patient with COPD. In contrast, class IA and IC antiarrhythmic drugs are often contraindicated, owing to the presence of concomitant congestive heart disease. When pharmacologic rhythm control is desired, use of amiodarone is a consideration, but the potential risk of pulmonary fibrosis also must be considered. Daily doses of $\leq$ 200 mg is associated with a 0.1%– 0.5% risk; given this, routine monitoring is required.[39] Sotalol, a class III antiarrhythmic, should be avoided, given its potential to induce bronchoconstriction as a result of its nonselective binding to both β1 and β2 adrenergic receptors. COPD also has been shown to be associated with an increased risk of ventricular arrhythmias (VAs). In patients with COPD, several potential risk factors are present for development of VA, including hypoxia, acidosis, and decreased lung function (as measured by forced expiratory volume in 1 second [FEV1]).[40] Patients who have an average level of saturated oxygen (SaO_2) < 0.80 were found to have a particularly high frequency of VA incidence (OR, 1.76; 95% CI, 1.64-1.89).[41,42]

Cerebrovascular disease

Cerebrovascular disease has an OR of 1.32 (95% CI, 0.99-1.76) in COPD patients,[20] a population that also carries a 3.8-fold increased prevalence of stroke (HR, 2.20; 95% CI, 2.07-2.32). Notably, stroke occurs in 10% of patients with stable COPD, and in roughly 20% of patients hospitalized with COPD exacerbation.[19,43] Exacerbations of COPD are associated with an increase in inflammation, suggesting that an association exists between exacerbation frequency and stroke risk. In a study that explored the prevalence of COPD among hospitalized stroke patients, 12% of the patients were found to have COPD (95% CI, 11.48-11.94), and COPD was found to be an independent risk factor for early mortality.[40]

Hypertension

In COPD patients, although hypertension is the comorbidity that occurs most frequently, it does not directly change the prognosis of the condition. The prevalence of hypertension is similar to that in the general population, increases with age, and has been estimated to range from 28% to 65%.[19,44,45] However, hypertension is a risk factor for the development of CVD, and via this route, it can lead to the

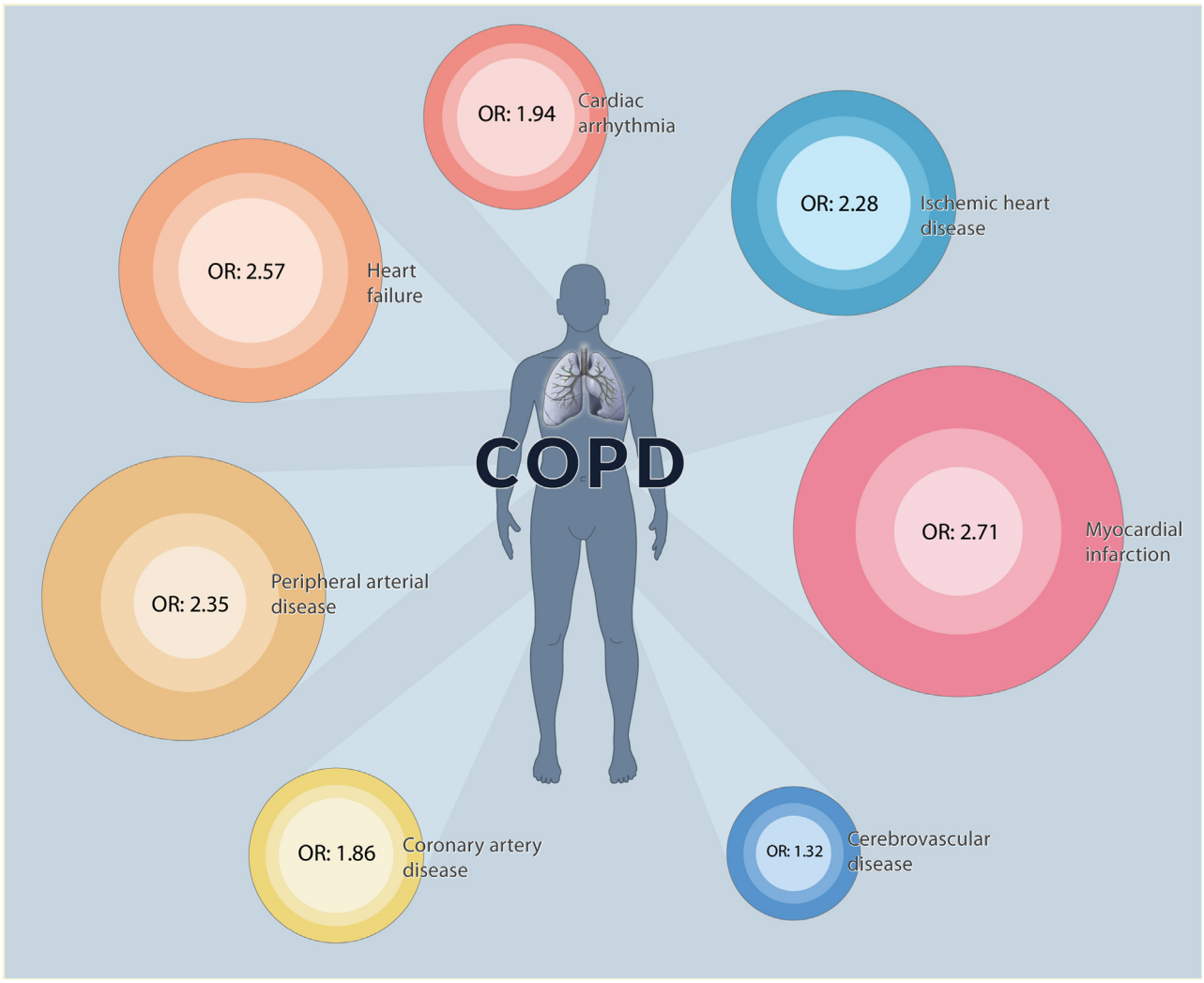

Figure 1. Prevalence of cardiovascular diseases by odds ratio (OR) in a chronic obstructive pulmonary disease (COPD) population.[20] A larger *circle* represents a greater OR. Cardiac arrhythmia has an OR of 1.94 (95% confidence interval [CI], 1.55-2.43); ischemic heart disease has an OR of 2.28 (95% CI, 1.76-2.96); myocardial infarction has an OR of 2.71 (95% CI, 1.69-4.35); cerebrovascular disease has an OR of 1.32 (95% CI, 0.99-1.76); coronary artery disease has an OR of 1.86 (95% CI, 1.51-2.30); peripheral artery disease has an OR of 2.35 (95% CI, 1.48-3.74); heart failure has an OR of 2.57 (95% CI, 1.90-3.47).[20]

development of HF and IHD. Currently, no specific recommendations have been made regarding a change in the approach to hypertension treatment in the COPD population, as compared to the treatment of those without COPD (Fig. 1).[20]

Shared Risks and Pathophysiological Mechanisms

Shared risk factors

Shared risk factors for COPD and CVD include the following: smoking, systemic inflammation, oxidative stress, environmental factors, aging, sedentary lifestyle, and diabetes (Fig. 2).[1-9,12] Smoking is a predominant shared risk factor for patients with both of these conditions, which highlights the significant role it plays in the development of these conditions.[1,2,4,8] Additionally, chronic inflammation is a common denominator in the 2 diseases, [1,2,4,6-9] and several studies have demonstrated that patients with COPD and/or CVD have high levels of systemic inflammatory biomarkers, such as C-reactive protein and interleukin-6. In fact, patients with combined COPD and CVD have higher levels of these biomarkers than those in patients with COPD alone.[4] Furthermore, oxidative stress, as measured by elevated oxidant activity and decreased antioxidant activity, has been shown to be up to 30 times higher in patients with COPD and CVD, in comparison to levels in healthy controls ($P < 0.001$).[1,2] Additional shared risk factors include environmental exposures, such as air pollution and harmful occupational exposures, advanced age, and a sedentary lifestyle.[6] These factors all are associated with an increased risk of developing both respiratory and CV conditions.[1,4,8] Lastly, diabetes is an important comorbidity that increases the risk of both COPD and CVD. Individuals with diabetes are more likely to develop

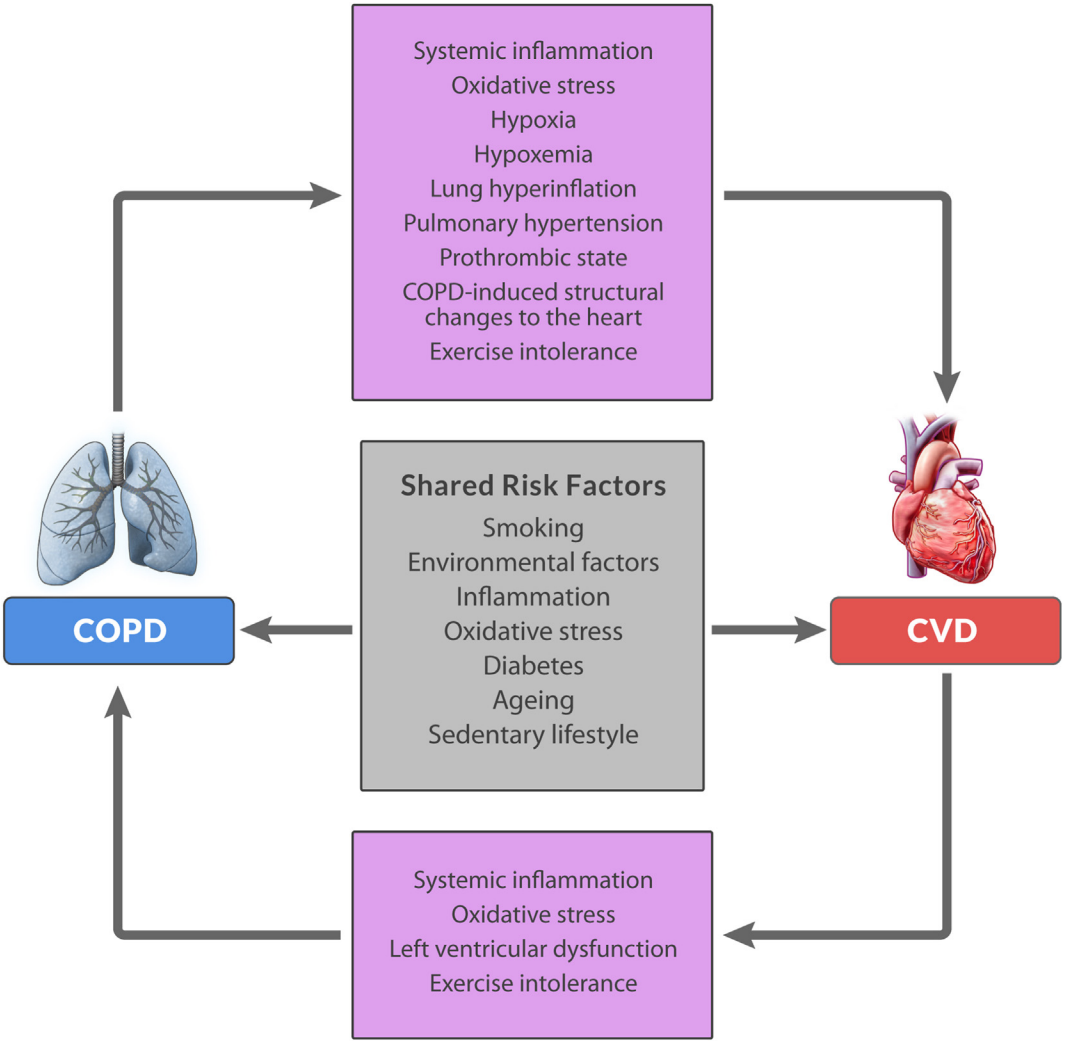

Figure 2. Shared risk factors and interactions of chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD).[1-13]

these conditions, and the presence of diabetes contributes to a higher disease burden for those with COPD and/or CVD.[4,6,8,9,12]

Mechanisms linking COPD and CVD

Although shared risk factors can contribute to the development of COPD and/or CVD, the high prevalence of comorbid COPD and CVD also may be secondary to shared pathologies (Fig. 2). COPD can drive the pathogenesis of CVD through systemic inflammation, oxidative stress, hypoxemia, hypoxia, lung hyperinflation, and the induction of a prothrombotic state.[1,2,4,6,8,9,12,13] COPD-mediated inflammation has been shown to promote atherosclerotic heart disease.[1,2,4,6,8,9,12,13] In addition, oxidative stress, which is increased in COPD and is characterized by an imbalance between reactive oxygen species and antioxidant defenses, can lead to endothelial dysfunction and an increase in the incidence of CV events.[1,2,4,6,13] In both chronic inflammation and oxidative stress, the resulting damage to the endothelium leads to impairment of regulation of the following: vascular tone, blood flow, vessel integrity, and clotting factors.[1,2,4,9,12] This endothelial dysfunction skews the balance of autoregulated blood flow toward vasoconstriction, resulting in increased vascular resistance and thereby hypertension.[1,2,4,9,12] In addition, these adverse vascular effects can lead to various other CV complications, such as atherosclerosis, MI, HF, and stroke.[1,4,9,12] The likelihood that COPD-related systemic inflammation can exacerbate systemic endothelial dysfunction and thereby amplify the risk of CVD is underappreciated.[1,2,4,12]

Hypoxemia is another consequence of COPD that can lead to adverse CV outcomes. COPD-mediated ventilation–perfusion mismatch, and the resulting low blood oxygen levels, can contribute to pulmonary vasoconstriction, hypertension, and vascular remodeling, leading to right-ventricular dysfunction and/or hypertrophy.[6,12,13] In turn, right-ventricular dysfunction can impair left-ventricular filling and thereby reduce cardiac output.[12,13] In parallel, COPD-induced hypoxia induces systemic inflammation and oxidative stress, leading to the consequences of endothelial dysfunction outlined previously.[4,6,12] An additional

pulmonary complication of COPD is lung hyperinflation due to air trapping and reduced lung elasticity.[13] Lung hyperinflation can lead to compression of cardiac chambers, resulting in pulmonary hypertension, right-ventricular dysfunction, reduced left-ventricular filling, and reduced cardiac output.[1,6,12,13] Finally, COPD is associated with a prothrombotic state that can increase the risk of deep vein thrombosis and/or pulmonary embolism.[1,2,4,6]

These mechanisms are bidirectional, and thus, CVD has the potential to impact COPD through systemic inflammation, oxidative stress, left-ventricular dysfunction, and exercise intolerance. Although the effect of CVD-associated systemic inflammation on COPD is unknown, risk factors of systemic and vascular inflammation, including visceral obesity, diabetes, and inactivity, are associated with reduced pulmonary function, airway hyperreactivity, and ultimately COPD.[46] This finding is supportive of the concept that systemic inflammation associated with CVD may affect COPD. In addition, increased left-ventricular wall stress may contribute to a worse COPD prognosis.[6] Finally, reduced exercise capacity due to CVD may exacerbate COPD, and the opposite is also true[1,6,8,11,13] (Fig. 2).

Given the fact that COPD and CVD share common risk factors and mechanisms, addressing these diseases in tandem, rather than in isolation, is important, to improve patient outcomes. This approach needs to be multidisciplinary, involving respirologists, cardiologists, and primary care providers.[3,4,6,8,12] In a collaborative approach of this type, a crucial consideration is the guideline-directed medications for each condition, taking into account their potential interactions.

Differentiating the Cause of Dyspnea: The Heart-Lung Axis

Addressing the complex interplay between pulmonary and CV conditions presents a significant challenge, necessitating thorough screening and precise diagnoses. This undertaking is particularly challenging in patients who have both conditions. To distinguish between the cardiac and pulmonary etiologies of dyspnea, or in some cases a combination of the 2, various investigations and assessments are required. Although the history and physical examination are central in the diagnostic algorithm, key diagnostic tools are particularly important, given the low level of specificity of dyspnea as a presenting complaint both for COPD and various cardiac causes. Important diagnostic tests include spirometry and/or full pulmonary function testing (including spirometry and body plethysmography to determine lung volumes and diffusing capacity), echocardiography, and serum levels of N-terminal pro-B-type natriuretic peptide (NTproBNP).

Spirometry is the gold standard for identifying airflow obstruction, and it is essential in assessing obstructive lung diseases, such as COPD. A post-bronchodilator ratio of FEV1 to forced vital capacity (FVC) that is below the lower limit of normal is diagnostic of airflow obstruction, and COPD should be suspected in this context, particularly in the presence of risk factors, such as smoking or environmental exposures. Body plethysmography is the gold standard for measuring lung volumes, offering critical insight into restrictive or hyperinflated lung conditions (such as COPD) that spirometry alone cannot provide. In addition, an assessment of the diffusing capacity of the lungs for carbon monoxide (DLCO) can provide valuable information on abnormalities of gas exchange, which may assist further in differentiating pulmonary from cardiac causes of dyspnea. In general, lung volumes tend to decrease in both cardiac and restrictive pulmonary conditions, whereas COPD patients demonstrate hyperinflation (ie, large lung volumes). The DLCO is more likely to show marked reductions in COPD compared to the DLCO in cardiac-related dyspnea, in which DLCO may remain closer to normal.

Echocardiography is an important tool that can support a diagnosis of HF, including HF with a preserved ejection fraction (HFpEF) and HF with a reduced ejection fraction (HFrEF). NTproBNP levels also play a role in distinguishing HFpEF and HFrEF from pulmonary causes of dyspnea, with elevated levels most often being indicative of a cardiac cause of dyspnea.[47,48] However, equivocal levels of NTproBNP can be present in the setting of cor pulmonale, which can make the differentiation challenging. Therefore, a comprehensive approach that incorporates spirometry, body plethysmography, diffusing capacity, echocardiography, and NTproBNP testing enables clinicians to more accurately identify cardiac, pulmonary, or mixed etiologies of dyspnea, thereby guiding effective management strategies.[47,48]

Comorbid Patients: The Impact of CVD Medications for Comorbid COPD and CVD

When diagnostic testing reveals comorbid COPD and CVD, therapies for these conditions can have a significant impact on the treatment of each. CV conditions, including, but not limited to, hypertension, CAD and/or IHD, HF, cardiac arrhythmias, and cerebrovascular disease, have established evidence-based therapies. Although these therapies each target a specific CVD or several CVDs, clinicians must consider their effect on COPD when a patient is comorbid for both conditions. The impact of selective therapies is discussed below and is summarized in Figure 3.

β-blockers

Misconceptions among physicians regarding the use of β-blockers in CVD patients with COPD are not uncommon.[3,8] The lack of clear guidelines to navigate the use of these medications has been evidenced by the underusage of β-blockers in this patient population, owing to fears of inducing bronchospasm.[3,8] However, a crucial point to recognize is that β1-selective blockers can offer significant benefits for patients with both COPD and CVD, by reducing heart rate, blood pressure, ischemia, and the incidence of HF.[3,6,8,12,14]

Nonselective β-blockers act on both β1 and β2 adrenoreceptors in the heart and lungs to inhibit the action of epinephrine and/or norepinephrine.[3] This method results in a decrease of cyclic adenosine monophosphate production, negative chronotropic and inotropic effects on cardiac tissues, decreased heart rate and blood pressure, and increased airway smooth muscle tone.[3,6,8,12,14] In comparison, β1-selective blockers, such as bisoprolol and metoprolol, are cardioselective, acting primarily on β1-adrenoreceptors.[3,6,8,12,14] A Cochrane review assessing the effect of β1-blockers on respiratory function of patients with COPD found these to be generally safe for patients with both COPD and CVD.[49] This

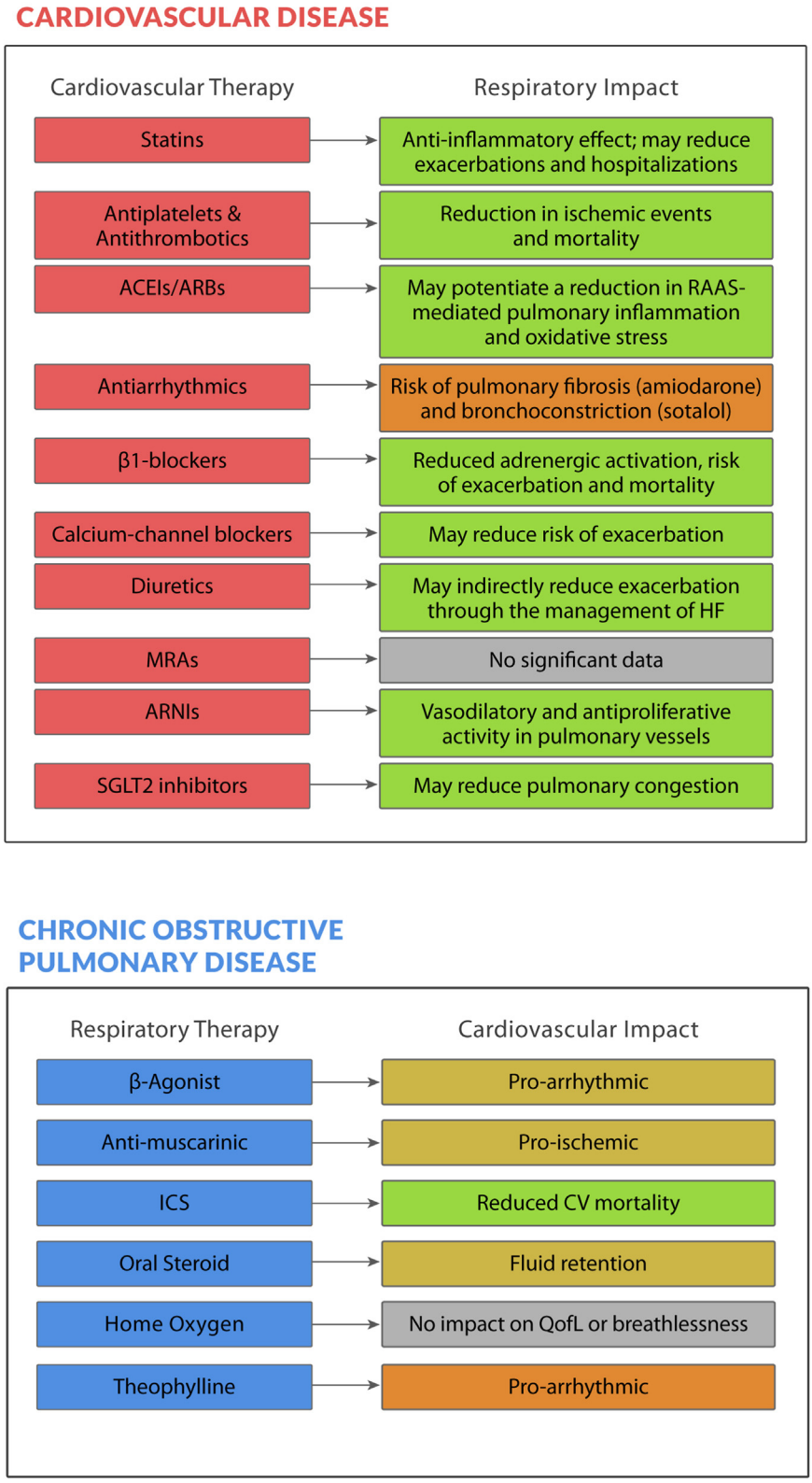

Figure 3. Summary of chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD)-specific therapies and proposed effects in dual COPD and CVD treatment.[1-14,19,48-63] ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CV, cardiovascular; HF, heart failure; ICS, inhaled corticosteroid; MRA, mineralocorticoid receptor antagonist; QofL, quality of life; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose transporter 2.

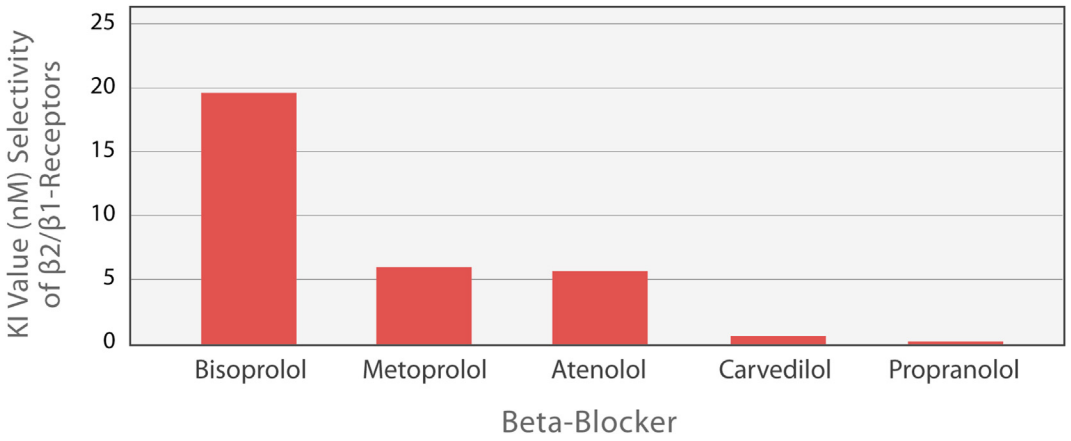

Figure 4. Selectivity of cardioselective beta-blockers.[51] KI value, dissociation constant describing binding affinity; nM, nanometre.

review, which includes 22 randomized controlled trials (RCTs), showed no adverse effects of β1-blockers on lung function or respiratory symptoms; moreover, it demonstrated a reduction in mortality in CVD patients, without an exacerbation of concurrent COPD symptoms.[49] In addition, several studies have demonstrated that β1-blocker use in patients with COPD can significantly reduce COPD exacerbations and death, possibly owing to improved myocardial and ventilatory efficiency.[49,50] Therefore, although use of β-blockers carries a concern that this may aggravate COPD symptoms mechanistically, by promoting bronchoconstriction, evidence suggests that cardioselective β1-blockers have minimal impact on pulmonary function and are unlikely to provoke COPD exacerbation.[49,51] In summary, a β1-selective blocker is the recommended therapy for patients who have both COPD and CVD and for whom it is clinically indicated (eg, those with HFrEF and/or coronary ischemia).[3,6,8,13,14] The preferred cardioselective β -blocker in patients with COPD is bisoprolol, as it has been shown to have the highest level of selectivity for β1-receptors (Fig. 4).[52]

Statins

Statin therapy is common among COPD patients, given the high prevalence of CVD comorbidity.[6] Statins not only lower cholesterol but also have anti-inflammatory effects.[2,6] Retrospective analyses and prospective observational studies support the use of statins in COPD patients, for whom they have been shown to potentially reduce the incidence of exacerbation, hospitalization, and mortality.[6,8] In a retrospective, time-matched, nested, case−control study, use of a combination therapy, including statins and either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), was examined. The incidences of both CV and pulmonary events were reduced with use of a combination of statins, with either ACEIs or ARBs; a significant reduction occurred in COPD hospitalization (RR, 0.66; 95% CI, 0.51-0.85), total mortality (RR, 0.42; 95% CI, 0.33-0.52), and MI (RR, 0.39; 95% CI, 0.31-0.49) in high−CV risk patients.[1,6,53] In summary, statin use is supported in patients with both COPD and CVD; such therapy has an anti-inflammatory effect and may reduce the incidence of exacerbation and hospitalization.

ACEIs and ARBs

ACEIs and ARBs are renin-angiotensin-aldosterone system (RAAS) inhibitors. These therapies are beneficial in the treatment of CVD, through the reduction in both the activity of angiotensin II and blood pressure. Moreover, the RAAS is implicated in inflammatory pathways, oxidative stress, and pulmonary fibrosis, all of which are potential contributors to the pathogenesis of COPD.[6] Therefore, RAAS inhibitors, such as ACEIs and ARBs, may provide a therapeutic benefit to patients with COPD, y yet only a few studies have explored these agents in the context of COPD. Of note, the Multi-Ethnic Study of Atherosclerosis found that in a general population, aged 45-84 years and without clinical evidence of CVD, baseline use of ACEIs or ARBs protected against the progression of emphysema.[6] ACEIs and ARBs also exhibit positive effects on morbidity and mortality in patients who have COPD and IHD.[6,8] Additionally, the combination of statins with ACEIs or ARBs, as described earlier, has shown reductions in the incidences of CV events, pulmonary morbidity, and total mortality in high−CV risk COPD patients.[1,2,6,8,12,13] In summary, the use of ACEIs and ARBs is supported in treating patients with COPD and/or CVD. These therapies may have a dual cardiopulmonary protective effect[2] and potentiate a reduction in RAAS-mediated pulmonary inflammation and oxidative stress.

Antithrombotic therapies

Anticoagulants and antiplatelet therapies are used to prevent thrombotic events and reduce the incidence of mortality in individuals with CVD. Patients with severe COPD are at an increased risk of acquiring secondary venous thromboembolism. Thus, anticoagulants, such as warfarin or non−vitamin K oral anticoagulants, may help reduce the incidence of thrombosis-related morbidity and mortality in at-risk COPD patients.[6,12] Antiplatelet therapy in the management of patients with COPD and/or CVD has been investigated in multiple trials. A systematic review and meta-analysis of these studies found that antiplatelet agents significantly reduced the incidence of all-cause mortality in COPD patients (OR, 0.81; 95% CI, 0.75-0.88).[19,54] Similarly, a national prospective study demonstrated that antiplatelet therapy increases the likelihood of survival in COPD patients (HR, 0.86; 95% CI, 0.75-0.99; P = 0.030).[19,55] The **Plat**elet Inhibition and Patient **O**utcomes

(PLATO) multicentre RCT demonstrated that antiplatelet therapy significantly reduces the risk of the occurrence of ischemic events in COPD patients (HR, 0.72; 95% CI, 0.54-0.97).[19,56] In summary, the use of antithrombotics and/or antiplatelets is supported in patients with COPD and/or CVD, and they may reduce the incidences of ischemic events and mortality.

Diuretics

Diuretics, particularly loop diuretics, play a crucial role in managing symptoms of venous congestion in HF. Loop diuretics also are prescribed in COPD patients who do not have left-sided HF, to minimize venous congestion secondary to cor pulmonale.[48] This congestion can exacerbate lung-function decline and obstructive physiology. Moreover, the titration of HF medications, including diuretics, to reduce pulmonary artery pressure has been linked to a decreased incidence of hospitalization due to respiratory infections.[19] Improved management of HF, including appropriate diuretic use, also has been associated with a reduced risk of COPD exacerbation. In a comparative-effectiveness study on patients with hypertension and COPD, findings revealed that a combination therapy involving a thiazide diuretic significantly decreased the risk of hospitalization for congestive HF among patients without a prior history of the condition.[19,57] This approach included use of a thiazide diuretic and a β-blocker (adjusted HR, 0.49; 95% CI, 0.32-0.75), a thiazide and ACEI and/or ARB (adjusted HR, 0.50; 95% CI, 0.35-0.71), as well as a thiazide and CCB (adjusted HR, 0.55; 95% CI, 0.35-0.88), compared with a β-blocker and ACEI and/or ARB therapy.[57] In summary, use of diuretic therapy is supported in patients who have both COPD and CVD, and it may indirectly reduce exacerbation through its favourable impact on HF. However, potential diuretic use—associated side effects are important to recognize—eg, hypokalemia, elevated partial pressue of carbon dioxide (pCO_2) levels, metabolic alkalosis, and decreased cardiac output. Given this context, personalized treatment strategies are required when considering the specific type and dosage of diuretics that are appropriate to use for an individual with both COPD and CVD.[19]

CCBs

The aim of CCB use is to lower blood pressure by inducing vasodilation. In a recent retrospective cohort study, non-dihydropyridine (non-DHP) CCBs were found to be inferior to β-blocker therapy for treating AF patients with concurrent mild COPD. The β-blocker group showed a decreased risk of COPD exacerbation, compared to the risk in the non-DHP CCB group (HR, 0.75; 95% CI, 0.66-0.85).[58] In summary, CCB use is supported in patients with COPD and CVD patients, for whom they may reduce the risk of exacerbation.

Mineralocorticoid receptor antagonists (MRAs)

The impact of MRA use on COPD has been investigated in the context of HFrEF with HF subgroups in which patients also had COPD. The studies suggest that MRAs may contribute to improved outcomes in these patients. Experimental studies have demonstrated beneficial effects of MRA use in rodent models of pulmonary hypertension, in which MRA use led to improved heart function, protective effects against pulmonary vascular remodelling, reduction of pulmonary inflammation, and prevention of fibrosis.[59,60] These effects are critical, as both inflammation and fibrosis are common pathologic features in COPD.[61] In summary, although use of MRAs shows potential therapeutic benefits in conditions related to COPD, particularly in the context of HF and pulmonary hypertension, direct evidence focused specifically on COPD patients is limited.

Angiotensin receptor/neprilysin inhibitors (ARNIs)

ARNIs combine an ARB and a neprilysin inhibitor to mediate favourable cardiac benefits to patients with HF. Valsartan promotes vasodilation, whereas sacubitril inhibits the destruction of natriuretic peptides, such as brain natriuretic peptide and atrial natriuretic peptide, thereby increasing natriuresis, diuresis, and vasodilation.[62] The use of ARNI in patients with right HF and COPD reveals that neprilysin inhibition, and the subsequent increase of the level of natriuretic peptides, may be beneficial in patients who have both COPD and CVD. In addition to their vasodilatory effects, natriuretic peptides exhibit antiproliferative properties, which may provide a therapeutic benefit in the management of pulmonary arterial remodelling and hypertension, which occur frequently in patients with COPD.[62] Increasing the activity of natriuretic peptides also may induce immunosuppressive action for patients with COPD and acute lung injury caused by exacerbation.[62] In summary, the use of ARNI therapy is supported in patients who have both COPD and CVD, for whom it may produce vasodilatory and antiproliferative activity in pulmonary vessels.

Sodium-glucose transporter 2 (SGLT2) inhibitors

Use of SGLT2 inhibitors is indicated for the treatment of diabetes and HF. These agents inhibit SGLT2, which is responsible for reabsorbing sodium and glucose in the renal proximal convoluted tubule, leading to the excretion of glucose and sodium.[48] Although SGLT2 inhibitors initially were evaluated and approved for individuals with diabetes, subsequent landmark HF studies demonstrated that SGLT2 inhibitors reduce the incidences of HF hospitalization and mortality, irrespective of the left-ventricular ejection fraction and the diagnosis of diabetes. A meta-analysis of large SGLT2 inhibitor RCTs has demonstrated a significant reduction in the occurrence of various noninfectious respiratory disorders, including acute pulmonary edema, asthma, and sleep apnea syndrome. This work also demonstrated a trend toward a reduced risk of COPD; however, this trend was not statistically significant.[48,63] SGLT2 inhibitors have been shown to have benefits across various organ systems, which could influence COPD outcomes indirectly. These benefits include CV, renal, and metabolic improvements, as well as the possibility of a reduction in pulmonary congestion.[48,64] In summary, although preliminary evidence suggests that SGLT2 inhibitors may have a positive impact on COPD, particularly through the reduction of pulmonary congestion, further research is necessary to confirm these findings and elucidate the mechanisms involved (Fig. 3).

Impact of COPD Medications on Reduction of Mortality Incidence: The Promise of Combination Therapies

Following a severe COPD exacerbation, the rate of subsequent exacerbations increases, and the time between exacerbations decreases.[11] In addition, the mortality risk increases. The mortality incidence among patients discharged from the hospital can be as high as 6.1% within 90 days of admission, and as high as 11.1% when mortality incidence is assessed as a combination of in-hospital and 90-day postdischarge mortality.[11] An increased risk of mortality persists for up to 1 year following a severe COPD exacerbation. In a recent United Kingdom study, the authors found an immediate period of CV-event risk post any exacerbation, with HRs being highest at 1-14 days following severe exacerbations (adjusted HR, 14.5; 95% CI, 12.2-17.3) and at 14-30 days following moderate exacerbations (adjusted HR, 1.94; 95% CI, 1.63-2.31).[65] The heightened level of risk remains high even beyond 1 year (adjusted HR, 1.84; 95% CI, 1.78-1.91).[65] As a result, a major focus of therapy in this patient population involves treatments to reduce the incidence of exacerbations, as a means to preserve lung function, improve QoL, and reduce the incidences of mortality and CV events.[11] This area of study is less familiar to cardiologists, and an appreciation of the advancements that have taken place recently is relevant for practicing clinicians. Recent landmark COPD bronchodilator studies with a focus on reducing the incidences of mortality and CV events are summarized.

The Towards a Revolution in COPD Health (TORCH) study

The 2007 TORCH study was a landmark trial in the field of COPD management and was the first international study in this field to use all-cause mortality as the primary outcome measure.[10,15] This large, randomized, double-blind, placebo-controlled trial evaluated the long-term efficacy of use of an inhaled corticosteroid (ICS), specifically fluticasone propionate, in combination with the long-acting β2-agonist (LABA) salmeterol. The trial enrolled more than 6000 patients who had moderate-to-severe COPD, and it followed them over a period of 3 years. The primary endpoint of the TORCH study was the assessment of use of ICS and LABA combination therapy on all-cause mortality incidence, as well as its impact on the frequency and severity of COPD exacerbations. The results of this study demonstrated a reduction in the annual rate of moderate-to-severe exacerbations and an improvement in FEV1 among patients treated with the ICS and LABA combination. In addition, a 17.5% reduction occurred in the incidence of death, for the dual-therapy group vs the placebo group.[15] The HR for death in the dual-therapy vs the placebo group was 0.825 (95% CI, 0.681-1.002; $P = 0.052$, adjusted for the interim analyses).[15]

The results of the TORCH study did not impact clinical practice, because the primary endpoint (reduction in all-cause mortality incidence) did not reach the level of statistical significance.[15,66-68] An important point to note is that the patient population in the TORCH study was not enriched for a high-risk population, which may have contributed to the resulting lack of achievement of this primary endpoint.[11,66-68] Subsequent analyses of the TORCH study, however, have demonstrated that a significant reduction occurred in the incidence of respiratory and CV mortality, with use of the ICS and LABA combination in a higher-risk population with moderate COPD.[11,66-68] The TORCH study was the first bronchodilator study to suggest that a CV benefit may be derived from an ICS and LABA dual therapy in patients with COPD, particularly those with moderate COPD.

The Study to Understand Mortality and Morbidity in COPD (SUMMIT) study

The SUMMIT study sought to advance the learnings gained from the TORCH study in the use of dual bronchodilator therapy in patients with COPD.[16,69] This study investigated the effect of inhaled fluticasone furoate and/or vilanterol (FF and VI), a newer-generation ICS and LABA combination, as compared to the fluticasone propionate that was investigated in the TORCH study. The SUMMIT study population included patients with moderate COPD, and this population was enriched with patients who also had an established history of CVD or were at an increased risk for acquiring CVD. The study aimed to evaluate the impact of ICS and LABA combination therapy on COPD-related mortality, exacerbation rates, and lung function.[11,16,69] The results of the SUMMIT study revealed that FF and VI dual therapy significantly reduced the rate of moderate or severe COPD exacerbations and reduced declining lung function, as compared to placebo.[16,69] Similar to the results in the TORCH study, a nonsignificant reduction occurred in the incidence of all-cause mortality, of 12%, in the dual-therapy vs the placebo group (HR, 0.88; 95% CI, 0.74-1.04; $P = 0.137$).[16,67,69] The potential reasons for the nonsignificant outcome of the SUMMIT study include a significiant proportion of patients enrolled with mild COPD, and the study power, with the assumption of a 30% reduction in mortality.[67]

Despite nonsignificant primary outcomes, the TORCH and SUMMIT studies contributed to a growing volume of evidence supporting use of ICS and LABA combinations in the management of COPD, particularly in patients with established CVD.[11] These studies demonstrated a reduction in exacerbation rates, and improvements in lung function, further demonstrating the role of ICS use in the comprehensive care of COPD patients.[15,16] Although these studies failed to show a statistically significant benefit on the incidence of survival, they did demonstrate nonsignificant reductions in mortality incidence. Neither study required a history of frequent or severe COPD exacerbations for participant entry, and as a result, they did not include a patient population that had a sufficiently high risk of death from COPD to establish a significant mortality benefit.[11,15,66-69] This issue was addressed in the subsequent InforMing the Pathway of COPD Treatment (IMPACT) and **E**fficacy and Safety of Triple **Th**erapy in **O**bstructive Lung Di**s**ease (ETHOS) studies.[11]

Triple Therapy

Triple bronchodilator therapy (Table 1), involving a combination of ICS, LABAs, and long-acting muscarinic

Table 1. Components of triple therapy and mechanisms of action related to chronic obstructive pulmonary disease and cardiovascular disease[11,13]

Therapy	ICS	LABA	LAMA
Function	Reduces inflammation	Increases bronchodilation	Decreases bronchoconstriction
Mechanism	Binds to the C-terminal of glucocorticoid receptors, inhibiting the synthesis of inflammatory proteins; ICS also induces β2-adrenoreceptor expression, suppresses airway inflammation, and reduces serum CRP levels	Stimulates β2-adrenoreceptors on smooth muscle cells in the airways; activation of these receptors leads to the relaxation of smooth muscle in the airways; this results in the dilation of the airways, improved airflow, and reduced airway resistance	Blocks endogenous cholinergic tone through the inhibition of acetylcholine, which acts primarily on muscarinic receptors on airway smooth muscle cells; by inhibiting this, LAMAs prevent smooth muscle contraction in the airways; the relaxation of smooth muscle leads to dilation of the airways, improving airflow and reducing airway resistance

CRP, C-reactive protein; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist.

antagonist (LAMAs) in a single inhaler, has respiratory and CV benefits.[11,13] By combining the anti-inflammatory properties of corticosteroids with the bronchodilatory effects of LABAs and LAMAs, triple therapy addresses the airway inflammation and smooth-muscle constriction that is associated with COPD. Concurrently, the therapy has a positive impact on CV outcomes by reducing the incidences of inflammation and CV morbidity.[13]

Given the positive mortality trends and the reduced incidence of CV events seen in the TORCH and SUMMIT studies of dual therapies, the IMPACT and ETHOS studies aimed to investigate the effectiveness of ICS-containing triple therapies in reducing exacerbations in a broader COPD population. In these trials, more-definitive data and clinical endpoints were collected, compared with their dual–bronchodilator therapy study predecessors.[67,68,70,71] The ETHOS and IMPACT studies both assessed the risk of all-cause mortality as, respectively, a prespecified secondary endpoint, and another endpoint.[11,68,70]

The IMPACT and ETHOS Triple-Therapy Studies

The IMPACT study

The 2018 IMPACT study, with its primary focus on the annual rate of on-treatment moderate or severe exacerbations, has advanced our knowledge of COPD management.[11,70] This large-scale trial compared a once-daily single-inhaler triple therapy, consisting of the ICS fluticasone furoate, the LAMA umeclidinium, and the LABA vilanterol, to dual-therapy regimens in patients with COPD. The once-daily triple therapy significantly reduced the annual rate of moderate or severe exacerbations, as compared to the dual-therapy regimens (involving either fluticasone furoate and vilanterol or umeclidinium and vilanterol), similar to the therapies investigated in the TORCH and SUMMIT studies. Additionally, this triple therapy showed improvements in FEV1 and various QoL scores, highlighting its comprehensive benefits in COPD management. Most notably, the study found that the triple therapy significantly reduced the risk of all-cause mortality (both with on- and with on- and off-treatment), emphasizing its potential to improve long-term outcomes in COPD patients.[11,67,70] The triple-therapy HR for death was 0.72 (95% CI, 0.53-0.99; $P = 0.042$), compared to that for the dual therapy, which was 0.89 (95% CI, 0.67-1.16; $P = 0.387$), and independent adjudication confirmed that the rates of CV and respiratory death were lower.[67]

The ETHOS trial

The 2020 ETHOS trial, which investigated the effects of triple inhaled therapy, at 2 glucocorticoid doses of budesonide and glycopyrrolate and formoterol, provided further clarity on the benefits of ICS use for COPD patients.[68,71] As with the IMPACT study, the ETHOS study sought to evaluate the annual rate of on-treatment exacerbations. The study enrolled a well defined population with moderate-to-very-severe COPD, and its primary endpoint focused on the estimated mean number of moderate or severe COPD exacerbations per patient per year in the intention-to-treat population.[11,71]

The ETHOS study revealed that the triple therapy at both doses significantly reduced the annual rate of moderate or severe exacerbations, as compared to the dual-therapy regimens, involving glycopyrrolate and formoterol (24% lower: rate ratio, 0.76; 95% CI, 0.69-0.83; $P < 0.001$) and budesonide and formoterol (13% lower: rate ratio, 0.87; 95% CI, 0.79-0.95; $P = 0.003$).[71] These results are aligned with the findings of the IMPACT study, affirming the value of ICS-containing triple therapy in reducing COPD exacerbations.[11,68,71] The FEV1 and QoL improvements that occurred in the ETHOS trial also were consistent with those observed in the IMPACT study, and the study showed that triple therapy reduced the risk of all-cause mortality numerically.[11,68,71] In the final retrieved dataset, which included 99.6% of the intent-to-treat population, the risk of all-cause death in the 320-μg triple-therapy group was 46% lower than that in the glycopyrrolate and formoterol group (28 vs 49 deaths; HR, 0.54; 95% CI, 0.34-0.87; $P = 0.0035$) and 22% lower than that in the budesonide and formoterol group (28 vs 34 deaths; HR, 0.78; 95% CI, 0.47-1.30; $P = 0.1721$).[68,71]

Overall, the numerical risk reduction of on- and off-treatment all-cause mortality in the ETHOS study, the statistically significant reduction in the IMPACT study, and both reductions in risk of moderate or severe exacerbations contribute to accumulating evidence that ICS-based therapies can have a positive impact on the long-term outcomes of COPD patients.[11,67,68,70,71] Additional analyses were performed for both the IMPACT and ETHOS studies, to assess the mortality incidence reduction when near-complete (99%) vital status was obtained in the intention-to-treat population.[11,67,68,70] With the triple therapy, the incidence of all-

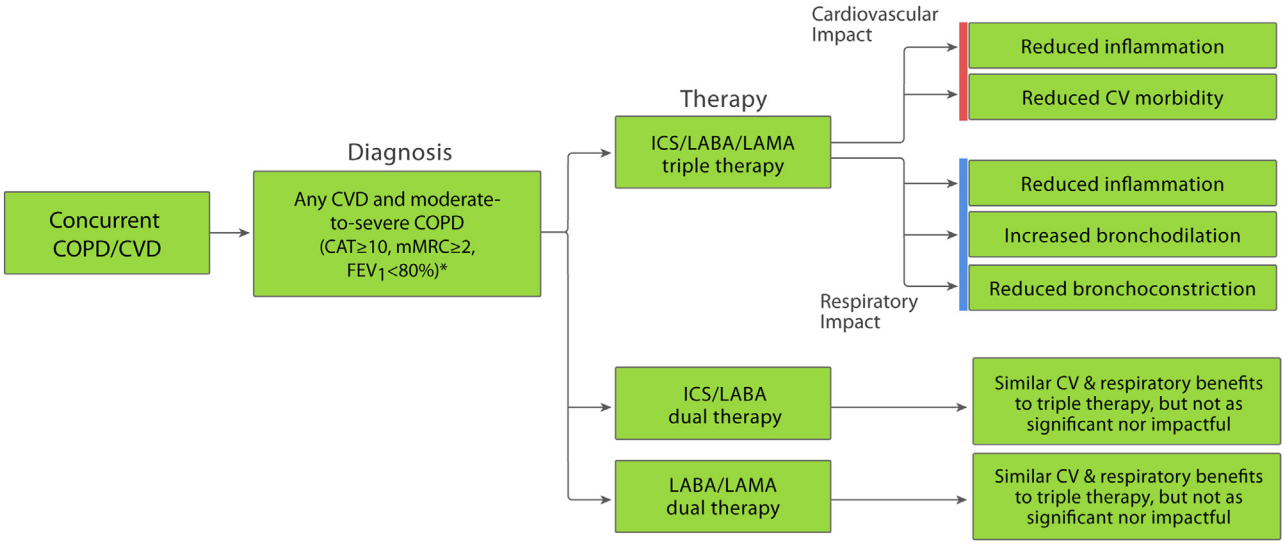

Figure 5. Summary of concurrent chronic obstructive pulmonary disease (COPD) and cardiovascular (CV) disease (CVD) therapy.[1-14,19,64-71] CAT, COPD assessment test; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified medical research council; QoL, quality of life. *Mild, moderate, and severe criteria for categorization of COPD populations appears as outlined by the Canadian Thoracic Society.[11]

cause mortality still was reduced, as compared to dual therapy, and lower rates of respiratory and CV death were confirmed.[67,68,70] These findings support the use of triple therapy in reducing exacerbations, enhancing lung function, and improving QoL, ultimately contributing to improved long-term survival outcomes for patients with COPD.[66-68,70,71] This conclusion is reflected further in the 2023 Canadian Thoracic Society Guidelines, which highlight the fact that triple therapy should be prescribed for patients with moderate-to-severe COPD, to reduce symptom burden, risk of acute exacerbation of COPD, and mortality incidence.[11]

Bottom Line: Reducing the Incidence of COPD Exacerbations Reduces the Incidence of CV Events

The presence of COPD exacerbations immediately increases the risk of subsequent exacerbations, mortality, and CV events, potentially due to inflammation and other shared mechanisms of these interconnected conditions.[11,65,68] Additional analyses of both the IMPACT and ETHOS studies demonstrate the importance of this finding, indicating that more-severe exacerbations increase CV risk, and that a reduction in exacerbations reduces the incidence of CV events. In the IMPACT study, these additional analyses prospectively confirmed a reduction in rates of on-treatment moderate or severe exacerbations using triple therapy, in patients at risk for future exacerbations.[67] This reduction in the rate of exacerbations was correlated with a decrease in the incidence of all-cause mortality.[67] Post hoc analysis of the IMPACT study results also evaluated the time-dependent risk of adverse CV events following exacerbations resulting in hospitalization or death, specifically for 1-30 days, 31-90 days, and 91-365 days after resolution of moderate or severe exacerbations. The risk was compared for the period before vs during and after exacerbation. Results demonstrate the following: the risk increased significantly during a moderate (HR, 2.63; 95% CI, 2.08-3.32) or severe (HR, 21.84; 95% CI, 17.71-26.93) exacerbation; the risk remained elevated for 30 days (for moderate—HR, 1.63; 95% CI, 1.28-2.08; for severe—HR, 1.75; 95% CI, 0.99-3.11; nonsignificant), and decreased over time, returning to baseline by 90 days.[16] The risk resulting in hospitalization or death also increased during an exacerbation (for moderate—HR, 2.46; 95% CI, 1.53-3.97; for severe—HR, 41.29; 95% CI, 30.43-56.03).[16] These results were consistent irrespective of exacerbation history, CV risk at screening, or study treatment. Therefore, the overall risk of CV events was higher during and in the 30 days following COPD exacerbations, even among those with a low CV risk. This finding emphasizes the importance of exacerbation prevention and of maintaining vigilance for CV events following exacerbations.[16]

Additional analyses of the ETHOS study emphasize that a reduction in the incidence of deaths from CV causes accounted for the majority of the treatment differences.[68] Triple therapy significantly reduced the incidence of CV and all-cause mortality.[68] In summary, the most common cause of death was CV in nature, in both the ETHOS and IMPACT studies. In addition, both studies correlate the occurrence of exacerbations with increased CV risk, and both report that fewer CV deaths occurred in the ICS groups, compared to the number in the dual-therapy groups.[71] Thus, a reduction in COPD exacerbations has been shown to reduce the incidence of CV events, underlining the promise of triple therapy in reducing the incidence of CV mortality in patients with COPD and CVD.[59,72]

Beyond the results of these trials, the evidence suggests that reducing exacerbations of COPD can decrease the risk of CV events. A meta-analysis found that the risk of acute MI and stroke significantly increases in the months following a COPD exacerbation (RR, 2.43; 95% CI, 1.40-4.20; RR, 1.68; 95%

CI, 1.19-2.38).[72] This finding indicates that prevention of exacerbations may reduce the risk of acute CV events.

Conclusion

The intricate relationship between COPD and CVD is marked by shared risk factors and pathologic mechanisms, resulting in an increase in the incidence of morbidity and mortality when these conditions coexist in a patient. Guideline-directed therapies for common CV conditions, including HF, IHD, arrhythmias, cerebrovascular disease, and hypertension, are highly advantageous and are well tolerated in patients with COPD, and these therapies should be prescribed when indicated. In addition, triple bronchodilator therapies for treatment of COPD have demonstrated a favourable CV signal, showing a reduction in the incidence of all-cause and CV mortality. With the evolving landscape of independent CVD and COPD therapies, an imperative is to identify patients who have both COPD and CVD, to provide pharmacologic options that reduce cardiopulmonary risk and thereby enhance patient outcomes and QoL (Fig. 5).

Ethics Statement

This is a systematic review and as such IRB review was not required.

Patient Consent

The authors confirm that patient consent is not applicable to this article, as it is a review of previously published studies.

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