REVIEW ARTICLE

Cardiopulmonary axis and cardiovascular mortality in patients with COPD

A. Calderón Montero

Health Centre Pedro Laín Entralgo, Madrid, Spain

Abstract Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of mortality in our environment and was usually considered to be confined to the lung territory. The latest studies suggest that it is a systemic disease whose most probable etiopathogenesis is a state of low-intensity chronic inflammation that worsens during exacerbations. And recent scientific evidence has highlighted that cardiovascular diseases are one of the main causes of hospitalisation and mortality in these patients. This relationship must be understood considering that both systems, the pulmonary and the cardiovascular, are closely related constituting the cardiopulmonary axis. Therefore, the therapeutic approach to COPD should not only include the treatment of respiratory complications, but also the prevention and treatment of cardiovascular diseases, which are very common in these patients. In this regard, studies have been carried out in recent years to analyse the effect of the different types of inhaled therapy on all-cause mortality and on cardiovascular mortality in particular.

Email: acalderonmontero@gmail.com

Introduction

Until recently, chronic obstructive pulmonary disease (COPD) was considered to be a condition strictly linked to the airway and lung. However, evidence from epidemiological studies and clinical trials has shown that it is a systemic disease in which cardiovascular disease (CVD) is a common reason for admission and one of the main causes of morbidity and mortality in these patients[1]. It is estimated that at least 40% of COPD mortality is due to cardiovascular causes[2], though this figure may be underestimated. The results of the *Lung Health Study* have already shown how CVD is responsible for 42% of first admissions of COPD patients and 48% of readmissions[3]. Likewise, exacerbations are one of the main causes of cardiovascular events in these patients[4].

The substrate on which this intimate relationship between COPD and CVD develops is the cardiopulmonary axis. Although the relationship between the respiratory system and the circulatory system has always been present, only in recent years have studies shown the importance of the axis and the cardiopulmonary continuum (Fig. 1). Since COPD, after CVD and cancer, is the fourth leading cause of mortality in our environment[5], it is essential to review the epidemiological evidence, physiological mechanisms, and early and appropriate therapeutic approach to cardiovascular complications in patients with COPD.

Relationship between COPD and CVD

The prevalence of CVD in COPD is currently sufficiently documented, but ranges from 15-70% depending on the studies and the selected populations[6,7], with heart failure (HF) being the main cause of mortality in patients with COPD[8]. The presence of CVD is associated with an increased risk of hospitalisation, longer length of stay, and higher all-cause mortality. In addition, the economic impact associated with CVD in this population is considerable, and the cumulative cost of treating comorbidities may exceed that of treating COPD itself[9].

Subclinical pulmonary functional impairment and CVD

The evidence supports that initial impairments in lung function are a risk factor for the development of CVD[10]. Data from the N HAN ES I study show that patients aged 40-60 years with a peak expiratory flow in one second (FEV1) of 63% have twice the risk of cardiovascular mortality and hospitalisation as compared to those with an FEV1 of 109%[11]. Even those with an FEV1 of 88%, which can be considered within the normal range, have a risk of cardiovascular events of 78% (RR 1.78, 95% CI 1.18-2.70) as compared to those with an FEV1 of 109%[11].

When considering dynamic lung function variables, the results of the ARIC study showed that an annual decrease of 1.9% in FEV1 or 2.1% in forced vital capacity (FVC) was independently associated with an increased incidence of left-sided HF[12]. Likewise, data from the cohorts of the CARDIA studies and from the ARIC study itself showed an association between cardiovascular accident and decreased FEV1 and FVC and decreased FVC, respectively[12,13].

Established CVD in COPD

A. Heart failure

The prevalence of COPD in HF ranges from 11-52%, while the prevalence of HF in COPD patients ranges from 10-46%[14,15]. In a large meta-analysis including 27 studies, the risk of HF in COPD was 2.57 (95% CI 1.90-3.47)[6]. The risk of admission for HF in COPD patients increases by 2.9 per year compared to non-COPD patients, and mortality is directly related to exacerbations[15].

B. Ischaemic heart disease:

The prevalence of COPD in patients with acute myocardial infarction (AMI) ranges from 7%-28%, but it is difficult to accurately determine this due to the different selected populations and different diagnostic criteria[16].
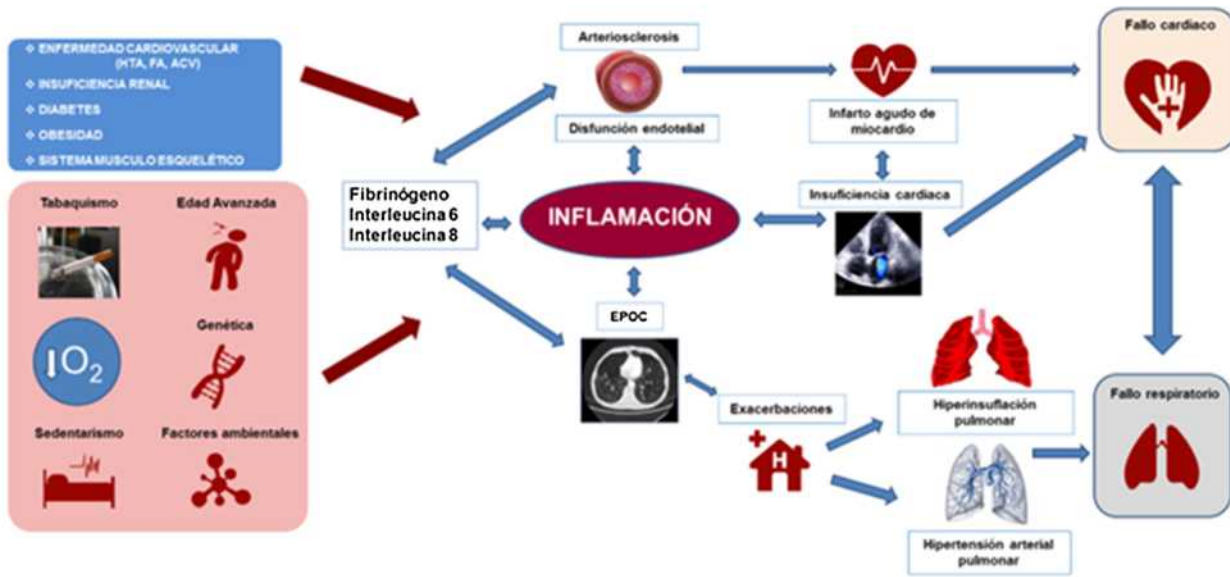
ENFERMEDAD CARDIOVASCULAR (HTA, FA, ACV)	CARDIOVASCULAR DISEASE (HT, AF, CVA)
INSUFICIENCIA RENAL	RENAL FAILURE
DIABETES	DIABETES
OBESIDAD	OBESITY
SISTEMA MUSCULO ESQUELÉTICO	MUSCULOSKELETAL SYSTEM
Tabaquismo	Smoking
Edad Avanzada	Advanced age
Genética	Genetics
Sedentarismo	Sedentarism
Factores ambientales	Environmental factors
Fibrinógeno	Fibrinogen
Interleucina 6	Interleukin 6
Interleucina 8	Interleukin 8
Arteriosclerosis	Arteriosclerosis
Disfunción endotelial	Endothelial dysfunction
INFLAMACIÓN	INFLAMMATION
EPOC	COPD
Infarto agudo de miocardio	Acute myocardial infarction
Insuficiencia cardiaca	Heart failure
Exacerbaciones	Exacerbations
Hiperinsuflación pulmonar	Lung hyperinflation
Hipertensión arterial pulmonar	Pulmonary arterial hypertension
Fallo cardiaco	Heart failure
Fallo respiratorio	Respiratory failure

Figure 1 Schematic of cardiopulmonary continuum. With permission from: Trinkmann F. et al.

Conversely, the relative risk of AMI in patients with moderate COPD is 1.40, and 3.00 in patients with severe disease[17]. The frequency and severity of exacerbations influence the risk of AMI, which is greater in severe than in moderate exacerbations (RR 2.58, 95% CI 2.26-2.95 and RR 1.58, 95% CI 1.46-1.70, respectively)[18]. Risk increase is not limited to hospitalisation, but is maintained in subsequent weeks, while troponin on admission is a predictor of AMI and cardiovascular mortality at discharge[19].

C. Arrhythmias

COPD is associated with an increased incidence of ventricular arrhythmias (VA), atrial fibrillation (AF) and sudden cardiac death (SCD)[20]. The severity of arrhythmias is related to the severity of COPD, age, exacerbations and airflow obstruction. Hypoxia, hypercapnia, nocturnal desaturation, direct myocardial damage, ventricular dysfunction, atrial dilatation, and drug treatments account for, at least partially, the high incidence of arrhythmias. Long-acting muscarinic antagonists (LAMAs) and long-acting beta-adrenergic agents (LABAs) as monotherapy appear to be safe in terms of arrhythmogenicity. However, there is little evidence of their safety in combination. Most trials evaluating the combination are not specifically designed to analyse cardiovascular safety and exclude high-risk patients with comorbidities and cardiovascular disease. In addition, information from real-life studies is also scant and inconclusive. On the other hand, short-acting beta-2-agonists (SABAs)

may have a greater predisposition to trigger arrhythmias by affecting the nodal refractory period[21].

Etiopathogenic mechanisms of the cardiopulmonary axis

The potential factors increasing the incidence of CVD in COPD patients can be divided into two groups (Table 1).

Common etiopathogenic factors

A. Smoking

Tobacco smoke is the main risk factor in the etiopathogenesis of COPD and is also one of the main risk factors for atherosclerotic disease, with a special impact on coronary ischaemia and peripheral arterial disease (PAD). Smoking triggers a systemic inflammatory response with increased oxygen-related stress, endothelial dysfunction, and atherosclerotic plaque development and progression predisposing to arterial disease[22].

B. Age

Age is related to both COPD and CVD. Some authors have recently considered COPD to be a disease linked to early and accelerated ageing of the lungs[23]. The lungs of the elderly have many structural and anatomical physiological changes similar to COPD. Endothelial cell senescence, decreased cell regeneration, and telomere changes are more common in COPD patients, particularly in those with emphysema[24].

Table 1 Etiopathogenic mechanisms involved in the development of cardiovascular diseases in patients with COPD

Common risk factors	COPD-dependent factors
Smoking	Low-intensity chronic systemic inflammation
Age	Platelet dysfunction Endothelial dysfunction Oxidative stress
Cardiovascular risk factors	Hypoxia
Environmental pollution	Hypercapnia
Overweight	Incomplete pulmonary development
Family history of CVD	Lung dysfunction Elastin breakdown
	Protease/antiprotease system imbalance Side effects of bronchodilators
	Underdiagnosis and undertreatment of CVD Accelerated cellular senescence
	Leukocytosis and monocytosis in COPD

CVD: cardiovascular disease.
Partially taken from: Qu S, Zhu J. A Nomogram for Predicting Cardiovascular Diseases in Chronic Obstructive Pulmonary Disease Patients. J Healthc Eng. 2022;2022:6394290.

C. Classic cardiovascular risk factors

Hypertension (HT), obesity, type 2 diabetes mellitus (T2DM), dyslipidaemia, and sedentary lifestyle occur more frequently in COPD patients than in the general population of the same age and sex. HT is the most common cardiovascular risk factor (CVRF) in COPD, being 1.71 times more common after adjusting for all other CVRFs (OR 1.71, 95% CI 1.37-2.13)[25]. Similarly, the prevalence of T2DM and metabolic syndrome (MS) is higher in COPD patients, especially in those with more severe disease (1.47, 95% CI 1.09-1.88)[26].

D. Environmental pollution

Exposure to environmental particles, especially small particles, has been related to a harmful effect on the lung and heart, increasing the incidence of CVD and exacerbating pre-existing lesions[27].

Intrinsic COPD factors

A. Systemic inflammation

The systemic inflammatory response of COPD is the main hypothesis relating it to CVD. Different studies have shown that biomarkers of systemic inflammation are higher in patients with COPD and concomitant CVD[28,29]. Biomarkers such as C-reactive protein (CRP) and fibrinogen are increased in COPD and are related to disease severity and increased morbidity and mortality[30]. Other inflammatory markers of CVD such as troponin and pro-BNP are also elevated, both during the stable phase and during disease exacerbations[31].

The consequences of this state of systemic subacute chronic inflammation are alteration of the arterial structure, with development, progression and ultimately detachment of the atherosclerotic plaque, the main mechanisms of acute coronary disease and peripheral arterial disease.

B. Platelet dysfunction

Platelet aggregation and reactivity and thrombocytosis are particularly relevant during exacerbations and in the weeks immediately after. Data from the SUMMIT study showed a ten-fold increase in the risk of suffering a cardiovascular event after an exacerbation (RR 9.9, 95% CI 6.6-14.9)[32]. In addition, thrombocytosis on admission is related to hospital mortality and mortality in the first year[33].

C. Endothelial dysfunction

Impaired endothelial function is more severe in patients with COPD than in patients without COPD. This endothelial dysfunction has been related to increased degradation of pulmonary and arterial elastin[34], though the ultimate cause is not well known. It is argued that this may be the result of an imbalance in the protease/antiprotease system, a circumstance that is also related to age. Endothelial dysfunction appears to positively correlate with severity of obstruction, inflammation, and prior exacerbations[35].

D. Hypoxia

Hypoxia, which is one of the major clinical consequences of COPD, enhances systemic inflammation, oxidative stress, fat cell production and cell adhesion to the endothelium,[36] all of which are predisposing factors for CVD. It also induces arterial remodelling, pulmonary endothelial dysfunction, and arterial vasoconstriction that increases pulmonary circulation pressure (PAH) and leads to right ventricular hypertrophy (RVH) and right atrial dilatation (RAD). RAD may predispose to severe arrhythmias, while RVH eventually causes right HF. Furthermore, hypoxia reduces oxygen supply to the myocardium, predisposing to coronary ischaemia and type 2 AMI (due to myocardial oxygen supply/demand mismatch).

E. Pharmacological treatments of COPD

COPD management has sometimes been linked to increased CVD, especially theophylline and inhaled beta-adrenergics (Table 2).

It is true that theophylline has virtually disappeared from drug treatment, while short-acting beta-adrenergic agonists (SABAs) and long-acting beta-adrenergic agonists (LABAs) are part of the background treatment. Stimulation by SABAs and LABAs of the adrenergic system could be a predisposing factor for arrhythmias and trigger HF, but this effect is minimised or absent with selective beta-2 drugs[24]. Inhaled corticosteroids, on the other hand, appear to reduce cardiovascular mortality, though they have been attributed to be a risk factor for AF and VA[37]. However, overall, the evidence from the studies shows that inhaled COPD therapy has no significant effect on the development of CVD, as reflected in the recently published 2023 GOLD guideline[38]. Results of the SUMMIT study show how LABA therapy alone or in combination with inhaled corticosteroids decreases FEV1 decline, and improvement of FEV1 correlates to a neutral or positive effect on CVD[30]. However, it should be noted that the evidence on the effects of COPD on CVD has some gaps, since most studies excluded patients with established CVD, so it is difficult to assess the effect of therapy in these patients, who, on the other hand, are very common in the COPD population.

F. Underdiagnosis and undertreatment of CVD in patients with COPD

The symptoms of CVD, particularly dyspnoea from HF, are often difficult to differentiate from dyspnoea due to respiratory failure, which often leads to underdiagnosis of HF and consequently to undertreatment. In addition, the chest pain of ischaemic heart disease in COPD patients is often atypical, which causes the same problems as in HF.

In the field of established ischaemic heart disease, there has been a controversy in the past about the use of beta-blockers and their possible deleterious effect on pulmonary function, so that some physicians are/were reluctant to use these drugs in patients with COPD. Evidence shows that use of beta-blockers in patients with ischaemic coronary disease and COPD is associated with a 27% decrease in cardiovascular and all-cause mortality (RR 0.73, 95% CI 0.60-0.90 and RR 0.77, 95% CI 0.61-0.97, respectively)[39]. In another study, survival was reduced by 50% in COPD patients admitted with AMI who were prescribed beta-blockers as compared to those not prescribed these drugs (RR 0.50, 95% CI 0.36-0.69)[1]. Despite the unquestionable evidence, observational studies in populations with AMI show that prescription at discharge of beta-blockers is 4-30% lower in COPD patients as compared to patients without COPD[19]. Thus, both underdiagnosis and undertreatment of drugs may be a cause of the greater prevalence and incidence of CVD in these patients.

Cardiovascular safety of COPD bronchodilator therapy

Standard bronchodilator therapy for COPD is based on inhaled beta-agonists, inhaled muscarinic antagonists, and inhaled corticosteroids, either as monotherapy or in combination.

Cardiovascular safety of beta-2-agonists as monotherapy

The available evidence of the effect of long-acting beta-2-agonists (LABAs) on cardiovascular safety is inconclusive. Beta-2-agonists increase heart rate and potassium levels and, in some studies, increase the incidence of cardiovascular events, such as ischaemic heart disease and arrhythmias, particularly in patients with severe airflow obstruction, with pre-existing HF and during the first weeks of treatment[40,41]. In contrast, in the SUMMIT study that included patients at high cardiovascular risk, vilanterol did not cause increased arrhythmias or cardiac complications compared to placebo.[42] Conflicting results are also available for short-acting beta-2 agonists.

On the other hand, beta-2-agonists improve hyperinflation, pulmonary function and hypoxia, so that cardiac haemodynamics of both the right chambers and the left ventricle may benefit[43].

Cardiovascular safety of long-acting muscarinic antagonists (LAMAs)

The evidence on the effect of LAMAs on cardiovascular events is not conclusive either. By inhibiting the parasympathetic system, they can induce tachyarrhythmias.[44] Cohort studies and meta-analyses do not confirm the above data and consider LAMAs safe in terms of cardiovascular risk[45,46]. A recent meta-analysis found no increase in cardiovascular events with LAMAs, while they may have a beneficial cardiovascular effect by increasing FEV1, decreasing exacerbations, and improving hypoxia[47].

Safety of dual bronchodilator therapy

A. LABA and LAMA combination

Dual therapy is a common strategy in COPD patients. In principle, since they act by stimulating the sympathetic system and inhibiting the parasympathetic system, the potential adverse cardiovascular effects could be additive. The safety results of LAMAs in combination were initially discordant, though with a majority of studies showing their cardiovascular safety versus those suggesting a greater risk[48].

Table 2 Potential cardiovascular effects of drugs used in the treatment of COPD[13] (Adapted)

Treatment	Respiratory effects	Potential cardiac effects	Evidence
LABAs	Improved airflow obstruction Decreased dyspnoea Increased exercise tolerance	Myocardial ischaemia Arrhythmias QT prolongation	Overall, they have not been shown to increase the risk of cardiac events, although they may induce arrhythmias in patients with established HF, so it is recommended to individualise treatment
LAMAs	Decreased dyspnoea Reduced exacerbations Increased exercise tolerance	Arrhythmias Acute myocardial infarction Heart failure	In some studies, they have been associated with a higher incidence of arrhythmias and mortality, but the evidence is poor and therefore they are considered safe
ICS + LABAs	Improved airflow obstruction Decreased dyspnoea Reduced exacerbations Improved exercise tolerance	Inhaled corticosteroids can worsen established HF while having a protective effect on AMI	The evidence for worsening HF is insufficient and further studies are needed.
Theophylline	Broncodilatator	Arrhythmias	Predispose to arrhythmias at high doses. They also induce ectopic beats and sinus tachycardia at low doses.
Roflumilast	Improved lung function	Arrhythmias (AF)	There is no evidence of adverse cardiovascular effects

LABAs: long-acting beta-adrenergic agonists; LAMAs: long-acting muscarinic antagonists; ICS: inhaled corticosteroid.

In a recent meta-analysis of Zhang, no increased incidence of arrhythmias, stroke, ischaemic heart disease or HF was found when using the combination of LABAs and LAMAs[49], which is consistent with recent recommendations of the 2023 GOLD guideline[38]. In any case, further studies specifically designed to assess cardiovascular safety are needed, and in the meantime treatment should be individualised, with special attention in patients with prior HF.

B. Inhaled corticosteroids as monotherapy and in combination

The post hoc analysis of the EUROSCOP study showed that after a three-year follow-up, 800 µg/day of inhaled budesonide reduced the incidence of ischaemic heart disease compared to placebo in a population with a FEV1 of 75% and average age of 52 years (3.0% vs. 5.3%; p = 0.048, 95% CI -4.7-0.0%)[50]. In the TORCH study, the combination of fluticasone and salmeterol showed a 17.7% reduction in all-cause mortality versus placebo (0.825, 95% CI 0.681-1.002; p = 0.052), with lower cardiovascular mortality in the salmeterol monotherapy group versus dual and fluticasone therapy alone[51]. Subsequently, the SUMMIT study found no differences in total mortality and cardiovascular mortality for the fluticasone/vilanterol combination versus placebo[52]. With regard to intermediate cardiovascular variables, the LABA/ICS combination reduces lung hyperinflation and, as a result, improves right ventricular function and left chamber volume[42,53]. In general, the combination of corticosteroids with LABA does not appear to increase cardiovascular risk, but has not been shown to reduce cardiovascular events either.
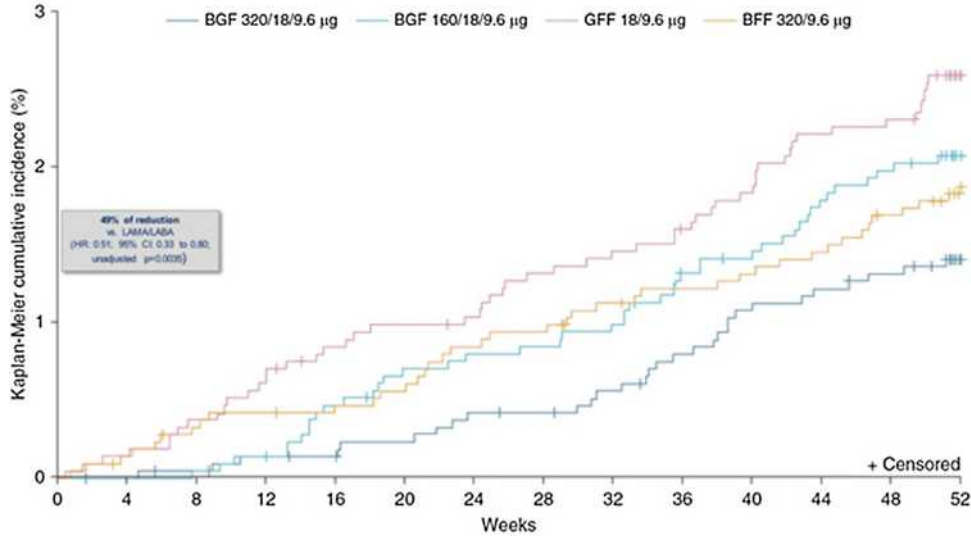
Triple therapy and cardiovascular mortality

The efficacy and safety of LABA/LAMA/ICS triple therapy has been evaluated in various clinical trials.

The TRIBUTE clinical trial[54] in patients with severe and very severe COPD with previous exacerbations found no significant differences in total mortality when comparing beclomethasone/formoterol/glycopyrronium versus indacaterol/glycopyrronium, though exacerbations were reduced by 15% in favour of triple therapy.

The IMPACT clinical trial (10,355 patients with COPD with FEV1 <50% and previous exacerbations) compared triple therapy with fluticasone/umeclidinium/vilanterol versus two dual therapies with ICS/LABA or LABA/LAMA. Triple therapy reduced the incidence of exacerbations, COPD-related hospitalisations and all-cause mortality by 28% (RR 0.72, 95% CI 0.53-0.99) compared to umeclidinium/vilanterol dual therapy[55]. With regard to cardiovascular mortality, the IMPACT study found no significant benefits in the

fluticasone/umeclidinium/vilanterol group versus the dual therapy group[56].

The ETHOS study included 8509 patients aged 40-80 years with FEV1 <50% and a history of exacerbations in order to compare two doses of triple therapy with formoterol/glycopyrronium/budesonide (320 or 160 µg) versus two dual therapies with LAMA/LABA and LABA/ICS. Seventy percent of the patients had at least one CVRF.

Kaplan-Meier cumulative incidence (%)	Kaplan-Meier cumulative incidence (%)
49% of reduction vs. LAMALABA (HR: 0.5t; 95% Ct: 0.33 to 0.80; unadjusted p= 0.0035)	49% reduction vs LAMA/LABA (HR: 0.5t; 95% Ct: 0.33 to 0.80; unadjusted p= 0.0035)
+ Censored	+ Censored
Patients at risk	Patients at risk
BGF 320/18/9.6 µg	BGF 320/18/9.6 µg
BGF 160/18/9.6 µg	BGF 160/18/9.6 µg
GFF 18/9.6 µg	GFF 18/9.6 µg
BFF 320/9.6 µg	BFF 320/9.6 µg
Weeks	Weeks
El riesgo de muerte con BGF 320 fue significativamente menor que con CFF (CRI. 0.51: intervalo de confianza del 95%. 0.33 -0.80; P sin ajustar = 0.0035)	The risk of death with BGF 320 was significantly lower than with GFF (HR 0.51; 95% confidence interval 0.33 -0.80; unadjusted P = 0.0035)
*Variable secundaria del estudio	*Secondary study variable
Martinez FJ, et al. Am J RespirCritCare Med. 2021;203:553-564	Martinez FJ, et al. Am J RespirCritCare Med. 2021;203:553-564

Figure 2 All-cause mortality in the ETHOS study[57].

Table 3 Causes of mortality in the ETHOS study[57] (Adapted)

	BGF 320/18-9.6 (n = 2137)	BGF 160/18-9.6 (n = 2121)	GFF 18/9.6 (n=2120)	BFF 320/9.6 (n = 2131)	All (n = 8509)
Total deaths					
Original dataset	30 (1.4)	44 (2.1)	52 (2.5)	38 (1.8)	164 (1.9)
Final retrieved dataset	37 (1.7)	55 (2.6)	64 (3.0)	46 (2.2)	202 (2.4)
Adjudicated deaths					
Original dataset	27 (1.3)	42 (2.0)	47 (2.2)	35 (1.6)	151 (1.8)
Final retrieved dataset	28 (1.3)	43 (2.0)	50 (2.4)	35 (1.6)	156 (1.8)
Cardiovascular	11 (0.5)	16 (0.8)	29 (1.4)	11 (0.5)	67 (0.8)
Respiratory	7 (0.3)	13 (0.6)	8 (0.4)	6 (0.3)	34 (0.4)
COPD	5 (0.2)	7 (0.3)	5 (0.2)	5 (0.2)	22 (0.3)
Pneumonia	2 (< 0.1)	3 (0.1)	3 (0.1)	1 (< 0.1)	9 (< 0.1)
Other	0	3 (0.1)	0	0	3 (< 0.1)
Cancer	2 (< 0.1)	6 (0.3)	3 (0.1)	7 (0.3)	18 (0.2)
Other	8 (0.4)	8 (0.4)	10 (0.5)	11 (0.5)	37 (0.4)
Unadjudicated deaths					
Original dataset	3 (0.1)	2 (< 0.1)	5 (0.2)	3 (0.1)	13 (0.2)
Final retrieved dataset	9 (0.4)	12 (0.6)	14 (0.7)	11 (0.5)	46 (0.5)

BFG: budesonide/formoterol/glycopyrronium; GFF: glycopyrronium/formoterol; BFF: budesonide formoterol.
Units of treatments in micrograms. Data are absolute values and percentages (%).

Triple therapy reduced exacerbations as compared to dual therapy, with a higher reduction in the budesonide 320 µg arm. In the post hoc analysis excluding missing cases, triple therapy with budesonide 320 µg significantly reduced all-cause mortality by 49% compared with dual therapy with LABA/LAMA (RR 0.51, 95% CI 0.33-0.80) and non-significantly by 28% versus ICS/LABA and triple therapy with budesonide 160 µg[57] (Fig. 2).

Cardiovascular mortality was also reduced with triple therapy with budesonide 320 µg (0.5%) versus LABA/LAMA (1.4%) and with triple therapy budesonide 160 µg (0.8%), and was similar to dual therapy with LABA/ICS (0.5%) (Table 3).

Consequently, the update of the 2023 GOLD guideline includes triple therapy as an effective treatment in reducing all-cause mortality in patients with symptomatic COPD according to the results of the ETHOS and IMPACT studies[38].

Potential mechanisms involved in mortality reduction with triple therapy

Pulmonary hyperinflation is one of the main consequences of COPD and has a significant impact on cardiac haemodynamics. Both triple and dual therapy have been shown to improve pulmonary function, decrease FEV1 decline and decrease pulmonary hyperinflation and, as a result, improve cardiac haemodynamic parameters, which indirectly could reduce cardiovascular comorbidity[58].

Triple therapy also improves hypoxaemia in COPD patients, which reduces pulmonary territory vascular resistance, decreasing right ventricular afterload and RAH, and increases cardiac output[59].

Third, both dual and triple therapy have been shown in different studies and populations to reduce exacerbations. During moderate and severe exacerbations, activation of pulmonary and systemic inflammation occurs, with an increase in inflammatory biomarkers, which are in turn implicated in the development and progression of atherosclerosis, cardiac arrhythmias, and HF.

Fourth, cardiac complications are closely related to the state of low-intensity chronic systemic inflammation that is one of the main pathophysiological mechanisms of COPD. The inflammatory state is more specifically related to the formation, progression and rupture of atherosclerotic plaque, and thus to ischaemic heart disease and stroke. The presence of corticosteroids in triple therapy could reduce systemic inflammatory activity and the atherogenic biomarker cascade. The reduction in cardiovascular mortality in ETHOS was superior in the budesonide 320 µg arm compared with budesonide 160 µg (Table 3)[57], suggesting a dose-dependent relationship with inhaled corticosteroids, consistent with the results of the EUROSCOP study[50].

Finally, studies with dual LABA + ICS therapy did not achieve benefits in terms of all-cause and cardiovascular mortality, while triple therapy, particularly the ETHOS study, has shown benefits in both variables. It should therefore be suggested that the combination of LAMAs with dual LABA + ICS therapy may have an added relevant

role in total and cardiovascular mortality, even more so considering that their benefit in monotherapy was previously demonstrated[60].

In summary, as a hypothesis, it may be suggested that triple therapy with budesonide 320 µg /glycopyrronium/formoterol provides a benefit in cardiovascular mortality as a result of improving cardiac haemodynamics by reducing hyperinflation and hypoxia and decreasing both chronic and acute systemic inflammatory activity during exacerbations.

Management of cardiovascular comorbidities in COPD

Beta-blockers

The use of beta-blockers (BBs) in COPD has always been controversial, despite the fact that HF guidelines have long recommended their use regardless of the presence of the disease. Inhaled beta-2 agonists stimulate bronchial wall receptors by producing bronchodilation, which may be reversed by non-selective beta-blockers such as propranolol. There is abundant evidence that this is not the case with selective beta-1 blockers such as bisoprolol, carvedilol, metropolol, or atenolol, which have a 20-fold greater affinity for beta-1 receptors than beta-2 receptors. Moreover, blockade of beta receptors could increase the expression and sensitivity of beta-2 receptors, converting the effect of BBs and beta-2 agonists into synergistic[61]. A systematic review showed that use of selective BBs in the presence of airflow obstruction does not cause an increase in exacerbations, worsen FEV1 or FVC, increase dyspnoea or cause other respiratory adverse effects[62], and furthermore, their use is associated with significant cardiovascular benefits also in patients with COPD, reducing mortality, hospital admissions, exacerbations and not increasing peri-hospital mortality[63,64].

Renin-angiotensin-aldosterone system (RAAS) inhibitors

RAAS inhibitors play a role in the etiopathogenesis of COPD through mechanisms such as proinflammatory activity and pulmonary fibrosis. Data from the *Multi-Ethnic Study of Atherosclerosis* including patients aged 45 to 84 years without CVD suggest that high-dose RAAS blockade protects against the progression of emphysema[65]. There is a disadvantage that angiotensin-converting enzyme inhibitors (ACEIs) frequently induce cough, so in another study they have been associated with increased airflow obstruction[66]. Therefore, although they appear to have a beneficial effect on COPD, their use should be individualised and AT2 receptor antagonists should be selected preferentially. A subanalysis of the PARADIGM-HF study has recently been published showing that the benefit of sacubitril valsartan versus enalapril is similar in patients with COPD and without COPD, so patients with COPD may benefit from this dual RAAS blockade[67].

Statins

The potential benefits of statins in patients with COPD are controversial in light of the existing evidence, but they appear to be safe and do not adversely affect pulmonary function.

Some studies show that statin use is associated with a decrease in long-term mortality in COPD patients as compared to those who did not use them, while other studies suggest a reduction in airflow obstruction and a slowing of FEV1 decline[68,69]. In a study in patients with HF comorbidity, no benefits in terms of morbidity and mortality were observed[70]. In any case, statins have anti-inflammatory effects that may be beneficial in COPD, and have clear and unequivocal indications for use in cardiovascular comorbidity, particularly atherosclerotic.

Antiplatelet drugs

Thrombocytosis and platelet dysfunction are present in COPD, particularly during moderate and severe exacerbations, and are a risk factor for atherothrombosis, stroke and ischaemic heart disease. Although the evidence is inconclusive, two studies appear to show a reduction in mortality in patients with COPD[33,71].

Other drugs used in cardiovascular comorbidity

Mineralocorticoid receptor antagonists (MRAs) are drugs of first choice in patients with HF and reduced ejection fraction, a common comorbidity in patients with COPD. A pooled analysis of the RALES (spironolactone) and EMPHASIS-HF (eplerenone) studies showed that the benefits of MRAs versus placebo on the primary endpoint of

cardiovascular mortality and HF hospitalisation are consistent between patients with and without COPD (RR 0.66 and 0.65, interaction p 0.93)[72].

Other recently introduced first-line agents for the treatment of HF include SGLT2 receptor inhibitors (SGLT2is). A recent meta-analysis including 1,292 patients with COPD showed that SGLT2is versus placebo reduced the composite endpoint of cardiovascular mortality and HF hospitalisation by 28% (RR = 0.72, 95% CI 0.60-0.86)[73]. With regard to safety, another meta-analysis analysing 86 cardiovascular adverse effects and 58 respiratory adverse effects showed that SGLT2is versus placebo reduced the incidence of six respiratory adverse effects, including COPD (RR 0.77, 95% CI 0.62-0.96), with no differences in the remaining 52[74].

Diuretics are used in the treatment of symptomatic HF. Although the evidence is not abundant, thiazides do not increase exacerbations or respiratory complications in patients with COPD, while the evidence on loop diuretics is less conclusive[75]. Therefore, the use of diuretics should be individualised, taking into account that the use of high doses can reduce hydration and hinder the expulsion of bronchial secretions.

Finally, a prothrombotic and procoagulant state is common in patients with COPD and in some phenotypes in particular. Therefore, in addition to antiplatelet drugs, anticoagulants may play an important role not yet well defined. A recent review of the effect of anticoagulants in patients with COPD suggests that they can reduce mortality without increasing the risk of major bleeding in these patients[76].

In conclusion, the association of cardiovascular disease in COPD patients is based on the common link of the cardiopulmonary axis. Cardiovascular comorbidity is very common in patients with COPD and markedly increases the risk of mortality and hospitalisation in these patients. Indeed, cardiovascular complications and HF in particular are the main cause of second admissions above respiratory causes. Therefore, reducing exacerbations using early intensive triple therapy may be the most effective therapy for reducing mortality and morbidity associated with the cardiopulmonary axis. Intensive management of cardiovascular disease in COPD patients is also very important, because most cardiovascular drugs have been shown to be safe and in many cases to reduce the incidence of cardiovascular events.

Ethical considerations

As this is a review, there is no research in humans.

Funding

Conflicts of interest

The author reports receiving fees as a consultant or speaker in the past five years for Astra Zeneca, Boheringer Ingelheim, Casen-Recordati, Daiichi Sankyo, Glaxo, Lilly, Novo Nordisk, Sanofi, and Viatris.

References