Review Article

Interventional Cardiology

COPD as a major risk factor for cardiovascular disease

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Received date: 06-Mar-2023, Manuscript No. FMIC-23-91113;
Editor assigned: 08-Mar-2023, PreQC No. FMIC-23-91113(PQ);
Reviewed date: 22-Mar-2023, QC No. FMIC-23-91113;
Revised date: 29-Mar-2023, Manuscript No. FMIC-23-91113(R);
Published date: 07-Apr-2023, DOI: 10.37532/1755-5310.2023.15(S16).403

Abstract

Chronic Obstructive Pulmonary Disease (COPD) is the fifth leading cause of mortality in the Western world. Approximately 35%-40% is due to cardiovascular complications in the broad spectrum of heart failure, atherosclerotic disease, arrhythmias, and sudden death. The underlying pathophysiological substrate is an alteration in the functioning of the cardiopulmonary axis by different mechanisms. Despite the evidence, COPD is not included as a specific entity in the different cardiovascular risk tables and calculators, which leads to an underestimation of risk and insufficient treatment, both in the field of inhaled bronchodilators and drugs. Commonly used in cardiovascular diseases. Recent intervention studies have revealed how cardiovascular complications exceed respiratory complications in some populations with COPD, and how new strategies are being developed with inhaled bronchodilator drugs potentially capable of modifying the course of the disease.

Keywords: COPD; Cardiovascular risk factors; Cardiovascular events; Triple therapy inhalation; Cardiopulmonary axis

Abbreviations: AF: Atrial Fibrillation; AMI: Acute Myocardial Infarction; BBs: Beta-Blockers; BNP: Brain Natriuretic Peptide; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-Reactive Protein; CVD: Cardiovascular Disease; CVR: Cardiovascular Risk; EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; ETHOS: Efficacy and Safety of Triple Therapy in Obstructive Lung Disease; EUROSCOP: European Respiratory Society Study on Chronic Obstructive Pulmonary Disease; GOLD: Global Initiative for chronic obstructive pulmonary disease; HF: Heart Failure; ICS: Inhaled Corticosteroid; LABA: Long-Acting-β2-Agonist; LAMA: Long-Acting Muscarinic Antagonist; MACE: Mayor Cardiovascular Events; MRAs: Mineralocorticoid Receptor Antagonists; NNT: Number of Patients to Treat; RAAS: Renin-Angiotensin Aldosterone System; RALES: Randomized Aldactone Evaluation Study; SCD: Sudden Cardiac Death; SGLT2: Sodium-glucose co-transporter type 2 inhibitors; SUMMIT: Study to Understand Mortality and Morbidity; COPD VA: Ventricular arrhythmias

Introduction

The estimation of Cardiovascular Risk (CVR) is one of the main activities of medical professionals to address the prevention and treatment of cardiovascular diseases. Since the early days of the Framingham cohorts, different scales and algorithms have been designed to estimate cardiovascular risk in populations and establish different strategies for both primary and secondary prevention. Likewise, the variables that have been incorporated into the different tables and algorithms have been changing as new evidence emerged. The Framingham risk tables incorporated the classic risk factors mainly for coronary diseases, such as age, arterial hypertension, gender, cholesterol levels, and smoking [1]. More recently, the SCORE risk estimate has been modified by stratifying four geographical areas in Europe, including a specific table for the population over

70 years of age that was not previously considered [2]. In addition, the current SCORE table estimates not only fatal coronary events but the 5- and 10-year risk of cardiovascular disease. Like the Framingham and other cardiovascular risk estimation tables [3], the variables included are mostly the classic risk factors with some variants. However, it is significant that pathologies as relevant to cardiovascular diseases as Chronic Kidney Disease (CKD) [4], are not always included in the estimation of cardiovascular risk. And in this sense, it is even more striking that Chronic Obstructive Pulmonary Disease (COPD) is not clearly defined as one of the main variables when estimating cardiovascular risk in the population [1-3].

Literature Review

COPD and cardiovascular disease

Unfortunately, until just a decade ago, COPD was considered a disease restricted to the lung territory and with little impact on other organic territories. In recent years, epidemiological evidence and experimental studies have revealed how COPD is a systemic disease with a low-intensity inflammatory pathophysiological basis, which increases during exacerbations [5,6]. This systemic activity entails the simultaneous affectation of other organs and especially the coronary and cardiovascular territory. It is estimated that at least 40% of COPD mortality is due to cardiovascular causes [7], though this figure may be underestimated. The results of the Lung Health Study have already shown how Cardiovascular Disease (CVD) is responsible for 42% of first admissions of COPD patients and 48% of readmissions [8]. Likewise, exacerbations are one of the main causes of cardiovascular events in these patients [9]. Even more, in a large meta-analysis including 27 studies [10], the risk of HF in COPD was 2.57 (95% CI 1.90-3.47), the relative risk of Acute Myocardial Infarction (AMI) in patients with moderate COPD is 1.40, and 3.00 in patients with severe disease compared with people without COPD and COPD is associated with an increased incidence of Ventricular Arrhythmias (VA), Atrial Fibrillation (AF) and Sudden Cardiac Death (SCD). Therefore, COPD is not only a risk factor for coronary heart disease and could affect all cardiovascular diseases. Data from observational and randomized studies show how cardiovascular mortality can reach up to 39% of all deaths in patients with COPD and how cardiovascular mortality in patients with moderate COPD exceeds mortality from lung cancer and respiratory causes (Figures 1 and 2) [11,12].

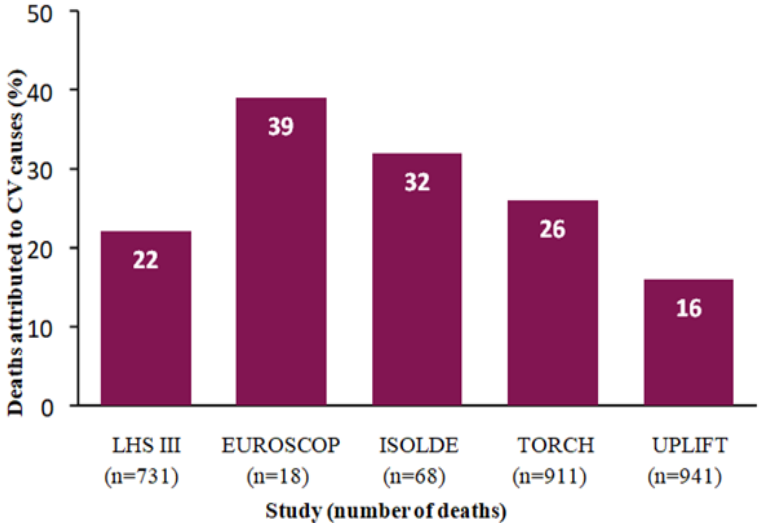

Figure 1: Cardiovascular events in COPD patients [11]. **Note:** (■) Respiratory causes

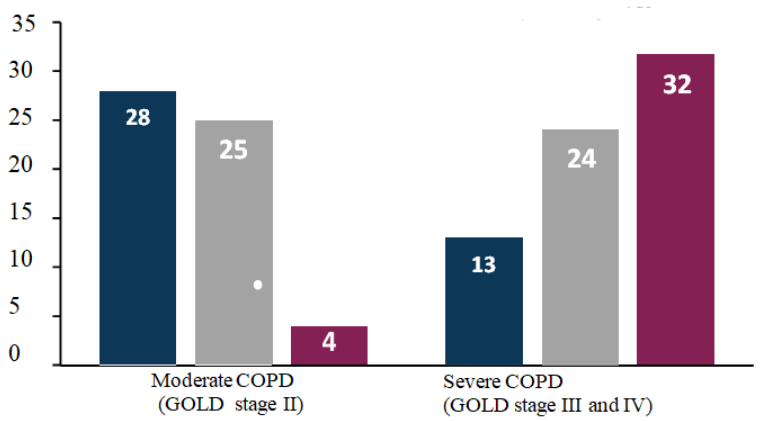

Figure 2: Comparison of causes of mortality according to GOLD stage [12]. **Note:** (■) Cardiovascular; (■) Lung cancer; (■) Respiratory causes

Based on all the evidence currently available, is no doubt that COPD must be considered a higher risk factor of cardiovascular complications and it is essential to include it in the risk estimation tables. It is true that the smoking habit is usually included in risk estimators, but it is no less true that the pathophysiology of COPD including other mechanisms dispose for cardiovascular disease in other ways than the dependents directly of tobacco. Consequently, it is necessary to know and understand the relationship between COPD and cardiovascular disease as an alteration of the cardiopulmonary axis [13], and thus adopt a new vision in the estimation of cardiovascular risk. And in that line, it is essential to keep in mind those therapeutic measures that can stabilize, delay and, where appropriate, reverse the alterations of the cardiopulmonary axis at least partially.

Cardiopulmonary axis alterations

Regardless of risk factors that COPD and cardiovascular disease share, such as smoking habit, age, cardiovascular risk factors, environmental pollution, overweight, and family history of CVD, some relevant factors are intrinsic COPD mechanisms.

Systemic low-intensity inflammation, moderate systemic inflammation during exacerbations, pulmonary insufflation, endothelial dysfunction, platelet alterations, and hypoxia plays a relevant role in the relationship between COPD and cardiovascular disease [13]. Biomarkers such as C-Reactive Protein (CRP) and fibrinogen are increased in COPD and are related to disease severity and increased morbidity and mortality. Other inflammatory markers of CVD such as troponin and pro-BNP are also elevated, both during the stable phase as well as exacerbations [14]. Data from the SUMMIT study showed a ten-fold increase in the risk of suffering a cardiovascular event after exacerbation (RR 9.9, 95% CI 6.6-14.9) [15]. In addition, thrombocytosis on admission is related to hospital mortality and mortality in the first year. 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 [16], all of which are predisposing factors for CVD. Furthermore, hypoxia reduces oxygen supply to the myocardium, predisposing it to coronary ischemia and type 2 AMI [17]. In older patients, low levels of lymphocytes have been observed to be associated with increased cardiovascular mortality due to heart failure [18]. Likewise, endothelial dysfunction, hypoxia, and neuroadrenergic activation common in COPD and obstructive sleep apnea syndrome are associated with increased development of atherosclerosis disease [19].

Therapeutic strategies that act on the cardiopulmonary axis

The reduction of all-cause mortality and cardiovascular mortality in particular should therefore be one of the priorities when considering the treatment of the patient with COPD. This treatment should be approached from a double perspective:

a) Optimize bronchodilator treatment with an effect on the cardiopulmonary axis to prevent cardiovascular complications.

b) Adapt cardiovascular treatment to the characteristics of the patient with COPD.

Bronchodilator treatment with effect on mortality: Most of the studies carried out on patients with COPD have been based on demonstrating the benefit of inhaled therapy on symptoms, lung function, exacerbations, and quality of life. Only recently have hard variables such as all-cause mortality and cardiovascular mortality begun to be considered as treatment goals.

Monotherapy and dual therapy have been evaluated with respect to all-cause mortality in observational and randomized studies with conflicting results. Two observational studies showed a reduction in all-cause mortality when dual therapy included an Inhaled Corticosteroid (ICs) combined with a Long-Acting-β2-Agonist (LABA), especially in those patients with prior exacerbations (HR 0.48, CI 95% 0.31-0.73 and HR 0.83, CI 95% 0.72-0.97 respectively) [20,21]. Randomized studies, however, did not demonstrate homogeneous results in terms of all-cause mortality reduction, including the SUMMIT study in which patients had a high cardiovascular risk profile (HR 0.88, 95% CI 0.74-1.04) [22].

In recent years, new trials have been published to test the possible benefit of triple bronchodilator therapy compared to dual bronchodilator therapy on all-cause mortality and cardiovascular mortality [23,24]. In a pooled analysis of three studies, a non-statistically significant benefit on all-cause mortality was found for ICs-containing versus non-ICS-containing regimens (HR 0.71, 95% CI 0.50-1.02) [23]. However, an interesting aspect was that, when analyzed by causes of mortality, as opposed to respiratory mortality, ICs- regimens did significantly reduce non-respiratory mortality (HR 0.62, 95%CI 0.43-0.97) [25]. Given that a significant percentage of non-respiratory mortality is of cardiovascular origin, it could be suggested that triple therapy has a beneficial effect on cardiovascular mortality.

This hypothesis has been at least partially endorsed in the ETHOS study. Briefly, the patients included in the study were classified as moderate to very severe with previously moderate or severe exacerbations in the year prior to inclusion. The study evaluated two types of triple therapy (budesonide/glycopyrronium/formoterol) in which the IC dose varied (budesonide 320 and budesonide 160) versus dual therapy and confirmed a reduction in all-cause mortality when comparing triple therapy with budesonide 320 versus dual therapy LABA+LAMA (Long-Acting Muscarinic Antagonist) (HR 0.51, CI 95% 0.33-0.80). Especially interesting was that 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 like dual therapy with LABA/ICS (0.5%) [24].

Different mechanisms may explain the beneficial effects of triple therapy on cardiovascular mortality in the ETHOS study. First,triple therapy has been shown to reduce exacerbations and improve pulmonary function and as a result, improve cardiac hemodynamic parameters, which indirectly could reduce cardiovascular comorbidity [23-26]. The frequency and intensity of exacerbations are directly related to the prognosis of the patient with COPD (Figure 3). Second, triple therapy also improves hypoxemia in COPD patients, which reduces pulmonary territory vascular resistance, decreases right ventricular afterload, and increases cardiac output [27]. Third, 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, suggesting a dose-dependent relationship with inhaled corticosteroids, consistent with the results of the EUROSCOP study [28]. Likewise, the effect of triple therapy on pulmonary hyperinflation improves cardiac hemodynamics as another possible additional mechanism of cardiovascular protection.

Therefore, cardiovascular mortality in COPD can be considered to have a multi- etiological origin. And as occurs in other cardiovascular pathologies such as heart failure or type 2 diabetes mellitus, triple therapy acts on the different alterations of the cardiopulmonary axis by different mechanisms, which produces a global effect greater than the sum of the individual therapies.

The importance of intervention with triple therapy has a double perspective from the cardiovascular point of view:

a) Firstly, the greatest benefits are obtained in patients in less advanced stages of COPD, which suggests that treatment should be instituted early, especially in those patients with a history of exacerbations and high risk and/or cardiovascular comorbidity.

b) The results of the studies with triple therapy allow for estimating the efficiency of the intervention by estimating the Number of Patients to Treat (NNT) to prevent events in comparison with other interventions widely implemented in the cardiovascular field (Table 1).

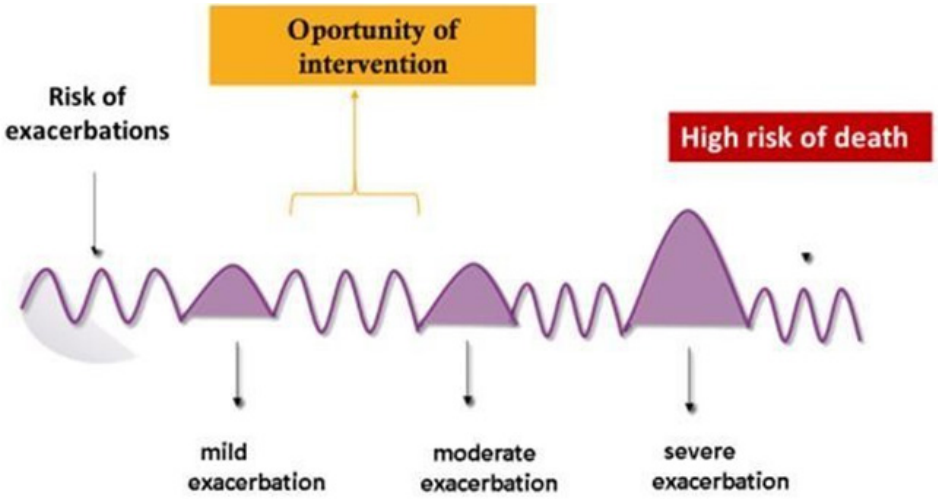

Figure 3: Impact of exacerbations on COPD patient mortality

Table 1: Number of patients Needed to Treat (NNT) for preventing cardiovascular events or all-cause mortality.

Disease	Intervention	Duration (years)	Outcome	NNT (CI 95%)	Reference
COPD	FF/UMC/VI vs dual therapy	1	All-cause mortality	121 (59, infinity)	[23]
COPD	BD/GLP/FOR vs dual therapy	1	All-cause mortality	80 (58-198)	[24]
Primary prevention	Atorvastatin vs placebo	5	MACE		[29]
			Low risk	146 (117-211)	
			High risk	53 (39-88)	
Diabetes	Dulaglutida vs placebo	5,4	MACE	67 (38-802)	[30]
Diabetes	Empaglifozina vs placebo	3,1	MACE	61 (31-2152)	[31]
Diabetes	Metformin vs diet	10	All-cause mortality	141	[32]
Tobacco	Smokers vs non-smokers	14,5	All-cause mortality	196	[33]

Note: COPD: Chronic Obstructive Pulmonary Disease; NNT Number of patients Need to Treat; MACE: Mayor Cardiovascular Events (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke); CI Confidence Interval; FF Fluticasone; UMC: Umeclidinium; VI: Vilanterol; BD: Budesonide; GLP: Glycopirronium; FOR: Formoterol.

Optimization of cardiovascular treatment in the patient with COPD: The prevention and treatment of cardiovascular disease in patients with COPD have often been controversial. On the one hand, the selection criteria for patients in randomized cardiovascular studies have frequently excluded patients with COPD, even more so in moderate or more advanced stages. On the other hand, observational studies and clinical practice conditions show that cardiovascular drugs are underused in these patients [34]. This may be another additional cardiovascular risk factor of the high cardiovascular morbidity and mortality of the patient with COPD, so it is essential to optimize treatments in this field.

Beta-Blockers (BBs) are indicated in patients with cardiovascular disease regardless of the presence of COPD according to the ESC guidelines. However, they are underused based on the risk of bronchospasm. 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.

Different studies show how selective BBs do not act negatively on the different pathophysiological mechanisms involved in cardiovascular complications in COPD, such as exacerbations, inflammation, worsening lung function, pulmonary hyperinflation, or hypoxemia [35,36]. Likewise, maintenance of beta-blocker treatment during hospitalization does not increase the length of stay or in-hospital mortality [37]. Consequently, they should be used under the same conditions as in patients without COPD, and thus avoid increasing the cardiovascular risk of these patients due to under treatment.

Blockade of the Renin-Angiotensin Aldosterone System (RAAS) may have a beneficial effect by inhibiting inflammatory products that contribute to pulmonary fibrosis. In general, AT2 receptor blockers should be preferred because of their lower incidence of coughing. A sub analysis 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 [38].

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

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 hospitalization are consistent between patients with and without COPD (RR 0.66 and 0.65, interaction p 0.93) [39].

Finally, a recent meta-analysis of SGLT2i receptor inhibitors (SGLT2i) including 1,292 patients with COPD showed that SGLT2i versus placebo reduced the composite endpoint of cardiovascular mortality and HF hospitalization by 28% (RR=0.72, 95% CI 0.60-0.86) [40].

Conclusion

Cardiovascular complications account for approximately more than 40% of morbidity and mortality in patients with COPD, especially in those with a moderate stage of the disease (stage II GOLD). And it is very important to know how they affect the broad spectrum of heart failure, arrhythmias, ischemic heart disease, stroke, and sudden death. Despite this, COPD is not considered in the cardiovascular risk tables, which should be modified, since it leads to an underestimation of cardiovascular risk and, as a consequence, a less proactive attitude with the consequent undertreatment. For this reason, it is essential to sensitize the group of physicians who treat these patients about the importance of optimizing treatments. The implementation of bronchodilators, preferably triple therapy, early, taking into account the options that showed higher reduction of mortality, should be apply as well as the treatment with cardiovascular drugs in similar conditions to patients without COPD.

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