# Should We Treat Chronic Obstructive Pulmonary Disease as a Cardiovascular Disease?

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## ABSTRACT

**Introduction:** Chronic Obstructive Pulmonary Disease (COPD) is characterized by largely irreversible airflow limitation and is associated with several extra-pulmonary manifestations and comorbidities. Cardiovascular diseases are among the most frequent comorbid conditions affecting patients with COPD and have important prognostic implications for hospitalisation and mortality.

In turn, COPD shares common risk factors with several cardiovascular diseases (i.e. smoking habit), while several features of COPD can predispose to cardiovascular disease (i.e. gas exchange abnormalities, polycythemia, systemic inflammation and sedentary lifestyle). Cardiovascular comorbidities in patients with COPD are under-recognised and undertreated and should be actively sought and treated according to usual guidelines.

**Areas covered:** This review will discuss the increased prevalence and prognostic implications of cardiovascular comorbidities in patients with COPD. The effect of COPD on the outcomes in cardiovascular disease will also be highlighted. The pathogenic mechanisms that underlie cardiovascular comorbidities in patients with COPD will also be reviewed. Finally, options for the management of cardiovascular comorbidities in patients with COPD will be discussed.

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## KEY ISSUES SECTION

- Cardiovascular comorbidities are highly prevalent in patients with COPD
- COPD is a well-known risk factor for the development of cardiovascular disease
- Cardiovascular complications are a major contributor to morbidity and mortality in COPD
- COPD has negative prognostic implications in patients with cardiovascular disease
- Cardiovascular comorbidities are under-diagnosed in patients with COPD
- COPD and cardiovascular disease share common risk factors
- Several features of COPD are associated with increased cardiovascular risk
- Cardiovascular comorbidities should be actively sought and treated in COPD according to usual guidelines
- Management of COPD should be moving from a reductionist approach to an integrated approach to define, identify, and treat the multiple organ involvement of this complex syndrome

## Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive and is associated with an abnormal inflammatory response in the lungs to noxious particles or gases[1]. The natural course of COPD is complicated by the development of extra-pulmonary manifestations and comorbidities that have important prognostic implications for hospitalisation and mortality[2].

Cardiovascular comorbidities are among the most frequent comorbid conditions affecting patients with COPD[3,4]. COPD is a well-known risk factor for the development of atherosclerosis and consequent cardiovascular complications[5*, 6].

The expiratory volume in the first second of a forced expiratory manoeuvre ($FEV_1$) is also known to be an independent predictor of cardiovascular complications in COPD[7]. Even a moderate reduction in $FEV_1$ increase the risk of morbidity and death and relate to cardiovascular events by two to three times[8-11].

Coronary artery disease is common[12*] and undertreated in patients with COPD[13]. Heart failure (HF) is also very prevalent in patients with COPD[14]. Patients with COPD have also increased risk for cardiovascular arrhythmias[15]. Atrial fibrillation (AF) is more frequent in patients with COPD following coronary artery bypass grafting than in the general population[16].

Cardiovascular disease is a major contributor to both morbidity and mortality in patients with COPD[7, 17-20]. The presence of HF is associated with increased mortality in COPD[21] and AF is an independent predictor of increased mortality and poor Health Related Quality of Life (HRQoL) in COPD patients, in comparison to the general population[22].

The presence COPD also has a negative effect on outcomes in patients with

cardiovascular disease. For example, cardiovascular events such as MI have worse outcome in patients with COPD in comparison to those without COPD[9, 13]. Several features of COPD have been thought to explain, at least in part, the increased prevalence of cardiovascular comorbidities (**Table 1**).

This review will describe the prevalence of cardiovascular comorbidities and the prognostic implications in patients with COPD. The mechanisms linking cardiovascular disease and COPD will be also reviewed and the options for the management of cardiovascular comorbidities in patients with COPD will be discussed.

## Prevalence of cardiovascular comorbidities in COPD

COPD is an independent risk factor for cardiovascular disease. Coronary artery disease (CAD) is very prevalent in COPD patients[23]. Analysis of a population-based cohort showed a higher prevalence of hypertension, diabetes mellitus and cardiovascular disease in individuals with airflow limitation of GOLD stage 3 and 4[24*]. In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort, Miller et al demonstrated an increased prevalence of cardiovascular comorbidities; including hypertension, angina, AMI, stroke, heart failure and arrhythmias; in patients with COPD in comparison to smokers and non-smokers with normal lung function[25*]. Interestingly, these associations were independent of the degree of airflow limitation. Moreover, in a population of patients with COPD with no symptoms or signs of cardiovascular disease, Iwamoto et al showed increased carotid intimal thickening, as a measure of subclinical atherosclerosis, when compared to smokers and non-smokers without airflow limitation[12*] (**Figure 1**).

The lung health study, in 1,916 mild to moderate patients with COPD, showed a

significant relationship between airflow limitation and incidence of cardiovascular comorbidities[7]. In addition, the National Health Interview Survey, including 18,342 subjects older than 40 years, showed that the presence of COPD increased the odds of cardiovascular disease by 2.7[26].

COPD is a well-known risk factor for the development of atherosclerosis and cardiovascular complications[4, 27-29] and is associated with increased arterial stiffness, a good predictor of vascular disease, independently of cigarette smoke exposure.

Systemic arterial stiffness is increased in COPD patients compared to non-smokers and smokers with normal lung function, even after correction for smoking history[30]. In fact, arterial wall stiffness is associated with emphysema independently of other factors such as smoking history. This suggests that COPD constitutes an independent risk for CAD[31**]. The same is true for airflow limitation since the $FEV_1$ is an independent predictor of death from myocardial infarction[2].

A large population-based study using the Atherosclerosis Risk in Communities (ARIC) cohort with 14 years follow up showed a crude increase in prevalence of cardiovascular events in individuals with COPD in comparison to controls[32]. Interestingly, the relative risks were markedly reduced after adjusting for covariates that included traditional cardiovascular risk factors, in contrast to the majority of work that has examined increased cardiovascular risk in COPD. These results suggest that this co-morbid condition may be mediated by the high prevalence of traditional risk factors in COPD. Indeed, both assumptions are supported by the literature. COPD and cardiovascular disease share common risk factors, such as smoking, that can contribute to the development of both conditions. Also, an enhanced inflammatory response in the lungs and systemically that occurs in COPD could contribute to the development of CVD in COPD patients[33].

Heart failure is common in COPD and COPD is common in heart failure. However, the association of COPD with left ventricular dysfunction is less well documented. By contrast, there is evidence that a reduction in the size of all four cardiac chambers occurs with increasing airflow limitation[34]. Emphysema is associated with impaired ventricular filling, reduce stroke volume and, consequently, a lower cardiac output[35]. This relationship of emphysema with cardiac function likely involves increased pulmonary vascular resistance and pulmonary hyperinflation[36]. Static hyperinflation showed a stronger association with cardiac chamber size than airflow limitation or the diffusion capacity for carbon monoxide [34].

One study[37] showed a prevalence of 20% for left ventricular dysfunction among COPD patients. In turn, heart failure appears to be under-diagnosed in patients with COPD[14].

Pulmonary arterial hypertension (PAH) is another cardiovascular manifestation in patients with COPD. Pulmonary hypertension has been associated with worse prognosis in COPD. The presence of pulmonary arterial hypertension in COPD constitutes a significant risk factor for acute exacerbation and hospitalization, and is associated with a worse survival[54, 55].

Approximately 50% of severe and very severe COPD patients have PAH[38] . Patients with mild disease do not commonly have PAH at rest but may develop PAH during exercise. Right ventricular hypertrophy, dilation and dysfunction is linked to worse outcome in COPD[39, 40] and can be present even with a slight increase in mean pulmonary arterial pressure[41]. A Spanish study assessing cardiovascular function after a first hospital admission for COPD identified that 64% of patients have cardiovascular dysfunction, 27% left- and 48% right-heart disorders, as assessed by heart ultrasound.

Pulmonary hypertension is usually mild in patients with COPD. In 1 to 3% of COPD patients, however, in whom pulmonary arterial pressure is very high (> 50mmHg) and is out of proportion to the severity of the airflow limitation, it behaves like idiopathic PAH[42].

**Prognostic implications of cardiovascular comorbidities in COPD**

The presence of cardiovascular comorbidities increases the risk of death in patients with COPD. Miller et al study on the ECLIPSE cohort showed that the survival probability was significantly reduced in those patients with cardiovascular comorbidities[25*] (**Figure 2**). Systemic arterial stiffness, an independent marker of cardiovascular risk[43, 44**] that is increased in COPD patients[30], is associated with cardiovascular mortality[45**]. Moreover, for every 10% decrease in $FEV_1$, cardiovascular mortality increases by approximately 28% and non-fatal coronary events increase by approximately 20% in mild to moderate COPD[7].

Hypertension, the most frequent cardiovascular comorbidity in COPD, also has implications for prognosis[46].

A study by Boudestein et al in a cohort of 405 patients with COPD showed that the presence of newly diagnosed heart failure significantly increased all-cause mortality independently of gender, age, history of ischaemic heart disease (IHD), hypertension, diabetes, atrial fibrillation, smoking history, and cardiovascular drug use[47].

While patients with myocardial dysfunction and co-morbid COPD have an increased mortality, impaired cardiac function can also contribute to reduced physical activity in COPD[48] which, in turn, is an independent prognostic factor for hospitalisations and mortality[49].

Left ventricular function assessed by echocardiography and N-terminal pro b-type natriuretic peptide (NT-pro-BNP - a biomarker of left ventricular strain) has a negative independent association with physical activity levels, after adjustment for GOLD stage or BODE score. A further study demonstrated an increase in NT-pro-BNP during ECOPD compared to recovery, and in particular in individuals who required admission to the intensive care unit[50].

A recent study of 186 consecutive patients with left ventricular systolic dysfunction in a heart failure clinic found that 39% had COPD diagnosed on spirometry, and those patients with heart failure and severe COPD had a worse prognosis than those with mild to moderate disease or normal lung function[21]. This higher mortality was again reported in patients with COPD compared to individuals without lung disease in a study of 800 patients hospitalized with cardiac failure[51].

There is an increased risk of death from myocardial infarction in COPD that is independent of age, sex and smoking history[23]. In a cohort of 14,703 patients with AMI from the Acute Myocardial Infarction Trial (VALIANT) study in which 8.6% subjects had COPD, all-cause mortality was increased in the COPD population (30%) in comparison to those patients without COPD (19%), a hazard ratio 1.14 (95% CI 1.02-1.28)[52].

In the ECLIPSE COPD cohort the presence of coronary artery calcification (CAC) on CT scan, a measure of atherosclerotic burden, was significantly higher in the COPD population than matched control subjects and was related to mortality[53**].

**Pathogenesis of the cardiovascular comorbidities**

COPD shares common risk factors with CAD such as cigarette smoking and older age. Cigarette smoking is the most important established risk factor for COPD and constitutes a major risk factor for other comorbidities.

The effects of smoking are possibly related to the following comorbidities or extra-pulmonary manifestations of COPD: heart failure, arrhythmias, hypertension, peripheral and coronary artery diseases, pulmonary vascular abnormalities, diabetes, osteoporosis, cancer, psychiatric disorders, muscle dysfunction/wasting, and infections[54].

Possible mechanisms relating cigarette smoking with cardiovascular comorbidities include increased systemic inflammation and oxidative stress, altered nitric oxide (NO) bioavailability and endothelial dysfunction[55-57]. However, the presence of COPD itself can constitute an increased risk for cardiovascular disease. In patients with COPD admitted due to an acute exacerbation, 8.3% had chest pain and/or serial ECG changes, fulfilling the 2007 universal definition of myocardial infarction[58]. Several features of COPD can be associated with increased cardiovascular risks, namely gas exchange abnormalities, polycythemia, systemic inflammation, lung hyperinflation and a sedentary lifestyle. **Figure 3** illustrates the interaction of the different pathogenic mechanisms leading to cardiovascular disease in association with COPD discussed below.

*Systemic Inflammation*

Systemic inflammation has been implicated in the pathogenesis of cardiovascular disease and endothelial dysfunction and the genesis of atherosclerotic plaques [59*]. In turn, several studies and a meta-analysis have shown that a proportion of clinically stable patients with COPD have evidence of persistent systemic inflammation[60].

Systemic inflammation, either as increased circulating cytokines, chemokines and acute phase proteins, or as abnormalities in circulating cells, has been shown in COPD patients, particularly when the disease is severe or during exacerbations[60, 61]. Moreover, platelet-monocyte aggregates increased during exacerbations of COPD[62]. Platelet activation may represent one mechanism by which inflammation may enhance cardiovascular risk in COPD.

Systemic inflammation in COPD is associated with an accelerated decline in lung function[63]. Elevated levels of circulating c-reactive protein (CRP), a marker of systemic inflammation, have been related to a reduced exercise tolerance and health related quality of life[64] and with increased risk of hospitalizations and mortality[65].

Several origins have been proposed for the systemic inflammation in COPD patients, namely an effect of smoking, “spill-over” from lung inflammation, skeletal muscle, hyperinflation and bone marrow as sources of systemic inflammation, and the effect of tissue hypoxia. There is direct evidence that protein movement occurs from the lung to lymph and blood. Experimental data indicate that alveolar macrophages and bronchial epithelial cells are critically important in processing inhaled noxious gases and particles, and that the mediators they produce are also identified in the systemic response in COPD[4]. Moreover, systemic inflammation is a recognized risk factor for a number of medical conditions that are associated with COPD. Thus, COPD and some

of the extra-pulmonary manifestations and comorbidities share the same risk factors. On the other hand, COPD may trigger inflammation, inducing a cause-effect relationship between COPD and some of its extra-pulmonary manifestations.

Systemic inflammation is now a recognised feature of COPD. Higher plasma fibrinogen during the stable phase has now been shown to independently predict exacerbation frequency[66]. However, in a study of subjects with moderate to severe COPD, CRP was not associated with survival, unlike airflow limitation and the BODE index[67].

A further analysis of the Lung Health Study investigated whether an imbalance of lung injury and repair (measured using serum highly sensitive CRP [hsCRP] and fibronectin respectively) could contribute to mortality[68]. In this large study of individuals with mild to moderate COPD followed for up to fifteen years, the ratio of fibronectin to hsCRP was significantly associated with all-cause mortality. A cross-sectional study of 2,553 patients with airflow limitation from the Framingham cohort showed further relationships between systemic inflammatory markers and severity of COPD[69]. There were negative associations between $FEV_1$ and CRP and IL-6, as well as p-selectin and ICAM, markers of endothelial function and predictors of cardiovascular risk.

Inflammation is integrally involved in the initiation and progression of chronic diseases such as CVD[70-72]. Therefore, systemic inflammation, a feature of COPD, may be a link between COPD and the increased risk of cardiovascular disease in these patients. However, the association between systemic inflammation and poor outcome should be interpreted cautiously. Descriptive studies show associations but do not prove causality. Moreover, the inflammatory response is complex and most of the studies only report a limited panel of biomarkers

*Vessel wall abnormalities and endothelial dysfunction*

Arterial stiffness is associated with increased emphysema, $FEV_1$ per cent predicted and systemic inflammation[31**]. A large case-control study confirmed previous findings of an increase in systemic arterial stiffness in COPD in comparison with age and sex matched controls[73]. Arterial stiffness can be assessed using carotid-femoral pulse-wave velocity (PWV), a measure that is predictive of cardiovascular events in healthy individuals and in patients with ischaemic heart disease. Increased arterial stiffness is associated with decreased coronary perfusion[74**]. Emphysema is thought to result from elastin degradation in the alveolar walls[75]. Recent evidence also suggests that increased arterial stiffness may also result from systemic elastin degradation in the arterial walls[76**]. Thus, lung and systemic elastin degradation may represent the mechanistic link between COPD and the increased risk of cardiovascular disease associated with this condition[30].

Endothelium function is usually assessed as the flow mediated dilation after reactive hyperaemia[77]. Early studies established that attenuated vascular responses occur prior to the development of atherosclerosis in response to a milieu of risk factors, thus making measurements attractive as a screening tool for cardiovascular risk[78]. A mechanistic study reported impaired brachial artery vasodilatation in patients with stable COPD in comparison with healthy smokers and non-smokers[79].

There has been further work examining the potential mechanisms of the increased cardiovascular morbidity and mortality associated with COPD, particularly related to abnormal systemic vascular function. However, some[79, 80], but not all[30], studies have demonstrated abnormal endothelial function in COPD patients in comparison with

smokers who have not developed COPD.

There seem to be, therefore, more evidence supporting the role of arterial stiffness in the development of cardiovascular disease in COPD than endothelial dysfunction for which the evidence is more controversial.

*Accelerated Ageing*

Ageing is among the greatest known risk factor for most chronic diseases[81]. Around 100,000 people worldwide die each day of age-related causes[82].

The number of changes in the body that occur with age is remarkably long and include changes in appearance, such as wrinkled skin, gradual reduction in height and weight loss due to loss of muscle and bone mass, decline in sexual activity (and menopause in women), and decline in the function of most organs such as renal, pulmonary, cardiac and cerebral function.

Similarities between features of COPD and the ageing lung suggest that COPD may be a condition related to accelerated ageing[83*]. A simple example of this is the association between emphysema and facial wrinkling[84]. Animal models of premature ageing show structural changes in the lungs and skeletal muscle that resemble those in COPD[85].

Lung function declines with ageing. An accelerated rate of lung function decline is a key feature of COPD[86]. It has been proposed that a decline in organ function (such as the lung) is a feature of ageing in response to the accumulation of molecular and cellular damage until the balance between cell death and cell replication (regeneration) is affected by the “intrinsic biological clock” that regulates the number of cell divisions. Therefore, any noxious exposure that increases cellular damage has the potential to

accelerate the process of ageing in a particular organ. Thus, noxious inhalants, such as cigarette smoke, accelerate these age-related events in the lung due to modification of proteins, reduction in anti-ageing molecules and/or stimulation of pro-ageing molecules[87].

Ageing itself is associated with chronic degenerative disorders and when compared to healthy controls, telomere length, a marker of cellular ageing, is reduced in smokers with normal lung function[88] and reduced further in COPD patients[89], particularly in patients with emphysema[90]. These events may enhance lung inflammation[79], since telomere shortening leads to cellular senescence and as a consequence enhanced inflammation in the lungs[91].

Exposure of human epithelial cells to cigarette smoke result in cell senescence as shown by an increase in the senescent markers, senescence associated β-galactosidase (SA-B-gal) and p21 protein[92]. Increased markers of cell senescence have been found in Type II epithelial cells and fibroblasts from emphysematous lungs[93, 94] that would contribute to the pathogenesis of COPD.

With increasing age the prevalence of cardiovascular disease increases by several times, and is the leading cause of death in people aged above 65 years and older. More than 80% of cases of coronary artery disease and more than 75% of cases of congestive heart failure occur in people over the age of 65 years[95].

Ageing is associated with several molecular, biophysical and biochemical changes in the heart[96, 97]. The predominant change that occurs in the cardiovascular system with ageing is a reduction in elasticity of the vasculature and consequent increased arterial stiffness[98, 99]. In fact, telomere length correlates negatively with pulse wave velocity[100].

It is of note that elastin degradation in the skin is related to emphysema and to arterial stiffness in patients with COPD[76**] providing a link between skin ageing, COPD and

atherosclerosis. In turn, telomere length has also been shown to correlate with arterial stiffness, which reflects ageing of the vasculature[100].

Tobacco smoke is the logic candidate to explain the accelerated ageing process that can be the link to the co-existence of COPD and cardiovascular disease. Interestingly, however, COPD patients have increased skin elastin degradation, compared with controls matched for age and smoking history, and this was associated with arterial stiffness and emphysema severity. This suggests that besides similar chronological age, patients with COPD experience accelerated ageing that contributes to the emphysema severity and arterial stiffness irrespective of the smoking history. Taken together, these data suggest that the destruction of the lung parenchyma, leading to emphysema, and the cardiovascular risk may share mechanisms related to accelerate ageing.

*Physical inactivity*

Physical in-activity is a known risk factor for cardiovascular disease[70]. The recognition that physical activity (PA) can prevent or delay the appearance of chronic diseases such as cardiovascular disease or diabetes has now a solid scientific support[101, 102, 103-106]. Inactivity is also a risk factor for the development of COPD in smokers[7]. An example that illustrates this comes from the study by Garcia-Aymerich et al [107*]. In this cohort study, smokers who had moderate to high levels of regular PA had lower lung function decline over time and consequently had a lower risk of developing COPD. The benefits of physical activity are well known. Regular physical activity has been associated with an improvement in endothelial function, has anti-inflammatory effect, reduces body weight, fat mass and circulating lipids, the metabolic cost of activities, and improves

insulin sensitivity, angiogenesis and increases the resistance of myocardial cells to ischemia[108]. Exercise training constitutes the cornerstone of pulmonary and cardiac rehabilitation[109, 110].

Physical activity is markedly reduced in patients with COPD[111] and is an independent predictor of risk of hospitalizations due to acute exacerbations and early mortality in COPD[107*, 112]. Reduced physical activity levels, a feature of COPD, constitute a risk factor for cardiovascular disease[101] and can partially explain the higher risk of cardiovascular morbidity in patients with COPD.

*Hypoxemia and gas exchange abnormalities*

Patients with COPD can develop type I (hypoxemic) and type II (hypoxemic + hypercapnic) respiratory failure as the condition progresses. Hypoxemia, whether sustained in patients with severe disease or intermittent hypoxia during exercise, sleep or exacerbations, can influence atherogenesis by increasing systemic inflammation and oxidative stress, up-regulating cell-adhesion molecules, and producing hemodynamic stress[113-115]. Animal studies have shown hypoxia to be a contributor to atherosclerosis in the presence of dyslipidaemia, as increased lipid peroxidation, a marker of oxidative stress, and reduced levels of the antioxidant superoxide dismutase are found in the myocardial tissue of rats exposed to hypoxic environments[116, 117]. Hypoxia also induces hemodynamic stress, increasing the heart rate and cardiac index[118], and affects the renal circulation, reducing renal blood flow and activating the renin-angiotensin system, resulting in increased peripheral vasoconstriction and oxidative stress[119]. Respiratory failure in patients with COPD is also associated with

activation of the sympathetic nervous system[120], which is associated with an increased risk for cardiovascular disease[121].

In turn, hypoxic vasoconstriction, endothelial injury by cigarette-smoke and inflammation are the potential pathogenic mechanisms linked to the development of pulmonary arterial hypertension (PAH) in patients with COPD[122].

Respiratory acidosis resulting from hypercapnia is a well-known feature of advanced COPD, particularly in the advanced phase or during exacerbations. A recent study by Minet and colleagues has shown that respiratory acidosis could be one of the mechanisms resulting in endothelial dysfunction, thus adding to the burden of cardiovascular complications[123].

*Polycythemia*

Secondary polycythemia is a known complication of COPD, and occurs mainly as a result of chronic hypoxemia. A prospective study by Cote and colleagues[124], however, had shown that only 6% of 683 patients with COPD included in their study developed secondary polycythemia. The low incidence reported in this study may be related to the improvement of the management of patients with hypoxia, including the use of long-term oxygen therapy (LTOT). However, when present in COPD polycythemia can contribute to the development of pulmonary hypertension and pulmonary endothelial dysfunction with reduced cerebral and coronary blood flow, thus increasing the risk of cardiovascular events[125, 126].

Rather than isolated concomitant factors, the pathogenic mechanisms previously described can be interconnected pieces of the same puzzle linking COPD and its

cardiovascular comorbidities. For example cigarette smoking can constitute common risk factor for COPD and cardiovascular comorbidities. In turn, COPD can lead to cardiovascular disease through several features characteristic of the disease (e.g. hypoxemia, elastin degradation, systemic inflammation) (**Figure 3**).

**Interventions to treat cardiovascular comorbidities**

COPD associates with several comorbidities and extra-pulmonary manifestations, and is now considered a systemic disease with multiple organ involvement and different phenotypes[127, 128]. Cardiovascular comorbidities are significantly increased in patients with COPD[3, 4]. In turn, the presence of cardiovascular disease in these patients increases the risk of morbidity and mortality[7, 17-20*]. Therefore, to actively seek and treat, these comorbidities should contribute to a better management and outcomes of individual patients.

*Ischaemic Heart Disease*

Patients with COPD showed a significant increase on risk of adverse events and of hospital readmissions after an ischemic event[129**].

Current guidelines suggest dual antiplatelet therapy with aspirin and a $P2Y_{12}$ADP receptor inhibitor for the treatment of IHD and should also apply to patients with COPD. Clopidogrel has been reported to be used more frequently in COPD and asthma[130] than in the general population. This is possibly due to a lower association with dyspnoea and bleeding complications reported with other $P2Y_{12}$-ADP receptor inhibitors.

As mentioned previously, platelet-monocyte aggregates, increased during exacerbations of COPD[62]. Antiplatelet therapy with aspirin and clopidogrel has also been shown to reduce 1-year mortality in COPD[131].

Beta-blockers are indicated in all patients with heart failure or LV dysfunction after an ischemic event[132]. In patients with COPD undergoing vascular surgery, cardio-selective beta-blockers reduce mortality[133]. Observational studies have reported the safe use of beta-blockers in exacerbations of COPD (ECOPD), and even a reduction in mortality[134, 135]. However, prescription of beta-blockers was significantly lower in individuals with airways disease[136, 137]. There is now additional evidence on the safety of beta-blockers in COPD[138-140]. Moreover, the benefits of selective beta-blockers when indicated in IHD are considerably larger than the potential associated risks. International guidelines for the management of COPD, such as the Global Initiative for COPD (GOLD)[141], recommend the use of cardio-selective beta-blockers when indicated.

The use of statins, ACE inhibitors, and angiotensin receptor blockers has also a positive impact on morbidity and mortality in patients with COPD and IHD[142, 143]. A recent study showed no effects of statins on exacerbations, lung function, quality of life or mortality[144]. Interestingly, patients that fulfil criteria for the use of statins were excluded from this study. The underuse of statins in persons with cardiac risk factors who have been included in retrospective studies may account in part for the differences between this and those studies previously reported. This highlights the need for early identification and treatment of cardiovascular risk in COPD patients. ACE inhibitors are recommended in all patients with presence of heart failure,

hypertension or diabetes[132]. Additionally, in COPD patients, ACE inhibitors may protect against $FEV_1$ decline[145] possibly through an anti-inflammatory effect and improvement of endothelial function.

Usual COPD treatment is not contraindicated in patients with co-existing ischemic disease. Moreover, several lines of usual treatment for COPD may have a secondary benefit on reducing the risk of IHD[146-148].

Participation in cardiac rehabilitation programmes is advised for patients after an ischemic event[132]. The benefits of physical activity have been previously described in this review. Pulmonary rehabilitation is a key part of the management of patients with COPD[109].

*Heart Failure*

Heart failure (HF) should be treated accordingly to HF guidelines as there is no evidence that HF should be treated differently in the presence of COPD[141].

ACE inhibitors should be used in all symptomatic patients with a left ventricular ejection fraction (LVEF) ≤ 40% as it improves ventricular function, patient's well-being, reduces hospitalisations and increases survival[149]. Unlike the situation with beta-blockers, no differences have been reported in the prescription of ACE inhibitors in patients with or without COPD[150]. Moreover, as mentioned previously the use of statins, ACE inhibitors, and angiotensin receptor blockers has shown, in observational studies, to have a positive impact on morbidity and mortality in patients with COPD and IHD[142, 143].

Beta-blockers improve survival in patients with chronic HF. The use of selective beta-blockers has significant impact on survival in patients with HF with diagnosis of

COPD[151] and is considered to be safe[138-140]. A Cochrane meta-analysis concludes that selective β1 beta-blockers are safe[138]. Similarly to the treatment of IHD, the use of selective beta-blockers is preferable to a non-selective beta blocker[152.] The NICE and European Society of Cardiology stated that there is no contraindication for the use of beta-blockers in patients with COPD[149, 153].

However, this treatment is significantly under-prescribed in these patients[151] (**Figure 4**).

The use of a non-selective beta-blocker may cause a reduction on the $FEV_1$, however this does not translate into deleterious effects on symptoms and quality of life[154]. In fact, some studies have shown that treatment with bisoprolol and carvedilol was well tolerated and produced beneficial effects on lung function in patients with heart failure and COPD[155]. Moreover, bisoprolol was superior to carvedilol on respiratory parameters improvement. In resume, the benefit of selective beta- blockers for the treatment of HF on patients with COPD overweighs any potential risk, even in severe COPD patients.

The addition of a low-dose of an aldosterone antagonist should be considered in all patients with an LVEF ≤ 35% and severe symptomatic HF as it reduces hospital admissions and increases survival[149].

Angiotensin receptor blockers (ARBs) are recommended in patients with HF and an LVEF ≤ 40% who remain symptomatic despite optimal treatment with an ACEI and beta-blockers, unless also taking an aldosterone antagonist as it improves ventricular function and patient well-being, and reduces hospital admissions[149].

Digoxin should be considered in patients with symptomatic HF and AF to slow a rapid heart rate in addition to or prior to beta-blockers[149].

Diuretics are recommended in patients with HF and clinical signs or symptoms of pulmonary congestion[149]. Clinicians should be aware that high doses of loop diuretics could produce metabolic alkalosis with subsequent induction of hypoventilation that could worsen hypercapnia[37, 156].

Warfarin is recommended in patients with HF and AF[149]. In elderly patients with HF caused by IHD, statins may be used to reduce hospitalisations[149].

*Pulmonary hypertension*

ACCF/AHA[157] and the European Society of Cardiology[158] guidelines for the management of pulmonary hypertension recommend that in the vast majority of patients with COPD, in whom PH is mild, treatment should be directed to the underlying COPD. LTOT is indicated earlier in patients with COPD if there is evidence of PH. In more severe PH, specific treatment of PH in patients with COPD has not been adequately studied. Open label, uncontrolled observations with both *Bosentan* and sildenafil have suggested benefit, although adequately designed trials are lacking[159-161]. Worsening V/Q mismatch, resulting in further hypoxemia due to non-selective vasodilatation is a potential risk[162, 163]. Likewise, the use of endothelium-modulating agents is not recommended until data on their safety and efficacy in COPD are available[164].

*Atrial Fibrillation*

This condition should be treated according to the usual guidelines for the treatment of AF. The reader is referred to guidelines on the treatment of AF published elsewhere[166-168]. When beta-blockers are required, selective beta-blockers are preferable over non-selective beta-blockers[141].

*Hypertension*

Hypertension should be treated according to usual hypertension guidelines. The reader is referred to guidelines on the treatment of hypertension published elsewhere[169, 170]. Again, a selective beta-blocker is preferred over a non-selective beta blocker[141] when these drugs are required.

**Summary and Conclusions**

Cardiovascular disease is one of the most frequent associated comorbidities in patients with COPD and is a major contributor to morbidity and mortality. These comorbidities are under-recognised and, therefore, undertreated. COPD shares common risk factors with several cardiovascular diseases including cigarette smoking. In turn several features of COPD can be associated with increased cardiovascular risk, namely gas exchange abnormalities, polycythaemia, systemic inflammation and sedentary habit. Understanding the mechanisms linking COPD and cardiovascular disease may help to identify new targets for treatment. Cardiovascular comorbidities should be actively sought and treated according to usual guidelines in patients with COPD. Management of patients with COPD should be moving from a reductionist approach to an integrated approach to define, identify, and treat the multiple organ involvement of this complex syndrome.

## EXPERT OPINION SECTION

COPD is a multiple organ involvement syndrome. Common risk factors lead to the co-existence of COPD and extra pulmonary comorbidities. Moreover, features of COPD (e.g. inactivity, gas exchange abnormalities, systemic inflammation, etc.) can also lead to extra-pulmonary manifestations of COPD. Both comorbidities and extra-pulmonary manifestations of COPD are major contributors to morbidity and mortality and are often under-diagnosed. There is a need for COPD management to move from a reductionist approach to an integrated approach that considers the disease as the multiple organ syndrome that COPD is. Cardiovascular diseases are of the most frequent associated extrapulmonary manifestations of COPD and, together with other comorbid conditions, should be actively sought and treated. The authors hope that the present review highlights the importance of cardiovascular diseases in patients with COPD and help to move a step forward in the management of this complex and heterogeneous syndrome.

## FIVE YEARS VIEW SECTION

There is already consensus on the heterogeneous nature and the multi-organ involvement of COPD, which has produced in the last decade a change in the paradigm in the field. There is still, however, a reductionist approach in the management of this condition. Evidence is continuously emerging and pointing at the heterogeneity of the disease where multiple phenotypes can be identified. This has implications for the prognosis of individual patients with COPD. The next five years are key to accelerate the switch towards an integrated approach in COPD management. This approach should incorporate an active effort to seek for, identify, and treat the multiple organ involvements characteristic of COPD. Cardiovascular disease is one of the most frequent associated comorbid conditions and contributes to increased morbidity and mortality. The next five years will bring new tools that will facilitate the management of cardiovascular comorbidities to the clinician. Biomarkers of cardiovascular comorbidities (e.g. circulating desmosine levels) should be made available to facilitate the identification of patients at risk and new therapeutic alternatives should emerge. The latter should improve the management of the common risk factors on one hand and the features of COPD that contribute to the development of cardiovascular disease in these patients, ultimately leading to a better and personalised management of the individual patients with COPD.

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## TABLE 1. Potential pathogenic mechanisms of cardiovascular disease in COPD

| **Potential pathogenic mechanisms of cardiovascular disease in COPD** |
|---|
| Vessel wall abnormalities/Endothelial dysfunction |
| Elastin degradation |
| Systemic and lung inflammation |
| Accelerated ageing |
| Sedentary habit |
| Gas exchange abnormalities |
| Lung hyperinflation |
| Polycythemia |

## Figure 1. COPD is associated with subclinical atherosclerosis

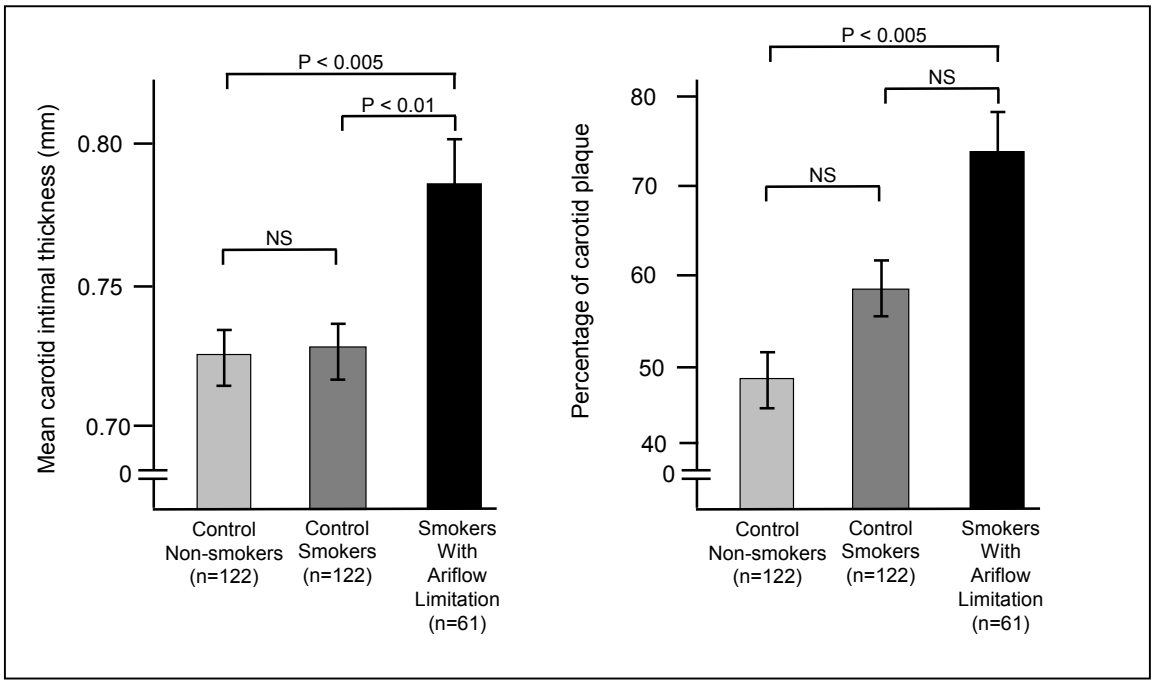


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**Figure 2. Heart disease is associated with increased mortality in the ECLIPSE cohort.**

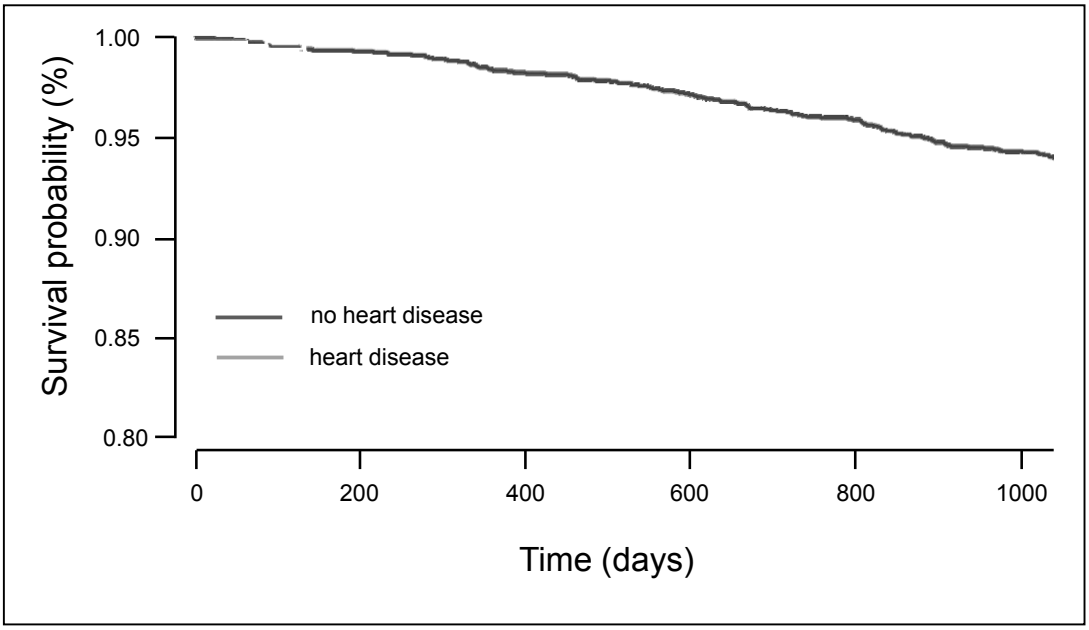


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**Figure 3. Interaction of the pathogenic mechanisms of cardiovascular disease in COPD**

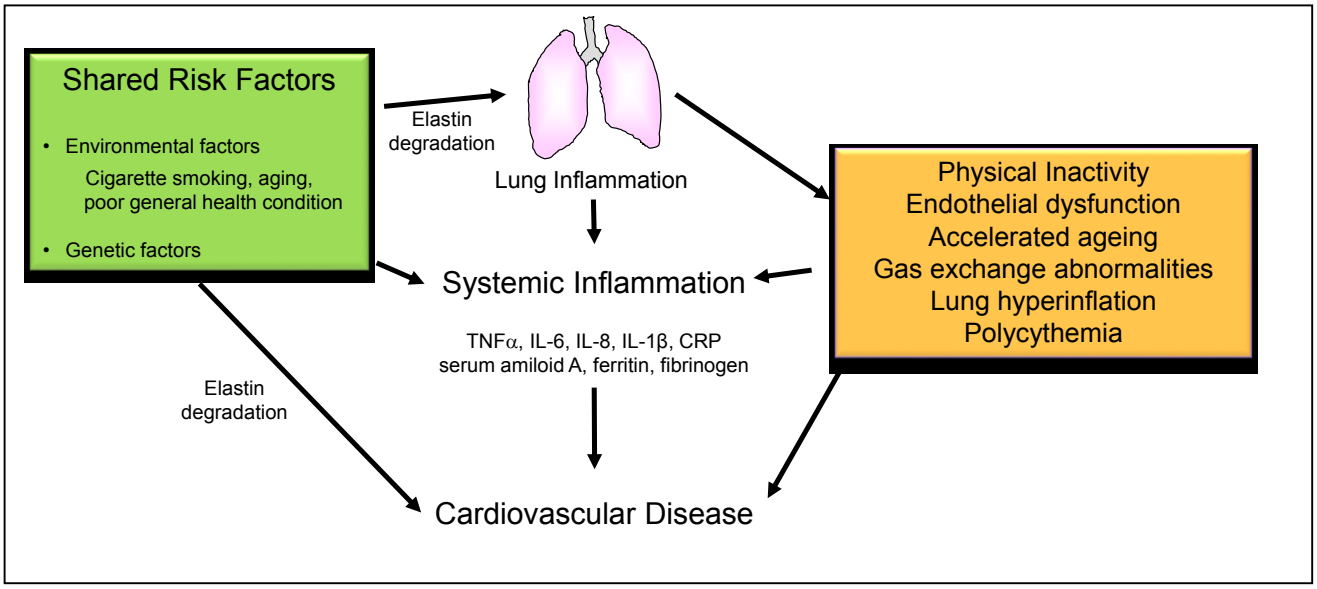
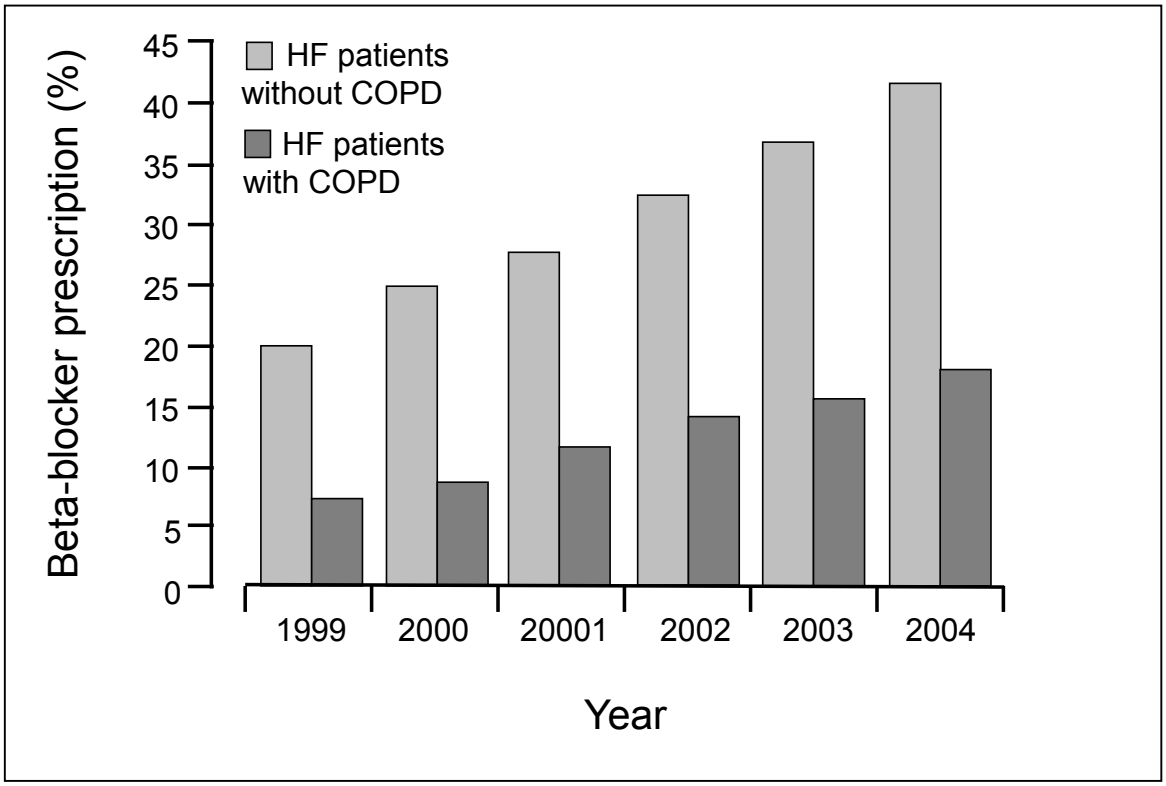


**Figure 4. Trends in beta-blockers prescribing in patients with HF, comparing those with and without COPD.**

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