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REVIEW

Insights into Chronic Obstructive Pulmonary Disease as Critical Risk Factor for Cardiovascular Disease

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Abstract: In patients with chronic obstructive pulmonary disease (COPD), cardiovascular comorbidities are highly prevalent and associated with considerable morbidity and mortality. This coincidence is increasingly seen in the context of a "cardiopulmonary continuum" rather than being simply attributed to shared risk factors, in particular, cigarette smoking. Both disease entities are centrally linked to systemic inflammation as well as aging, arterial stiffness, and several common biomarkers that led to the development of pulmonary hypertension, left ventricular diastolic dysfunction, atherosclerosis, and reduced physical activity and exercise capacity. For these reasons, COPD should be considered an independent factor of high cardiovascular risk, and efforts should be directed to early identification of cardiovascular disease (CVD) in COPD patients. Assessment of the overall cardiovascular risk is especially important in patients with severe exacerbation episodes, and the same therapeutic target levels for glycosylated hemoglobin, low-density lipoprotein cholesterol (LDL-C), or blood pressure than those recommended by clinical practice guidelines for patients at high cardiovascular risk, should be achieved. In this review, we will discuss the most recent evidence of the role of COPD as a critical cardiovascular risk factor and try to find new insights and potential prevention strategies for this disease.

Keywords: chronic obstructive pulmonary disease, cardiovascular disease, cardiovascular risk factors, inflammation, ischemic heart disease, heart failure

Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem with impressive statistics. The Global Burden of Disease Study reports a prevalence of 251 million cases of COPD globally in 2016, with 3.17 million deaths caused by the disease in 2015 (5% of all deaths globally in that year).[1,2] Moreover, COPD is likely to increase in the coming years due to higher smoking prevalence and aging populations in many countries. Cardiovascular diseases (CVD) are highly prevalent in patients with COPD and are a clinically relevant cause of morbidity and mortality. In a well-characterized cohort of 213 patients with moderate to very severe COPD, one or more comorbidities were present in 97.7% of the patients, and four or more in 53.5%.[3] However, establishing the true prevalence of individual comorbidities in COPD and their relationship with the prognosis of the disease is confounded by different factors, including shared risk factors for COPD and several comorbidities; underdiagnosis of both COPD and comorbid conditions, and the symptoms overlap between COPD and comorbidities.[4]

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The magnitude of the association between CVD, cardiovascular risk factors and COPD has been explored in systematic reviews and meta-analysis. Thus, the prevalence of cardiovascular comorbidities is twofold increase in COPD patients with an odds ratio (OR) between 1.90 and 2.46.[5,6] Two observational multicenter studies carried out in patients hospitalized due to COPD exacerbations in Spain, also showed elevated cardiovascular comorbidity, with a prevalence of 32.8% for chronic heart failure, 20.8% for ischemic heart disease and 16.8% for peripheral vascular disease, among others.[7,8] The presence of these diseases was related to a lower survival at 3-months after discharge.[8] In outpatients with stable COPD, the ECLIPSE study shows that CVD was related to greater 3-years mortality after their adjustment for age, gender and smoking history.[9] The relevance of CVD and other comorbidities in COPD patients for mortality and severe exacerbations can be assessed by the CODEX index.[10] The comorbidity, obstruction, dyspnoea, exacerbations (CODEX) index is a multicomponent scale designed to predict the risk of readmissions and mortality at 1 year for patients hospitalized for COPD. The index includes the comorbidities (Charlson index adjusted by age), the degree of airway obstruction (post-bronchodilator FEV_1%), dyspnea (stratified according to the modified Medical Research Council scale), and severe exacerbations in the previous year. It has shown to be useful at predicting survival and readmission after hospital discharge for a COPD exacerbation, with a prognostic capacity superior to other previously published indices.[11,12]

Since COPD is related with an increased risk of cardiovascular events, especially in the more advanced phase of the disease and in patients with exacerbations, assessment of the overall cardiovascular risk in these patients seems essential, and similar therapeutic target levels for glycosylated hemoglobin, low-density lipoprotein cholesterol (LDL-C), blood pressure, dietary interventions and adapted physical activity recommended by clinical practice guidelines for patients at high cardiovascular risk should be achieved.[13]

We aimed to describe salient findings of major cardiovascular comorbidities associated with COPD based on the current best evidence from the recent medical literature (published from 2015), which, on the other hand, will contribute to reinforce recommendations of a recent Spanish consensus on the management of COPD according to the CODEX index.[10]

Links Between COPD and CVD

Smoking

COPD and CVD share a number of common risk factors, including but not limited to smoking, the presence of which undoubtedly forms part of the explanation for the coexistence of COPD and CVD. Smoking and COPD are inextricably linked, while smoking is also a well-established major risk factor for COPD, atherosclerotic disease, coronary heart disease, heart failure, and peripheral artery disease.

Aging

Aging is closely related to the prevalence of chronic diseases, and some authors consider COPD as a disease of accelerated lung aging.[14,15] Aging lung is characterized by several physiological and structural changes similar to those found in COPD.[16,17] Several common pathways related to aging for COPD and CVD have been described, including oxidative stress, inflammation, telomere shortening, and genetic overlap, among others.[15,18-21]

Incomplete Lung Development

More recently, several cohort studies have shown that between 4% and 12% of the persons in the general population do not reach the peak lung considered normal for their age and sex in early adulthood. Many of those persons have chronic airflow limitation later in life, even though the rate of decline in FEV_1 after its peak is similar to the observed in people without disease.[22] Interestingly, these patients developed cardiovascular disease a decade before that the individuals with normal lung function in early adulthood, in an independent form to cumulative smoking exposure.[23]

Classical Cardiovascular Risk Factors

COPD patients have a higher prevalence of diabetes mellitus, arterial hypertension, dyslipidemia, and metabolic syndrome. Hypertension is the most common concurrent disorder among patients with COPD.[24] In the meta-analysis of Chen et al,[6] COPD patients showed an increased risk of arterial hypertension (odds ratio, OR 1.33, 95% CI 1.33–1.56). In a recent cross-sectional study, COPD was independently associated with hypertension (OR 1.71, 95% CI 1.37–2.13) after adjusting for age, obesity, smoking status, diabetes, and metabolic syndrome.[25] In another study, half of the patients hospitalized for COPD exacerbation had a previous diagnosis of

hypertension.[8] The prevalence of diabetes is also increasing in COPD, particularly in patients with worse lung function.[26] Similarly, the metabolic syndrome is more frequent in COPD patients, with an OR of 1.47 (95% CI 1.09–1.88).[27] Hypertension, abdominal obesity and hyperglycemia are the most prevalent components of the metabolic syndrome in COPD patients.[28] Hospitalized COPD patients with metabolic syndrome had more dyspnea and higher comorbidity, including CVD.[29]

Systemic Inflammation

Low-grade systemic inflammation is considered a hallmark of the pathogenesis in COPD and one of the key mechanisms that may be responsible for the systemic effects on distant tissues and the increased rate of comorbidities, including cardiovascular comorbidity.[30] The extent of the inflammatory reaction is correlated with the severity of the disease and is associated with an increase in mortality.[31] Also, low-grade systemic inflammation plays an increasingly recognized role in the pathogenesis of atherosclerosis. The most validated markers of systemic inflammation in COPD are fibrinogen and high-sensitivity C-reactive protein, and both are also useful predictors of cardiovascular events in COPD and general population.[32,33]

Thrombocytosis and Platelet Reactivity

Thrombocytosis and platelet aggregation are especially relevant during COPD exacerbation and in the following weeks after the episode. The data from the SUMMIT study conducted in more than 16,000 patients with COPD and moderate obstruction (FEV_1 > 50%) confirm that the risk of presenting a cardiovascular event after hospitalization for COPD increases almost 10 times in the first month (hazard ratio, HR 9.9, 95% CI 6.6–14.9) compared to patients without exacerbations.[34] Between the mechanisms that may account for this increased CVD risk during exacerbations, thrombocytosis and platelet aggregation can be a suggestive explanation. A study carried out in 1343 patients hospitalized for COPD exacerbation shows that thrombocytosis during admission was related to both 1-year mortality and in-hospital mortality.[35] In this study, antiplatelet therapy was associated with significantly lower 1-year mortality. In another prospective study, platelet reactivity was shown to be increased during COPD exacerbations.[36] Similarly, in patients with an acute coronary event diagnosed by percutaneous coronary intervention (PCI), platelet reactivity was significantly higher at the time of PCI in COPD patients and remains increased 1-month after the procedure.[37] A systematic review and meta-analysis suggested that antiplatelet therapy reduces all causes of mortality in COPD patients.[38]

Serum Biomarkers

Multiple serum biomarkers have been related to the progression of the disease and mortality in large cohorts of COPD patients.[39] Some of them, such as surfactant protein-D (SPD), ClubCell-16 (CC-16), and desmosine, are generated in the lungs and are increased in the serum of COPD patients, relating to a higher risk of cardiovascular events. SPD is predominantly produced in type 2 pneumocytes and is also expressed in the endothelium of the cardiovascular system, acting as a mediator on inflammatory signals.[40] SPD has been associated in longitudinal studies with an increase of cardiovascular mortality in COPD patients.[41] CC-16 are secreted mainly in the terminal portion of the bronchioles and their plasma levels are inversely associated with an increase in mortality in COPD.[42] Desmosine is a specific marker of elastin degradation and is increased in patients with COPD, especially in those with emphysema. Plasma desmosine levels in COPD patients are higher in those with a history of cardiovascular disease and are associated with higher levels of coronary calcification measured by CT and 3-years mortality.[43]

Especially relevant are biomarkers of myocardial damage in COPD. A cohort study performed in more than 15,000 patients with available data of spirometric and echocardiographic measures, alongside serum levels of ultrasensitive troponin and NT pro-BNP levels, has demonstrated the close relationship between lung function and these biomarkers.[44] On the other hand, several studies have shown that the elevation of troponin and pro-BNP, both during exacerbations and in the stable phase, is associated with higher mortality in patients with COPD, even in those without known ischemic heart disease or heart failure.[45,46] In a cohort study performed in patients with severe exacerbations of COPD and elevated levels of troponins at admission, coronary angiography performed 72 hours after hospitalization showed significant coronary stenosis (>50%) in major coronary arteries in 67% of patients, of which 39% required percutaneous coronary intervention.[47]

Arterial Stiffness

Arterial stiffness is a predictor of mortality and cardiovascular events in patients with CVD and in the general population.[48] Several studies and meta-analysis have shown that arterial stiffness is also increased in COPD

patients in whom it has been related to the severity of the obstruction, systemic inflammation, and previous history of exacerbations.[49] In a longitudinal study, arterial stiffness increase during COPD exacerbations jointly with serum troponin levels.[50] Of note, arterial stiffness in COPD patients is related to serum levels of SPD, CC-16, and desmosine.[42,43] Another study performed in patients with a coronary event diagnosed by coronary angiography and COPD diagnosed by spirometry confirmed that pulmonary function is closely related to arterial stiffness.[51]

Heart Failure

The combination of HF and COPD incur significant morbidity and mortality, and present major challenges to health-care providers. The reported prevalence of COPD in patients with HF varies largely (from 11% to 52%) in North American patients and (from 9% to 41%) in European cohorts.[52] Geographical variations largely relate to differences in population age structure and risk factor exposure, most notably smoking. On the other hand, cigarette smoking, the commonest cause of COPD, is associated with a substantial increased risk of HF.[53] The prevalence of left ventricular systolic dysfunction (LVSD) in patients with COPD varies considerably between 10% and 46%, with lower prevalences when excluding patients with coronary disease.[54]

Systematic Reviews and Meta-Analysis

In a systematic review of 25 studies published between 1990 and 2012 reporting cardiovascular comorbidity in patients with COPD (or vice versa), the adjusted risk ratio (RR) for the prevalence of HF in COPD ranged from 1.8 to 3.9 compared with patients without COPD, and the adjusted RR for hospitalization from 1.2 to 3.8.[55] In the meta-analysis of 29 datasets from 27 studies, a significant increase in the prevalence of HF in COPD was found in 14 datasets, yielding a pooled OR of 2.57 (95% CI 1.90–3.47; $P < 0.0001$).[6]

Primary Studies

In a longitudinal study of COPD patients hospitalized with decompensated heart failure all 11 medical centers in central Massachusetts during four study years: 1995, 2000, 2002, and 2004, and followed through 2010 for determination of their vital status, COPD was associated with a 10% increase in 1-year mortality and a 40% increase in 5-year mortality.[56] Moreover, the finding of undertreatment with β-blockers in patients with COPD despite temporal increases in use highlights a key area for quality improvement. In the Spanish consensus on the management of COPD according to the CODEX index, the panel agreed that patients with COPD and heart failure or ischemic heart disease have to be treated with β-blockers.[10]

In an analysis of the Spanish National Hospital Discharge Database (2001–2015), admissions for HF increased by 2.9% per year among men with COPD.[57] In a study of costs associated with readmissions in patients with both HF and COPD, 10 practical tips to reduce readmissions were presented, including 1) diagnose the population accurately, 2) detect admissions for exacerbations early and consider risk stratification, 3) use specialist management in hospital, 4) modify the underlying disease substrate, 5) apply and intensify evidence-based therapies, 6) activate the patient and develop critical health behaviors, 7) setup feedback loops, 8) arrange an early follow-up appointment prior to discharge, 9) consider and address other comorbidities, and 10) consider ancillary support services at home.[58] In a cross-sectional observational study carried out in Toronto, Canada, in which agreement between hospital and primary care on diagnostic labeling for COPD and heart failure was analyzed, COPD concordance was 34% and HF concordance 33%; moreover, 21–24% additional patients with COPD and 18–20% additional patients with HF did not have a label in either setting.[59] This calls for the need for integrated disease management between the different physicians and nurses of these patients and between the hospital and primary care.

Coronary Heart Disease

In the last few years, many studies focused their attention on the relationship between COPD and coronary heart disease showing that these disorders are mutually influenced. The prevalence of coronary heart disease – a term that includes myocardial infarction (MI), angina, coronary artery disease, and ischemic heart disease (IHD) – ranged between 4.7% and 60% among patients with COPD, with an adjusted RR ranging from 0.7 to 6.8.[55] Also, in a robust meta-analysis of the risk of cardiovascular comorbidity in COPD, it was found that patients with COPD had consistent higher risks of coronary heart disease (OR 1.96, 95% CI 1.51–2.30; $P < 0.0001$), MI (OR 2.71, 95% CI 1.69–4.35; $P < 0.0001$), and angina pectoris (OR 8.16, 95% CI 3.08–21.59; $P < 0.0001$).[6] Indeed, COPD patients with IHD may have worse outcomes. The three-year follow-up of 4284 patients who received hospital treatment for coronary heart disease reported mortality rates of 21% for

patients diagnosed with COPD versus 9% in those without COPD ($P < 0.001$).[60] Likewise, patients with ST segment elevation MI and concomitant COPD are at greater risk for death and hospital readmissions due to cardiovascular causes (eg recurrent MI, HF, bleeding) than patients without COPD.[61]

Systematic Reviews and Meta-Analysis

In a systematic review and meta-analysis of 10 studies (7518 patients with COPD and 65,451 patients without COPD), a comparison of major adverse cardiac events (MACEs) and mortality following percutaneous coronary intervention revealed that in-hospital (OR 1.40, 95% CI 1.19–1.65; $P = 0.001$) and long-term MACEs (OR 1.58, 95% CI 1.38–1.81, $P = 0.001$) were significantly higher in patients with COPD.[62] Therefore, COPD should be considered a risk factor for the development of adverse clinical outcomes following coronary revascularization procedures. Regrettably, in all of these studies, definition of COPD is based in the clinical history or discharge codes, without spirometric confirmation and underdiagnosis of COPD in IHD is about 80%.[63–65] In a meta-analysis of 24 observational studies, an increased risk of MI associated with COPD (HR 1.72, 95% CI 1.22–2.42) and with acute exacerbation of COPD (incidence rate ratio [IRR] 13.04, 95% CI 1.71 to 99.7) was found.[66] Therefore and from a clinical perspective, acute exacerbations of COPD represent periods of increased risk of MI.

Primary Studies

Recent studies have drawn attention to the economic burden of co-occurrence of COPD and IHD, particularly the high expenditure for medications involved with IHD pharmacotherapy in the course of COPD.[67] In an analysis of German Statutory Health Insurance claims data based on 26,318 COPD patients with and 10,287 COPD patients without IHD, IHD was a substantial cost driver in COPD with the highest excess costs in the age group between 70 and 80 years.[68]

In a Sweden population-based COPD cohort, the presence of self-reported IHD was estimated in comparison with age- and sex-matched subjects without COPD.[69] There was a significant association between self-reported IHD as well as probable ischemic ECG-changes and COPD disease severity assessed by spirometry. Also, in the same Sweden cohort, ischemic ECG changes were associated with an increased risk for death (RR 2.36, 95% CI 1.45–3.85) when compared with subjects with normal lung function, even after adjusting for common confounders (RR 1.65, 95% CI 0.94–2.90). The risk of death also persisted after adjustment for COPD severity.[70] Underuse of beta-blockers, statins, and antiplatelet drugs is frequent in patients with IHD and COPD, and possibly contributes to a worse prognosis.[71,72] Nevertheless, even in patients with IHD adequately treated, the presence of COPD confirmed by spirometry is associated with an increase in cardiovascular events and mortality during the follow-up.[63,73]

Peripheral Arterial Occlusive Disease

Peripheral arterial occlusive disease (PAOD) is the clinical expression of the artery obstruction, usually of the lower limbs, secondary to atherosclerotic disease. Tobacco smoking is the strongest risk factor for both COPD and PAOD. Intermittent claudication is the most characteristic symptom of PAOD, although more of the half of the patients can be asymptomatic. Since intermittent claudication is initially manifested with physical effort, and patients with severe COPD are often impaired for dyspnea at the exercise, the diagnosis of PAOD is frequently delayed. A simple method for evaluating PAOD is the ankle-brachial index (ABI). The ABI is also a strong marker of generalized atherosclerosis and CV risk. An ABI < 0.90 is strongly suggestive of PAOD, and is associated on average with a twofold to threefold increased risk of total and CV death.[74]

Systematic Reviews and Meta-Analysis

In the meta-analysis of Chen et al[6] based on seven datasets, the pooled risk for the prevalence of PAOD in COPD patients was 2.35 (95% CI 1.48–3.74; $P = 0.003$). These data are based on population studies and therefore, do not include subclinical PAOD. In another recent systematic review, based on six studies with diagnostic confirmation of PAOD with ABI and COPD with spirometry, COPD patients with PAOD were more frequently males with tobacco history, hypertension, dyslipidemia, higher values of fibrinogen and C-reactive protein, lower values of FEV_1%, and higher dyspnea levels.[75]

Primary Studies

A number of primary studies of the effect of PAOD in COPD patients have been published and included in systematic reviews and meta-analysis,[6,75] but a recent study sought to investigate the incidence of PAOD among COPD patients in Taiwan using a national database reports interesting data. In this study, 51,869 COPD patients were collected from the

National Health Insurance Research Database of Taiwan from 1996 to 2010 and compared with the same number of controls without COPD. The incidence of PAOD was higher in the COPD group than in the non-COPD group (HR 1.23, 95% CI 1.17–1.29).[76] Also, the risk of PAOD increased with the number of comorbidities, with HRs increasing from 3.7 to 4.9 when the number of COPD comorbidities increased from ≥1 to ≥3.[76]

Pulmonary Hypertension

Pulmonary hypertension (PHT) is a clinically relevant problem in COPD due to its high prevalence and the impact that it exerts on morbidity and mortality. Hypoxia is a critical precipitant in the pathogenesis of COPD-associated PHT and, at least in part, explains the correlation between the severity of COPD and the development of PHT. COPD patients with coexisting sleep apnea have a higher risk of developing pulmonary hypertension.[77] Hypoxia induces pulmonary vasoconstriction and pulmonary vascular remodeling in the form of intimal thickening and muscularization of arterioles, thereby increasing pulmonary vascular resistance. Dynamic pulmonary hyperinflation, endothelial dysfunction, polycythemia, inflammation, and parenchymal destruction have also been implicated in the pathogenesis of increased pulmonary vascular resistance in patients with COPD.[4] PHT is present in more than 25% and 50% of the patients with moderate-to-severe COPD, and the 5-year survival of patients suffering PHT is almost half of patients without PHT (36% and 62%, respectively).[78,79] Furthermore, signs of elevated pulmonary artery pressure are associated with more frequent exacerbation episodes. In the meta-analysis of Chen et al of the risk of cardiovascular comorbidity in COPD, the odds of patients with COPD having diseases of pulmonary circulation were 5.14 times higher as compared to matched controls without COPD.[6] A small proportion of COPD patients may present with "out-of-proportion" pulmonary hypertension, in these patients concomitant cardiac disorders, chronic pulmonary thromboembolic disease or a concurrent form of primary pulmonary hypertension should be considered.[80]

Systematic Reviews and Meta-Analysis

Angiotensin-converting enzyme (ACE) gene I/D polymorphism has been studied in relation to the susceptibility to COPD and COPD with PHT with inconclusive results. A systematic review with meta-analysis of 15 studies (2635 participants, 288 participants of the PHT subgroup) showed that ACE gene polymorphism, particularly the homozygote variant, was associated with an increased risk of PHT in Asian COPD patients.[79] These results, however, should be validated in larger sample populations and in more ethnicities.

Primary Studies

Patients with severe PHT associated with COPD present a poor outcome. Studies in a limited number of patients with severe PHT and moderate-to-severe COPD have shown that specific pulmonary arterial hypertension therapy can improve pulmonary hemodynamic parameters.[81]

Cerebrovascular Disease

In contrast to the evidence suggesting that COPD increases the risk of heart disease, studies conducted on the risk of cerebrovascular disease among COPD patients have generated conflicting results. In a systematic review of 25 studies, the adjusted RR for stroke ranged between 1.1 and 1.6, with apparently an increasing trend by increasing grade or airflow limitation.[55] However, in the systematic review of Chen et al, the current evidence on stroke risk among COPD patients was limited by a dependence on cross-sectional data, which precluded a firm establishment of causality between COPD and stroke.[6]

Systematic Reviews and Meta-Analysis

A recent systematic review and meta-analysis of eight studies, mostly conducted in Western countries and in patients with newly developed stroke, a significantly increased risk of stroke was observed among COPD patients (HR 1.30; 95% CI 1.18–1.43; $P < 0.001$).[82] The association between COPD and stroke risk remained robust in subgroup analyses by stroke subtype, study quality, and adjustment for socioeconomic status.

Primary Studies

Patients with COPD have a higher risk of stroke than the general population, and chronic inflammation associated with COPD is thought to contribute to this risk. Exacerbations of COPD are associated with a rise in inflammation, suggesting that there may be an association between exacerbation frequency and the risk of stroke. In a study using the UK Clinical Practice Research Datalink, COPD patients with a first stroke between January 2004 and December 2013 were identified as cases and matched on age, sex, and general practice to controls with COPD but without a stroke (6441 cases and 19,323 controls).[83] There was no evidence that frequent exacerbators (≥2

episodes in the previous year) had an increased stroke risk compared to infrequent exacerbators (≤1 episode) (OR 0.95, 95% CI 0-89-1.01). These results suggest that exacerbation frequency is unlikely to be the reason for increased stroke risk among COPD patients. However, in a study using Taiwan's National Health Insurance Research Database, a comparison cohort of 1918 adults with COPD exacerbations, 3836 adults with COPD no exacerbations, and 7672 adults without COPD who were frequency matched by age and sex, were selected.[84] Patients with exacerbations had increased stroke incidence (adjusted HR 1.28, 95% CI 1.03–1.59) and post-stroke mortality (OR 1.34, 95% CI 1.20–1.52) and complications, including, epilepsy and pneumonia. In a study that assessed the prevalence of COPD among hospitalized stroke patients in the National Inpatient Sample, a nationally representative dataset of US hospital admissions between January 2004 and December 2009, 12% of the hospitalized stroke patients have COPD. The crude and age-adjusted in-hospital mortality rates for these patients were 6.3% (95% CI 6.14–6.53%) and 6.0% (95% CI 4.05–7.94%), respectively, with greater risks of mortality seen among those with intracerebral hemorrhage. This study shows that the presence of COPD is an independent risk factor for early mortality in stroke patients.[85]

Concluding Remarks

Among the long list of comorbid conditions seen in patients with COPD, cardiovascular diseases rank not only among the most common but also as associated with an increased risk of death. However, despite the broad acceptance of prognostic significance of these diseases, including chronic heart failure, coronary artery disease, peripheral arterial occlusive disease and cerebrovascular events as shown in the present article, there remains widespread under-recognition and under-treatment of comorbid cardiovascular diseases in COPD population. The reasons for this are unclear but lack of specific evidence-based guidelines for the management of cardiovascular disorders and cardiovascular risk factors in people with COPD may be an important contributory factor. Optimizing the treatment of COPD and cardiovascular diseases, including the prevention of cardiovascular risk can improve the prognosis of these patients.[86]

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