

## Cardiovascular disease in chronic obstructive pulmonary disease

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## **TITLE PAGE**

### **Title**

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Cardiovascular disease in chronic obstructive pulmonary disease: a narrative review

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## ABSTRACT

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Patients with Chronic Obstructive Pulmonary Disease (COPD) are at increased risk of cardiovascular disease (CVD) and concomitant disease leads to reduced quality of life, increased hospitalisations, and worse survival. Acute pulmonary exacerbations are an important contributor to COPD burden and are associated with increased cardiovascular (CV) events. Both COPD and CVD represent a significant global disease impact and understanding the relationship between the two could potentially reduce this burden. The association between CVD and COPD could be a consequence of (i) shared risk factors (environmental and/or genetic) (ii) shared pathophysiological pathways (iii) co-association from a high prevalence of both diseases (iv) adverse effects (including pulmonary exacerbations) of COPD contributing to CVD and (v) CVD medications potentially worsening COPD and vice versa. CV risk in COPD has traditionally been associated with increasing disease severity, but there are other relevant COPD subtype associations including radiological subtypes, those with frequent pulmonary exacerbations and novel disease clusters. Whilst the prevalence of CVD is high in COPD populations, it may be under-diagnosed, and improved risk prediction, diagnosis and treatment optimisation could lead to improved outcomes. This state-of-the-art review will explore the incidence / prevalence, COPD subtype associations, shared pathophysiology and genetics, risk prediction, and treatment of CVD in COPD.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by persistent respiratory symptoms, chronic inflammation, progressive airflow obstruction and a strong association with smoking.[1] As estimated in 2010, COPD affects 384 million people globally.[2] COPD has a significant impact on patients and pulmonary exacerbations can result in hospitalisations with direct and indirect costs and economic effects through a reduced working days due to breathlessness and functional limitations.[3,4] In the European Union, an estimated €38.6 billion is spent on COPD annually and the Global Burden of Disease Study reported an increasing burden of COPD representing the 6<sup>th</sup> leading cause of disease burden amongst all age groups.[5] Cardiovascular disease (CVD) is the leading cause of mortality worldwide, affecting approximately 85 million people in Europe and commonly occurs in patients with COPD.[6] Coronary heart disease (CHD) and ischaemic stroke also represent the 2<sup>nd</sup> and 3<sup>rd</sup> highest causes of disease burden globally.[5] Coexisting COPD and CVD has been highlighted by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as being highly important, as it leads to reduced quality of life, increased hospitalisations and increased mortality.[7–9] GOLD recommends that COPD management includes identifying and managing comorbidities including CVD.[9] The association between CVD and COPD could be a consequence of (i) shared risk factors (environmental and/or genetic) (ii) shared pathophysiological pathways (iii) co-association from a high prevalence of both diseases (iv) adverse effects (including pulmonary exacerbations) of COPD contributing to CVD and (v) CVD medications potentially worsening COPD and vice versa

We aim to review CVD in patients with COPD focusing on: (i) the incidence and prevalence of CVD in COPD (ii) COPD subtype associations (iii) shared pathophysiology and genetics (iv) assessing the risk of CVD in COPD and (v) assessing the effects of CVD or COPD treatment on either disease. CVD is an umbrella term for diseases that affect the heart or vasculature, and this review will focus on CHD, ischaemic stroke, heart failure (HF) and arrhythmias. A literature review (Cochrane Database of Systematic Reviews, PubMed, EMBASE and Medline) was performed in September 2021 using the following search terms (including variations and acronyms): ‘Cardiovascular disease’, ‘coronary artery disease’, ‘heart disease’, ‘heart failure’, ‘myocardial infarction’, ‘ischaemic heart disease’, ‘arrhythmia’, ‘chronic

bronchitis', 'emphysema', 'chronic obstructive pulmonary disease', 'prevention', 'biomarker', 'incidence', 'prevalence', 'genetics', 'genome-wide association study', 'treatment', 'pathophysiology' and 'subtype'.

## **INCIDENCE AND PREVALENCE OF CVD IN COPD**

CVD occurs more frequently in COPD compared to age-matched cohorts without COPD (**table 1**).<sup>[10]</sup> The frequency of CVD in COPD varies throughout the literature depending on (i) the definition of CVD (ii) the COPD cohort (e.g. disease severity, number of comorbidities, primary/secondary care), (iii) whether prevalence or incidence is studied and (iv) adjustment for confounding factors.<sup>[11,12]</sup> The incidence and prevalence of CVD in COPD has recently been comprehensively reviewed by Chen et al., and salient study findings are summarised in this section.<sup>[13]</sup>

The prevalence of HF in COPD ranges from 7-42% <sup>[14,15]</sup> and is significantly higher in COPD compared to those without (odds ratio (OR) 8.48).<sup>[15]</sup> HF related hospitalisations are also increased in COPD compared to the non-COPD group (1807 vs. 352 per 100,000 person years (PY)).<sup>[15]</sup> Estimates for the prevalence of myocardial infarction (MI) and angina in COPD vary significantly from 2-18% and 1-55%, respectively.<sup>[15–17]</sup> A study by Sidney et al., reported an increased frequency of MI (OR 4.42) and angina (OR 4.38) in patients with COPD.<sup>[15]</sup> In addition, CHD related hospitalisations were more frequent in COPD patients compared to non-COPD (11 vs. 7 per 1000 PY).<sup>[18]</sup> The prevalence of arrhythmia in COPD varies from 3-21%, and atrial fibrillation (AF) is approximately five times more frequent in COPD compared to controls (5% vs. 1%; OR 4.4).<sup>[15,18]</sup> AF related hospitalisation is twice as likely to occur in COPD and patients with concurrent AF and COPD have higher rates of all-cause mortality.<sup>[18][14]</sup> Arrhythmia prevalence estimates may be confounded by asymptomatic and paroxysmal AF, as the diagnosis may be limited to self-reporting and diagnostic codes in many studies.<sup>[19]</sup> The prevalence of ischaemic stroke in COPD patients ranges from 1-15% and is approximately twice as likely to occur in COPD patients compared to non-COPD.<sup>[15,18,20]</sup> Hospitalisation for stroke is more frequent in COPD compared to controls (12 vs. 8 per 1000 PY).<sup>[18]</sup> The increased risk

of stroke may be partially attributable to the increased prevalence of AF and HF in COPD, which confer an increased risk.[21]

It can be challenging to adjust for shared risk factors (e.g., smoking, exercise) that may account for a co-association of diseases however, CVD is still associated with COPD when adjusted for smoking.[22] Whilst the prevalence of CVD is high in COPD populations, it may still be under-estimated, due to under-diagnosis of CVD. A study by Brekke et al., investigating under-diagnosis of MI in COPD found that 26% of participants had electrocardiogram (ECG) signs of a previous MI whereas only 16% had a diagnosed MI.[23] Symptoms of CVD and COPD (e.g. breathlessness, chest tightness, nocturnal cough and paroxysmal nocturnal dyspnoea) can overlap and this could impair recognition and diagnosis.[24] Diagnosing CVD in patients with COPD can also be challenging for other reasons that include, lung hyperinflation making optimal echocardiograms more difficult, and Brain Natriuretic Peptide (BNP) having reduced accuracy when diagnosing HF in patients with COPD.[25]

CVD	Prevalence in COPD Cohorts (%)	Prevalence in Control Cohorts (%)	OR (95% CI)	Incidence (Hospitalisations per 1000 person-years)		References
				COPD	Control	
Heart Failure	7 – 42	1 – 25	8.48 (7.65 - 9.40)	18	4	Rodríguez-Mañero et al.[14] Sidney et al.[15]
Myocardial Infarction and Angina	2 – 18	0.4 – 16	MI: 4.42 (3.77 - 5.17) Angina: 4.38 (3.55 - 5.42)	11	2	Sidney et al.[15] Schneider et al.[16] Behar et al.[17]
Arrhythmia	3 – 21	0.7 - 12	4.41 (4.00 - 4.87)	16	8	Curkendall et al.[18] Sidney et al.[15]
Stroke	1 – 15	0.5 - 14	2.44 (2.09 - 2.85)	12	8	Curkendall et al.[18] Song et al.[20] Sidney et al.[15]

**Table 1. Summary of incidence and prevalence of CVD in COPD.**

*The percentages and odds ratios included in the table are from studies reviewed in the [Incidence and prevalence of CVD in COPD](#) section. This topic has also recently been comprehensively reviewed by Chen et al.[13] Ranges of prevalence represent the highest and lowest values from the literature quoted. OR and CI refer to a particular*

*study and are not representative of meta-analysed OR/CI. Incidence figures relate to a particular study and are not representative of an average incidence. CI, confidence interval; COPD (chronic obstructive pulmonary disease), CVD (cardiovascular disease, MI (myocardial infarction), OR (odds ratio).*

## **COPD SUBTYPES ASSOCIATED WITH CVD**

COPD can be classified into different subtypes and the risk of CVD is heterogenous throughout the spectrum of COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages initially stratified COPD according to disease severity, measured by airflow limitation, with stage one being mild ( $FEV1 \geq 80\%$  predicted) and stage four being very severe ( $FEV1 < 30\%$  predicted).[9] CVD is more common with increasing COPD severity (i.e. GOLD stage four), however, some studies have reported higher rates of CVD with less severe COPD, which could be attributed to bias from premature CVD mortality in more severe COPD.[9,12] COPD is now categorised using the GOLD ABCD assessment tool, classifying COPD into groups A-D, based on symptom severity and exacerbation history.[9] There is a trend towards lower CVD risk in group A and higher risk in group D, the group with more severe symptoms and frequent exacerbations.[9,26] CHD was associated most strongly with more severe symptoms (groups B and D) whereas HF was associated strongly with both more severe symptoms and more exacerbations (groups C and D).[26] This may be confounded by difficulty in separating acute exacerbations of COPD (AECOPD) and heart failure leading to some misdiagnosis. There may be more nuanced subtype associations and a recent study by Pikoula et al., used unsupervised machine learning to identify 5 COPD clusters that were then investigated for CVD risk.[27] The CVD/diabetes cluster consisted predominantly of male ex-smokers with diabetes and high BMI, and had frequent CVD events.[27] Interestingly, the severe COPD/frailty cluster (predominately female, current smokers with very severe COPD and low/normal BMI) had a low prevalence of CVD. This suggests that COPD severity is not the only determinant of CVD risk in COPD, which has implications for risk prediction and diagnosis. Furthermore, the CVD/diabetes cluster had the highest rates of AECOPD requiring hospitalisation and the highest CVD mortality rate, suggesting that CVD comorbidity has a negative impact on COPD outcomes.[27]

Radiology, including thoracic computed tomography (CT) can be used to subtype COPD and inform CVD risk. Coronary artery calcification (CAC), which is associated with increased risk of CHD, is more frequent in centrilobular emphysema compared to paraseptal emphysema.[28,29]. COPD patients with airway predominant disease (e.g., increased airway-wall thickness) identified on CT, have more frequent CVD and higher inflammatory markers compared to those with emphysema predominant disease.[30]

### **PATHOPHYSIOLOGY OF CVD IN COPD**

CVD and COPD are inflammatory conditions involving the recruitment of neutrophils and macrophages at the site of pathology, but with differing pathobiological roles.[31,32] In atherosclerosis, macrophages accumulate intracellular cholesterol, whilst in COPD macrophages release inflammatory mediators. Local lung inflammation in COPD may “overspill” systemically resulting in endothelial dysfunction, atherothrombosis and increased CV risk. [33] There is accumulating evidence of shared and interacting pathobiological pathways between the two diseases.[10]

Smoking doubles the risk of MI and HF, and toxins from cigarette smoking augment the inflammatory response including increasing interleukin-8 (IL8) and tumour necrosis factor-alpha (TNF $\alpha$ ) levels, that promote inflammation in the lungs and systemically.[34,35,22] Cigarette smoke impairs the innate and adaptive response mechanisms and coupled with increased inflammation may result in tissue destruction in the lungs (e.g. emphysema) and vasculature (e.g. atherosclerosis).[35,36] Inflammatory mediators and toxins from smoking may increase oxidative stress and protease-antiprotease imbalances that further contributes to CVD and COPD pathogenesis.[37] Elastin is a key protein in connective tissue that helps maintain airway patency in the lungs and ensures elastic recoil in arteries. Age-related elastin degradation may increase the risk of emphysema and arterial hypertension, diseases that are more frequent in older populations.[10,38,39] Regular physical activity is associated with lower RHR and improved lung function, and COPD and CVD are more frequent in sedentary cohorts.[40,41] Whilst these associations may be causal, there are alternative explanations including disease manifesting more frequently with lower



physiological reserve, or breathless patients with established disease performing less exercise (reverse causality).

Pathophysiological factors in COPD may increase the risk of CVD by several different mechanisms: (i) hypoxia increasing the risk of atherosclerosis (ii) adverse effects of COPD contributing to cardiac disease and (iii) AECOPD increasing the risk of CV events.[37] Lung parenchymal damage and ventilation/perfusion mismatch in COPD can lead to alveolar hypoxia, which can stimulate pro-atherosclerotic processes including deficient lipid efflux, inflammation and impaired glucose metabolism.[42,43] Adaptive and maladaptive physiological processes in COPD may result in CV dysfunction through several mechanisms. Firstly, lung hyperinflation in COPD may cause cardiac compression and dysfunction which can be improved by lung volume reduction surgery, an intervention that can also improve endothelial function and blood pressure.[44,45] Secondly, pulmonary hypertension (PH) as a consequence of COPD increases with disease severity and can lead to right-sided HF.[46] Thirdly, the reduced physical reserve associated with many COPD patients may increase their risk of developing arterial stiffness and subsequent major CV events.[39] Furthermore, AECOPDs are associated with an increased risk of MI and ischaemic stroke within one month and the risk remains high up to 1 year.[7] The pathomechanisms associated with COPD and CVD are summarised in **figure 1**.

## **PREDICTING CVD IN COPD**

Identifying clinical and subclinical CVD in COPD could facilitate the administration of preventative treatments and treatment optimisation for patients with established disease (see [Treatment of concurrent CVD and COPD](#) section). Risk prediction tools for CVD could utilise (i) clinical phenotypes (ii) blood biomarkers (iii) radiological biomarkers (iv) genetic risk factors, or a combination. There are no current guidelines or consensus statements about the optimal screening approach for CVD in COPD and the following section highlights screening and diagnostic strategies.[47]

### **Clinical phenotype**

Clinical risk prediction tools used to risk stratify CVD in the general population may not be as accurate in COPD patients and may require different cut-off values. A

CHA2DS2-VASc score of 2 or more is used to guide anticoagulant treatment in AF however, patients with COPD the risk of AF is 5 times higher in those with a score of less than 2 compared to non-COPD.[48] This suggests that patients with COPD may benefit from anticoagulation at lower CHA2DS2-VASc scores. Furthermore, in patients with the same risk prediction scores, subclinical CVD is more frequent in patients with COPD than those without.[49] Other risk prediction scores that exclude COPD (e.g. Framingham, ASSIGN, QRISK) may also underestimate CVD risk in COPD cohorts.[50] Specific risk scores, such as the COPDCoRi that utilises sex, smoking history and dyslipidaemia may have improved accuracy for predicting CVD in COPD.[51]

### **Blood biomarkers**

Inflammation and its dysregulation are important in the pathogenesis of COPD and CVD.[31,32] In AECOPD, inflammatory markers including fibrinogen, leucocytes, C-reactive protein (CRP), interleukin-6 (IL6) and TNF $\alpha$  are raised and associated with more frequent CV events however, they have low specificity individually.[52] Elevated cardiac biomarkers that include troponin, BNP and copeptin have been associated with worse CV outcomes in COPD but also lack specificity and have limited prognostic utility when used in isolation.[53] Novel blood biomarkers may have a role in predicting CVD and elevated circulating desmosine, microfibrillar-associated protein 4, angiotensin-like protein 4 and monocyte to HDL-cholesterol ratio are associated with higher CVD risk in COPD.[54–57] However, CVD and COPD are heterogeneous diseases and greater predictive accuracy may be achieved with blood biomarker panels and the inclusion of longitudinal data to predict CVD in patients with COPD.

### **Radiological Biomarkers**

Lung density and bronchial wall thickness can be assessed by CT scans, enabling early detection of COPD and the risk of CHD can be evaluated by calculating CAC scores.[58] This could be particularly relevant when CT scans are performed for screening purposes such as lung cancer. However, these radiological biomarkers require good quality scans, and their accuracy could be limited in COPD patients with orthopnoea that are unable to lie flat. CAC is an independent non-invasive predictor of subclinical CVD in COPD that may outperform traditional risk prediction scores.[59] Subclinical CVD in COPD can be assessed using a range of additional non-invasive

techniques including carotid intima-media thickness, ankle-brachial index, and markers arterial stiffness (e.g., pulse wave velocity) and endothelial dysfunction (e.g., flow-mediated dilation).[60] Whilst these methods demonstrate that patients with more severe COPD have a greater burden of subclinical CVD, the studies have been limited by small cohort sizes and insufficient understanding of the best method to diagnose subclinical disease and the natural history of progression from subclinical to clinical CVD in COPD including when to intervene.[60] For example, arterial stiffness is an independent predictor of cardiovascular morbidity and mortality in addition to traditional CV risk factors, that can be assessed by a broad range of techniques that differ in validity, which impacts on their predictive accuracy. [61]

PH can occur due to both left heart disease and COPD, particularly with increasing disease severity and is associated with a poor prognosis.[46] Furthermore, right heart failure in COPD can impair left ventricular function due to ventricular interdependence.[62] Identifying COPD patients with PH can guide treatment optimisation (i.e., long-term oxygen, diuretics), inform prognostic discussions and identify patients for PH-specific clinical trials. The ratio of the diameter of the pulmonary artery compared to the aorta (PA:A ratio) may be used as a surrogate marker of pulmonary hypertension in stable COPD. [63] Furthermore, a PA:A ratio of greater than 1 is associated with more severe AECOPDs.[64] Novel strategies to monitor PH in COPD have included an implantable pulmonary pressure monitor, which can assist in optimising management and reducing hospitalisations.[65]

## **SHARED GENETICS OF COPD AND CVD**

CVD and COPD are heritable polygenic diseases associated with multiple genetic variants and genes.[66,67] The high prevalence of CVD in COPD may suggest shared genetic risk factors that predispose to CVD and COPD. A genome-wide association study (GWAS) of samples from the International COPD Genetics Consortium and UK Biobank identified 27 genes associated with either COPD or lung function, including pathways related to extracellular signalling.[67] The most common CVD phenotype investigated with GWAS is CHD, which is associated with single nucleotide polymorphisms in over 150 genes, including similar extracellular signalling pathways identified in COPD.[68]

A cross-trait GWAS (that examines shared genetic effects between diseases) in 12,550 COPD patients and 705,148 CVD patients found minimal overlap between COPD and CHD but modest overlap between COPD and both resting heart rate (RHR) and systemic hypertension.[69] The genetic overlap between COPD and RHR is of interest, as RHR is raised in COPD and associated with increased mortality.[70–73] Whilst this could suggest shared pathways between COPD and RHR, there are alternative reasons for a raised heart rate in COPD including medication effects and chronic inflammation.[74] The genetic overlap between COPD and hypertension may have important pathobiological consequences and arterial stiffness is increased in COPD which could result in increased CVD morbidity and mortality.[45,75] Additionally, shared genetic variants in non-coding genes may also affect pathways related to arterial pressure.[69]

Genetic variants could also increase the disease risk of COPD and/or CVD by their interaction with environmental risk factors (gene-environment interaction). Cigarette smoking is the main environmental risk factor for COPD and variation in disease outcomes related to smoking exposure suggests a potential role for gene-environment interaction influencing disease risk. Some smokers may be predisposed to developing COPD due to genetic variation in nicotine-related pathways.[76] Furthermore, genetic variation in the *IL6* gene may interact with smoking to increase the risk of CVD and COPD.[77] Individuals with a genetic variant in the *IL6* gene that is associated with increased IL6 levels had worse lung function and an increased risk of CVD.[77]

The treatment of coexisting CVD and COPD may be affected by genetic variation for example, angiotensin-converting enzyme (*ACE*) gene variants, which are more frequent in East Asian populations, may attenuate the effects of ACE inhibitor treatment in patients with HF and COPD.[78–80] Furthermore, individuals with certain *ACE* polymorphisms that are treated with ACE inhibitors are more susceptible to lung function decline in response to fluid overload.[81]

## **TREATMENT OF CONCURRENT CVD AND COPD**

Medication for CVD may worsen COPD and vice versa. Common medications in CVD include  $\beta$ -blockers, ACEi, angiotensin receptor blockers (ARBs), antiplatelets and statins and in COPD include bronchodilators and corticosteroids. This subsection explores the effect of these drugs on COPD and CVD.

Patients at high risk of CVD or with established disease have improved morbidity and mortality with primary and secondary preventative treatments, which may be underutilised in patients with COPD.[82] In study by Alter et al., that investigated the treatment of coexisting HF and COPD, 38% of participants with a reduced left ventricular ejection fraction, and 53% with left ventricular dilatation were not prescribed HF medication.[83] Despite being under-prescribed, ACEi, ARBs and  $\beta$ -blockers are associated with improved mortality in COPD.[84] Historically, there was concern about  $\beta$ -blockers causing bronchoconstriction and reducing the effectiveness of both emergency and long-acting  $\beta_2$ -agonist treatment.[85] More recent research demonstrates that cardioselective  $\beta$ -blockers do not have adverse respiratory effects and may reduce the risk of AECOPD.[86] However, a subsequent clinical trial was discontinued after metoprolol was shown to be associated with a higher risk of pulmonary exacerbations leading to hospitalisation.[87] Further trials are ongoing to establish the effect of  $\beta$ -blockers on AECOPD rates and adverse CV outcomes in COPD patients (ClinicalTrials.gov numbers: [NCT03566667](#), [NCT03917914](#)). Rate limiting medications with less off-target effects than  $\beta$ -blockers (e.g. Ivabradine) can also be considered in patients with COPD and HF.[88]

Medications used in CVD primary prevention including statins and antiplatelets are associated with improved mortality in both COPD and non-COPD populations.[89,90] Statins may be particularly beneficial in COPD, as they reduce inflammation and alter neutrophil function however, they do not reduce pulmonary exacerbations.[91] The role of antiplatelets in the management of COPD and CVD has been explored in several studies. An RCT found platelet functional inhibition to aspirin and ticagrelor was not observed in one-third of COPD patients without a history of CVD.[92] This was consistent with a high prothrombotic milieu in COPD that may account for excess

CVD and require additional antithrombotic therapies. Aspirin use has not been found to alter lung function but observational studies suggest it is associated with lower AECOPDs, reduced emphysema progression, improved mortality and better quality of life, however this needs confirmation in longer term RCTs.[89,93,94]

Treatments for COPD may have effects on CVD and CV outcomes. Whilst tachyarrhythmias and hypokalaemia are recognised side effects of bronchodilators, their key role in COPD disease management and optimisation is likely to have a net beneficial effect.[95,96] COPD severity and AECOPD are associated with increased inflammatory markers, more frequent CV events (MI and stroke) and worse CVD mortality.[97,98] Therefore, COPD inhaled therapies that reduce pulmonary exacerbation rates and stabilise or improve lung function. may have a beneficial effect on CV outcomes. Long-acting dual bronchodilators have been associated with an increased risk of cardiac events when compared to monotherapy however, in a meta-analysis, there was no difference in cardiac events or mortality between long-acting mono and dual bronchodilators, although many patients with CVD were excluded from the studies.[99,100] Inhaled corticosteroids improve lung function, reduce AECOPD and potentially reduce all-cause mortality, which may be driven by increased corticosteroid dosage reducing CV events.[101,102] However, in the SUMMIT trial, which recruited a large cohort of COPD patients enriched for those with CVD or significant risk factors, there was no difference in CV events due to inhaled corticosteroids.[98] Novel therapies including reactive oxygen species scavengers (e.g. apocynin) that suppress oxidation, a key feature of both COPD and CVD, may provide future strategies for treating COPD and CVD.[103]

A Cochrane review of interventions for patients with COPD and long-term conditions including CVD, found insufficient RCTs to guide recommendations although pulmonary rehabilitation and multicomponent interventions may improve quality of life and function status.[104] Several features of PR such as exercise and nutritional interventions have the potential to have an impact on CV risk. Vivodtzev et al found COPD patients who underwent aerobic endurance training had reduced arterial stiffness as measured by reduced carotid-radial pulse wave velocity (PWV).[105] Conversely, Vanfleteren et al found no difference in PWV measured by arterial stiffness in COPD patients after undergoing PR.[106] The effect of PR on different

COPD subtypes is unknown, and there may be differential CVD outcomes as arterial stiffness can vary in response to PR among patients with similar baseline characteristics.[106] Arterial stiffness is a proxy marker of CVD and it is unclear whether PR improves CV events and mortality in patients with COPD.

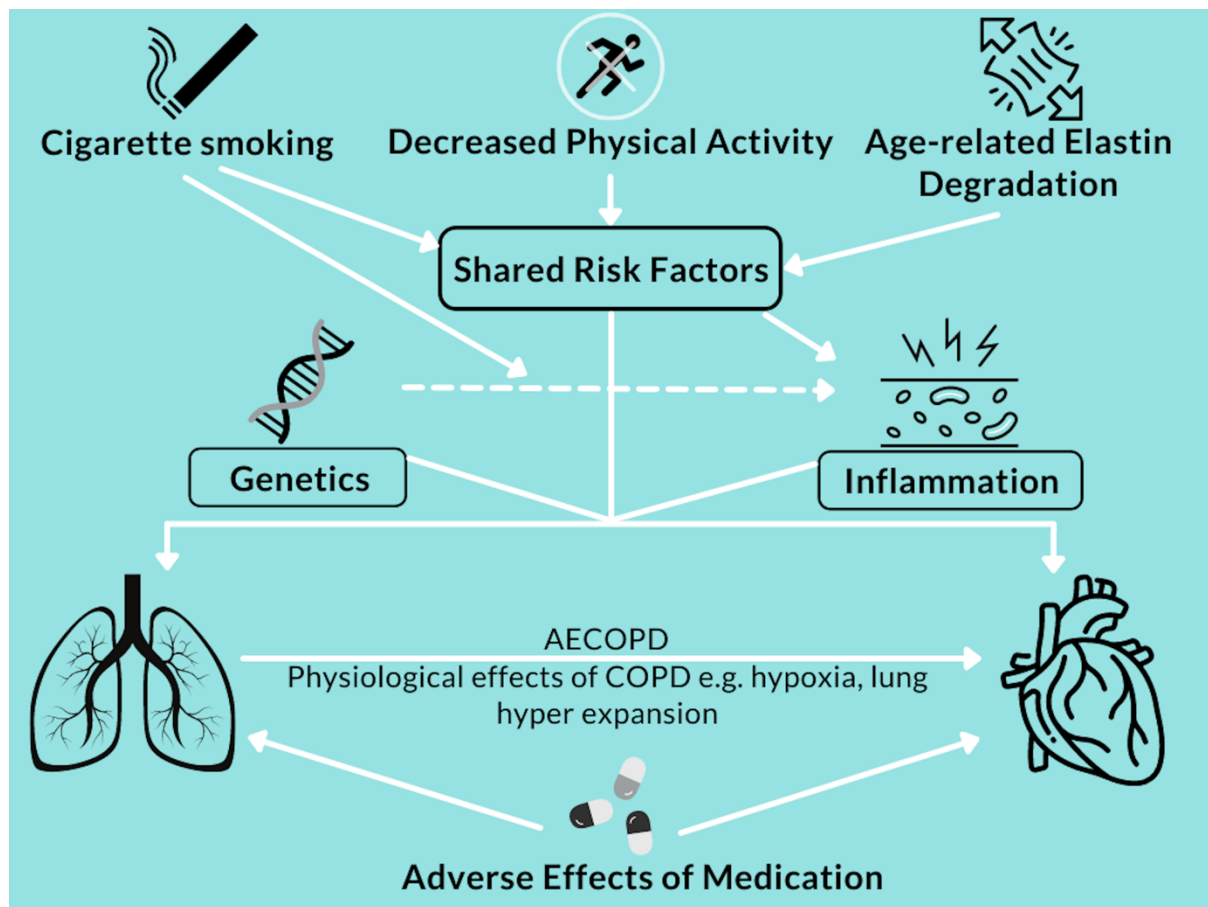
## **DISCUSSION**

Patients with COPD are at increased risk of CVD and concomitant disease leads to reduced quality of life and increased CV events, hospitalisations, and mortality. Diagnosing CVD in patients with COPD is challenging due to non-specific and overlapping symptoms, shared risk factors and reduced accuracy of some investigations, which can result in underdiagnosis and undertreatment. It has been proposed that the COPD spectrum should encompass those with “pre-COPD”.[107] Traditionally, COPD is spirometrically defined but a more recent proposed definition suggests individuals without spirometric evidence of COPD who have respiratory symptoms and radiological evidence of COPD may be at increased risk of morbidity and spirometric disease progression.[109] This is relevant as patients with pre-COPD may also be at increased risk of CVD and adverse CV outcomes, which should be explored in future studies. Whilst CVD has been associated with increasing severity of COPD, there are more nuanced relationships that have implications for risk prediction. A systematic review of COPD clinical phenotypes identified a common phenotype with poor long-term health outcomes that had moderate airflow obstruction, cardiometabolic comorbidities, were older and obese.[108] This COPD subtype also had increased inflammatory markers although whether this contributed to CVD aetiology or was an epiphenomenon of the cluster associations is uncertain. Inflammation is increased in COPD and is also associated with arterial stiffness, a CV risk factor that increases during exacerbations and is greater in frequent COPD exacerbators.[33,109] However, the mechanisms linking COPD and CVD are likely to be multifactorial and accurate risk prediction may require incorporating data from clinical phenotypes, blood/radiological biomarkers, and genetics, and then demonstrating superiority to traditional risk prediction models (i.e., QRISK). Furthermore, CVD risk may be dynamic, altering as COPD progresses or other CV risk factors change, which would necessitate utilising longitudinal data whilst considering cost effectiveness. Artificial intelligence could integrate this high

dimension data to improve CV risk prediction accuracy, which could improve preventative strategies.[110] This could have applicability to lung cancer screening cohorts that can identify CVD risk through CAC scores and where in a study by Ruparel et al., 57% of patients at significant risk of CVD were not taking statins for primary prevention.[111] Other interventions that may reduce CVD risk in COPD are summarised in **figure 2**. AECOPD are associated with increased CV risk and interventions that reduce exacerbations rates may have beneficial effects on CV outcomes. Furthermore, CV events are markedly increased following viral respiratory tract infections and therefore, influenzae vaccinations may reduce CV events and AECOPD.[112] There are currently no specific guidelines on managing CVD in COPD that differ from the non-COPD recommendations.[9] There is currently a lack evidence from prospective interventional studies to inform guidelines which are being addressed by ongoing and future studies (see [Treatment of concurrent CVD and COPD](#) section). Managing CVD and multimorbidity in COPD is complex, and requires improved risk prediction, interventional studies to guide treatment optimisation and an integrative approach to patient care.



## FIGURES



**Figure 1. Pathomechanisms associated with COPD and CVD.**

AECOPD, acute exacerbation of COPD.

# REDUCING CVD RISK IN COPD

## LIFESTYLE ADVICE

Smoking cessation can reduce the risk of COPD, myocardial infarction and heart failure



Increasing physical activity can lower resting heart rate and improve lung function

## WORSENING COPD

Prevention of advancement of COPD by careful management can reduce the risk of major adverse cardiac events



## ACUTE EXACERBATIONS OF COPD

Reducing rates of AECOPD could lead to reduced rates of MI post-AECOPD  
This includes optimising treatments and annual influenzae vaccination



## PRIMARY PREVENTION THERAPIES

Applying QRISK scores and offering lipid lowering therapies to those at increased risk of CVD



## RESPIRATORY FAILURE

Correction of respiratory failure with long term oxygen therapy reduces hypoxia and may reduce the development and progression of atherosclerosis



## HYPOTHESES FOR FURTHER RESEARCH

### LUNG VOLUME REDUCTION PROCEDURES

Endobronchial valves or surgery may improve endothelial function and blood pressure.  
Do they have beneficial effects on cardiovascular outcomes?



### PULMONARY HYPERTENSION

Do novel methods of monitoring pulmonary hypertension in COPD, pulmonary vasodilators or other novel therapies affect pulmonary hypertension outcomes, hospitalisation and CVD progression?



**Figure 2. Interventions that may reduce CVD risk in COPD.**

AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI, myocardial infarction.

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None

## **CONTRIBUTORS**

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VB and AM undertook the literature search, co-wrote the first draft and prepared the final draft. MN conceived the idea for the manuscript, co-wrote the first draft and prepared the final draft. AMT edited the first and final drafts. All authors approved the final manuscript.

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Not required.

## REFERENCES

- 1 Barnes PJ. Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2000;**343**:269–80. doi:10.1056/NEJM200007273430407
- 2 Adeloye D, Chua S, Lee C, *et al.* Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. *J Glob Health* 2015;**5**:020415. doi:10.7189/jogh.05-020415
- 3 Ray S, Guarascio, Finch, *et al.* The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *Clin Outcomes Res* 2013;**235**. doi:10.2147/CEOR.S34321
- 4 Sin DD, Stafinski T, Ng YC, *et al.* The Impact of Chronic Obstructive Pulmonary Disease on Work Loss in the United States. *Am J Respir Crit Care Med* 2002;**165**:704–7. doi:10.1164/ajrccm.165.5.2104055
- 5 Vos T, Lim SS, Abbafati C, *et al.* Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020;**396**:1204–22. doi:10.1016/S0140-6736(20)30925-9
- 6 European Heart Network. European Cardiovascular Disease Statistics 2017 Edition. 2017.<http://www.ehnheart.org/cvd-statistics.html> (accessed 1 Jun 2021).
- 7 Kunisaki KM, Dransfield MT, Anderson JA, *et al.* Exacerbations of Chronic Obstructive Pulmonary Disease and Cardiac Events. A *Post Hoc* Cohort Analysis from the SUMMIT Randomized Clinical Trial. *Am J Respir Crit Care Med* 2018;**198**:51–7. doi:10.1164/rccm.201711-2239OC
- 8 Black-Shinn JL, Kinney GL, Wise AL, *et al.* Cardiovascular Disease is Associated with COPD Severity and Reduced Functional Status and Quality of Life. *COPD J Chronic Obstr Pulm Dis* 2014;**11**:546–51. doi:10.3109/15412555.2014.898029
- 9 Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2020 Report. [https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19\\_WMV.pdf](https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf) (accessed 4 Dec 2020).
- 10 Morgan AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice? *Ther Adv Respir Dis* 2018;**12**:175346581775052. doi:10.1177/1753465817750524
- 11 Greulich T, Weist BJD, Koczulla AR, *et al.* Prevalence of comorbidities in COPD patients by disease severity in a German population. *Respir Med* 2017;**132**:132–8. doi:10.1016/j.rmed.2017.10.007

- 12 Mannino DM, Thorn D, Swensen A, *et al.* Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008;**32**:962–9. doi:10.1183/09031936.00012408
- 13 Chen W, Thomas J, Sadatsafavi M, *et al.* Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med* 2015;**3**:631–9. doi:10.1016/S2213-2600(15)00241-6
- 14 Rodríguez-Mañero M, López-Pardo E, Cordero A, *et al.* A prospective study of the clinical outcomes and prognosis associated with comorbid COPD in the atrial fibrillation population. *Int J Chron Obstruct Pulmon Dis* 2019;**12**:371–80. doi:10.2147/COPD.S174443
- 15 Sidney S, Sorel M, Quesenberry Jr CP, *et al.* COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* 2005;**128**:2068–75. doi:10.1378/chest.128.4.2068
- 16 Schneider C, Bothner U, Jick SS, *et al.* Chronic obstructive pulmonary disease and the risk of cardiovascular diseases. *Eur J Epidemiol* 2010;**25**:253–60. doi:10.1007/s10654-010-9435-7
- 17 Behar S, Panosh A, Reicher-Reiss H, *et al.* Prevalence and prognosis of chronic obstructive pulmonary disease among 5,839 consecutive patients with acute myocardial infarction. *Am J Med* 1992;**93**:637–41. doi:10.1016/0002-9343(92)90196-I
- 18 Curkendall SM, DeLuise C, Jones JK, *et al.* Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol* 2006;**16**:63–70. doi:10.1016/j.annepidem.2005.04.008
- 19 Lip GY, Tse HF, Lane DA. Atrial fibrillation. *The Lancet* 2012;**379**:648–61. doi:10.1016/S0140-6736(11)61514-6
- 20 Song S, Yang P-S, Kim T-H, *et al.* Relation of Chronic Obstructive Pulmonary Disease to Cardiovascular Disease in the General Population. *Am J Cardiol* 2015;**120**:1399–404. doi:10.1016/j.amjcard.2017.07.032
- 21 Boehme AK, Esenwa C, Elkind MSV. Stroke Risk Factors, Genetics, and Prevention. *Circ Res* 2017;**120**:472–95. doi:10.1161/CIRCRESAHA.116.308398
- 22 Rodríguez LAG, Wallander M-A, Martín-Merino E, *et al.* Heart failure, myocardial infarction, lung cancer and death in COPD patients: a UK primary care study. *Respir Med* 2010;**104**:1691–9. doi:10.1016/j.rmed.2010.04.018
- 23 Brekke PH, Omland T, Smith P, *et al.* Underdiagnosis of myocardial infarction in COPD – Cardiac Infarction Injury Score (CIIS) in patients hospitalised for COPD exacerbation. *Respir Med* 2008;**102**:1243–7. doi:10.1016/j.rmed.2008.04.010

- 24 Gunes Y, Tuncer M, Guntekin U, *et al.* Reliability of symptoms suggestive of angina in patients with chronic obstructive pulmonary disease. *Arq Bras Cardiol* 2009;**92**:334–8, 351–5, 364–8. doi:10.1590/s0066-782x2009000500005
- 25 Hawkins NM, Petrie MC, Jhund PS, *et al.* Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Eur J Heart Fail* 2009;**11**:130–9. doi:10.1093/eurjhf/hfn013
- 26 Kahnert K, Alter P, Young D, *et al.* The revised GOLD 2017 COPD categorization in relation to comorbidities. *Respir Med* 2018;**134**:79–85. doi:10.1016/j.rmed.2017.12.003
- 27 Pikoula M, Quint JK, Nissen F, *et al.* Identifying clinically important COPD subtypes using data-driven approaches in primary care population based electronic health records. *BMC Med Inform Decis Mak* 2019;**19**:86. doi:10.1186/s12911-019-0805-0
- 28 Hecht HS, Cronin P, Blaha MJ, *et al.* 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: A report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. *J Cardiovasc Comput Tomogr* 2017;**11**:74–84. doi:10.1016/j.jcct.2016.11.003
- 29 Bhatt SP, Nath HP, Kim Y, *et al.* Centrilobular emphysema and coronary artery calcification: mediation analysis in the SPIROMICS cohort. *Respir Res* 2018;**19**:257. doi:doi.org/10.1186/s12931-018-0946-1
- 30 Young KA, Regan EA, Han MK, *et al.* Subtypes of COPD Have Unique Distributions and Differential Risk of Mortality. *Chronic Obstr Pulm Dis* 2019;**6**:400–13. doi:10.15326/jcopdf.6.5.2019.0150
- 31 Marsh S. Smoking and COPD: what really are the risks? *Eur Respir J* 2006;**28**:883–4. doi:10.1183/09031936.06.00074806
- 32 Angkananard T, Anothaisintawee T, McEvoy M, *et al.* Neutrophil Lymphocyte Ratio and Cardiovascular Disease Risk: A Systematic Review and Meta-Analysis. *BioMed Res Int* 2018;**2018**. doi:10.1155/2018/2703518
- 33 Sindén NJ, Stockley RA. Systemic inflammation and comorbidity in COPD: a result of “overspill” of inflammatory mediators from the lungs? Review of the evidence. *Thorax* 2010;**65**:930–6. doi:10.1136/thx.2009.130260
- 34 Banks E, Joshy G, Korda RJ, *et al.* Tobacco smoking and risk of 36 cardiovascular disease subtypes: fatal and non-fatal outcomes in a large prospective Australian study. *BMC Med* 2019;**17**:128. doi:10.1186/s12916-019-1351-4
- 35 MacNee W. Pathology, pathogenesis, and pathophysiology. *BMJ* 2006;**332**:1202–4. doi:10.1136/bmj.332.7551.1202

- 36 Qiu F, Liang C-L, Liu H, *et al.* Impacts of cigarette smoking on immune responsiveness: Up and down or upside down? *Oncotarget* 2016;**8**:268–84. doi:10.18632/oncotarget.13613
- 37 Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? *Eur Respir Rev* 2018;**27**:180057. doi:10.1183/16000617.0057-2018
- 38 Sanada F, Taniyama Y, Muratsu J, *et al.* Source of Chronic Inflammation in Aging. *Front Cardiovasc Med* 2018;**5**:12. doi:10.3389/fcvm.2018.00012
- 39 Osman S, Ziegler C, Gibson R, *et al.* The association between risk factors and chronic obstructive pulmonary disease in Canada: A cross-sectional study using the 2014 canadian community health survey. *Int J Prev Med* 2017;**8**:86. doi:10.4103/ijpvm.IJPVM\_330\_17
- 40 Reimers A, Knapp G, Reimers C-D. Effects of Exercise on the Resting Heart Rate: A Systematic Review and Meta-Analysis of Interventional Studies. *J Clin Med* 2018;**7**:503. doi:10.3390/jcm7120503
- 41 Cheng YJ. Effects of physical activity on exercise tests and respiratory function. *Br J Sports Med* 2003;**37**:521–8. doi:10.1136/bjsm.37.6.521
- 42 Kent BD, Mitchell PD, McNicholas WT. Hypoxemia in patients with COPD: cause, effects, and disease progression. *Int J Chron Obstruct Pulmon Dis* 2011;**6**:199–208. doi:10.2147/COPD.S10611
- 43 Marsch E, Sluimer JC, Daemen MJAP. Hypoxia in atherosclerosis and inflammation: *Curr Opin Lipidol* 2013;**24**:393–400. doi:10.1097/MOL.0b013e32836484a4
- 44 Xu Y, Yamashiro T, Moriya H, *et al.* Hyperinflated lungs compress the heart during expiration in COPD patients: a new finding on dynamic-ventilation computed tomography. *Int J Chron Obstruct Pulmon Dis* 2017;**Volume 12**:3123–31. doi:10.2147/COPD.S145599
- 45 Clarenbach C, Franzen D, Kohler M, *et al.* Physical inactivity and arterial stiffness in COPD. *Int J Chron Obstruct Pulmon Dis* 2015;:1891. doi:10.2147/COPD.S90943
- 46 Nathan SD, Barbera JA, Gaine SP, *et al.* Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J* 2019;**53**:1801914. doi:10.1183/13993003.01914-2018
- 47 Natali D, Cloatre G, Hovette P, *et al.* Screening for comorbidities in COPD. *Breathe* 2020;**16**:190315. doi:10.1183/20734735.0315-2019
- 48 Perticone M, Sciacqua A, Tripepi G, *et al.* Competitive interaction between chronic obstructive pulmonary disease and CHA2DS2-VASc score in predicting incident atrial fibrillation. *Int J Cardiol* 2018;**255**:74–9. doi:10.1016/j.ijcard.2017.11.036

- 49 Stone I, Khanji M, James W-Y, *et al.* P21 The applicability of current cardiovascular risk scores and cardiovascular surrogates in chronic obstructive pulmonary disease: A case-control study. *Thorax* 2015;**70**:A85. doi:10.1136/thoraxjnl-2015-207770.158
- 50 van Staa T-P, Gulliford M, Ng ES-W, *et al.* Prediction of cardiovascular risk using Framingham, ASSIGN and QRISK2: how well do they predict individual rather than population risk? *PloS One* 2014;**9**:e106455. doi:10.1371/journal.pone.0106455
- 51 Cazzola M, Calzetta L, Matera MG, *et al.* Chronic obstructive pulmonary disease and coronary disease: COPDCoRi, a simple and effective algorithm for predicting the risk of coronary artery disease in COPD patients. *Respir Med* 2015;**109**:1019–25. doi:10.1016/j.rmed.2015.05.021
- 52 King PT. Inflammation in chronic obstructive pulmonary disease and its role in cardiovascular disease and lung cancer. *Clin Transl Med* 2015;**4**. doi:10.1186/s40169-015-0068-z
- 53 Roversi S, Hawkins NM. Time to move from prognostication to diagnosis and treatment of heart disease in acute exacerbation of COPD. *Eur Respir J* 2017;**49**:1700912. doi:10.1183/13993003.00912-2017
- 54 Yakar HI, Kanbay A. Could monocyte level/HDL cholesterol ratio predict cardiovascular diseases in patients with COPD? *Niger J Clin Pract* 2020;**23**:450–5. doi:10.4103/njcp.njcp\_54\_19
- 55 Waschki B, Kirsten A, Holz O, *et al.* Angiopoietin-like protein 4 and cardiovascular function in COPD. *BMJ Open Respir Res* 2016;**3**:e000161. doi:10.1136/bmjresp-2016-000161
- 56 Johansson SL, Wulf-Johansson H, Schlosser A, *et al.* Plasma microfibrillar-associated protein 4 is not prognostic of emphysema progression but is associated with cardiovascular disease history and mortality in COPD patients. *ERJ Open Res* 2019;**5**:00021–2019. doi:10.1183/23120541.00021-2019
- 57 Rabinovich RA, Miller BE, Wrobel K, *et al.* Circulating desmosine levels do not predict emphysema progression but are associated with cardiovascular risk and mortality in COPD. *Eur Respir J* 2016;**47**:1365–73. doi:10.1183/13993003.01824-2015
- 58 Bhatt SP, Kazerooni EA, Newell JD, *et al.* Visual Estimate of Coronary Artery Calcium Predicts Cardiovascular Disease in COPD. *Chest* 2018;**154**:579–87. doi:10.1016/j.chest.2018.05.037
- 59 Zagaceta J, Bastarrika G, Zulueta JJ, *et al.* Prospective comparison of non-invasive risk markers of major cardiovascular events in COPD patients. *Respir Res* 2017;**18**:175. doi:10.1186/s12931-017-0658-y
- 60 Ye C, Younus A, Malik R, *et al.* Subclinical cardiovascular disease in patients with chronic obstructive pulmonary disease: a systematic review. *QJM* 2016;**hcw135**. doi:10.1093/qjmed/hcw135



- 61 Segers P, Rietzschel ER, Chirinos JA. How to Measure Arterial Stiffness in Humans. *Arterioscler Thromb Vasc Biol* 2020;**40**:1034–43. doi:10.1161/ATVBAHA.119.313132
- 62 Boussuges A, Pinet C, Molenat F, *et al.* Left Atrial and Ventricular Filling in Chronic Obstructive Pulmonary Disease: An Echocardiographic and Doppler Study. *Am J Respir Crit Care Med* 2000;**162**:670–5. doi:10.1164/ajrccm.162.2.9908056
- 63 Pérez-Enguix D, Morales P, Tomás JM, *et al.* Computed Tomographic Screening of Pulmonary Arterial Hypertension in Candidates for Lung Transplantation. *Transplant Proc* 2007;**39**:2405–8. doi:10.1016/j.transproceed.2007.07.055
- 64 Wells JM, Washko GR, Han MK, *et al.* Pulmonary Arterial Enlargement and Acute Exacerbations of COPD. *N Engl J Med* 2012;**367**:913–21. doi:10.1056/NEJMoa1203830
- 65 Krahnke JS, Abraham WT, Adamson PB, *et al.* Heart Failure and Respiratory Hospitalizations Are Reduced in Patients With Heart Failure and Chronic Obstructive Pulmonary Disease With the Use of an Implantable Pulmonary Artery Pressure Monitoring Device. *J Card Fail* 2015;**21**:240–9. doi:10.1016/j.cardfail.2014.12.008
- 66 Kathiresan S, Srivastava D. Genetics of Human Cardiovascular Disease. *Cell* 2012;**148**:1242–57. doi:10.1016/j.cell.2012.03.001
- 67 Silverman EK. Genetics of COPD. *Annu Rev Physiol* 2020;**82**:413–31. doi:10.1146/annurev-physiol-021317-121224
- 68 van der Harst P, Verweij N. Identification of 64 Novel Genetic Loci Provides an Expanded View on the Genetic Architecture of Coronary Artery Disease. *Circ Res* 2018;**122**:433–43. doi:10.1161/CIRCRESAHA.117.312086
- 69 International COPD Genetics Consortium, Zhu Z, Wang X, *et al.* Genetic overlap of chronic obstructive pulmonary disease and cardiovascular disease-related traits: a large-scale genome-wide cross-trait analysis. *Respir Res* 2019;**20**:64. doi:10.1186/s12931-019-1036-8
- 70 Zhou D, Xi B, Zhao M, *et al.* Uncontrolled hypertension increases risk of all-cause and cardiovascular disease mortality in US adults: the NHANES III Linked Mortality Study. *Sci Rep* 2018;**8**:9418. doi:10.1038/s41598-018-27377-2
- 71 Kim S-H, Park J-H, Lee J-K, *et al.* Chronic obstructive pulmonary disease is independently associated with hypertension in men: A survey design analysis using nationwide survey data. *Medicine (Baltimore)* 2017;**96**:e6826. doi:10.1097/MD.00000000000006826
- 72 Jensen MT, Suadicani P, Hein HO, *et al.* Elevated resting heart rate, physical fitness and all-cause mortality: a 16-year follow-up in the Copenhagen Male Study. *Heart* 2013;**99**:882. doi:10.1136/heartjnl-2012-303375

- 73 Warnier MJ, Rutten FH, de Boer A, *et al.* Resting Heart Rate Is a Risk Factor for Mortality in Chronic Obstructive Pulmonary Disease, but Not for Exacerbations or Pneumonia. *PLoS ONE* 2014;**9**:e105152. doi:10.1371/journal.pone.0105152
- 74 Sears MR. Adverse effects of  $\beta$ -agonists. *J Allergy Clin Immunol* 2002;**110**:S322–8. doi:10.1067/mai.2002.129966
- 75 Mills NL, Miller JJ, Anand A, *et al.* Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. *Thorax* 2008;**63**:306. doi:10.1136/thx.2007.083493
- 76 DeMeo DL. Familial aggregation of FEF25-75 and FEF25-75/FVC in families with severe, early onset COPD. *Thorax* 2004;**59**:396–400. doi:10.1136/thx.2003.012856
- 77 Hackett, Stefanowicz, Aminuddin, *et al.* Effect of gene environment interactions on lung function and cardiovascular disease in COPD. *Int J Chron Obstruct Pulmon Dis* 2011;**277**. doi:10.2147/COPD.S18279
- 78 Forth R. ACE in COPD: a therapeutic target? *Thorax* 2003;**58**:556–8. doi:10.1136/thorax.58.7.556
- 79 Ma Y, Tong X, Liu Y, *et al.* ACE gene polymorphism is associated with COPD and COPD with pulmonary hypertension: a meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2018;**Volume 13**:2435–46. doi:10.2147/COPD.S168772
- 80 Contini M, Compagnino E, Cattadori G, *et al.* ACE-Inhibition Benefit on Lung Function in Heart Failure is Modulated by ACE Insertion/Deletion Polymorphism. *Cardiovasc Drugs Ther* 2016;**30**:159–68. doi:10.1007/s10557-016-6645-6
- 81 Marushchak M, Maksiv K, Krynytska I. ACE gene I/D polymorphism and arterial hypertension in patients with COPD. *Pneumologia* 2019;**68**:114–9. doi:10.2478/pneum-2019-0039
- 82 NICE. Cardiovascular disease risk assessment and prevention. NICE. 2020.<https://bnf.nice.org.uk/treatment-summary/cardiovascular-disease-risk-assessment-and-prevention.html> (accessed 10 Sep 2020).
- 83 Alter P, Mayerhofer BA, Kahnert K, *et al.* Prevalence of cardiac comorbidities, and their underdetection and contribution to exertional symptoms in COPD: results from the COSYCONET cohort. *Int J Chron Obstruct Pulmon Dis* 2019;**14**:2163–72. doi:10.2147/COPD.S209343
- 84 Bhatt SP, Wells JM, Kinney GL, *et al.*  $\beta$ -Blockers are associated with a reduction in COPD exacerbations. *Thorax* 2016;**71**:8–14. doi:10.1136/thoraxjnl-2015-207251
- 85 Baker JG, Wilcox RG.  $\beta$ -Blockers, heart disease and COPD: current controversies and uncertainties. *Thorax* 2017;**72**:271. doi:10.1136/thoraxjnl-2016-208412

- 86 Li X-F, Mao Y-M. Beta-blockers in COPD: A systematic review based on recent research. *Life Sci* 2020;**252**:117649. doi:10.1016/j.lfs.2020.117649
- 87 Dransfield MT, Voelker H, Bhatt SP, *et al.* Metoprolol for the Prevention of Acute Exacerbations of COPD. *N Engl J Med* 2019;**381**:2304–14. doi:10.1056/NEJMoa1908142
- 88 Zulkarneev R, Zagidullin N, Abdrahmanova G, *et al.* Ivabradine Prevents Heart Rate Acceleration in Patients with Chronic Obstructive Pulmonary Disease and Coronary Heart Disease after Salbutamol Inhalation. *Pharmaceuticals* 2012;**5**:398–404. doi:10.3390/ph5040398
- 89 Pavasini R, Biscaglia S, d’Ascenzo F, *et al.* Antiplatelet Treatment Reduces All-Cause Mortality in COPD Patients: A Systematic Review and Meta-Analysis. *COPD J Chronic Obstr Pulm Dis* 2016;**13**:509–14. doi:10.3109/15412555.2015.1099620
- 90 Soyseth V, Brekke PH, Smith P, *et al.* Statin use is associated with reduced mortality in COPD. *Eur Respir J* 2006;**29**:279–83. doi:10.1183/09031936.00106406
- 91 Walsh A, Perrem L, Khashan AS, *et al.* Statins versus placebo for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* Published Online First: 31 July 2019. doi:10.1002/14651858.CD011959.pub2
- 92 Kunadian V, Wilson N, Stocken DD, *et al.* Antiplatelet therapy in the primary prevention of cardiovascular disease in patients with chronic obstructive pulmonary disease: a randomised controlled proof-of-concept trial. *ERJ Open Res* 2019;**5**. doi:10.1183/23120541.00110-2019
- 93 Aaron CP, Schwartz JE, Hoffman EA, *et al.* A Longitudinal Cohort Study of Aspirin Use and Progression of Emphysema-like Lung Characteristics on CT Imaging: The MESA Lung Study. *Chest* 2018;**154**:41–50. doi:10.1016/j.chest.2017.11.031
- 94 Fawzy A, Putcha N, Aaron CP, *et al.* Aspirin Use and Respiratory Morbidity in COPD: A Propensity Score-Matched Analysis in Subpopulations and Intermediate Outcome Measures in COPD Study. *Chest* 2019;**155**:519–27. doi:10.1016/j.chest.2018.11.028
- 95 NICE. Chronic obstructive pulmonary disease. Natl. Inst. Health Care Excell. 2020.<https://bnf.nice.org.uk/treatment-summary/chronic-obstructive-pulmonary-disease.html> (accessed 10 Sep 2020).
- 96 Gupta P, O’Mahony MS. Potential Adverse Effects of Bronchodilators in the Treatment of Airways Obstruction in Older People: Recommendations for Prescribing. *Drugs Aging* 2008;**25**:415–43. doi:10.2165/00002512-200825050-00005
- 97 Malo de Molina R, Aguado S, Arellano C, *et al.* Ischemic Heart Disease during Acute Exacerbations of COPD. *Med Sci* 2018;**6**:83. doi:10.3390/medsci6040083

- 98 Vestbo J, Anderson JA, Brook RD, *et al.* Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *The Lancet* 2016;**387**:1817–26. doi:10.1016/S0140-6736(16)30069-1
- 99 Parkin L, Williams S, Sharples K, *et al.* Dual versus single long-acting bronchodilator use could raise acute coronary syndrome risk by over 50%: A population-based nested case-control study. *J Intern Med* Published Online First: 21 July 2021. doi:10.1111/joim.13348
- 100 Oba Y, Keeney E, Ghathehorde N, *et al.* Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis. *Cochrane Database Syst Rev* 2018;**12**:CD012620. doi:10.1002/14651858.CD012620.pub2
- 101 Calverley PMA, Anderson JA, Celli B, *et al.* Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2007;**356**:775–89. doi:10.1056/NEJMoa063070
- 102 Rabe KF, Martinez FJ, Ferguson GT, *et al.* Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. *N Engl J Med* 2020;**383**:35–48. doi:10.1056/NEJMoa1916046
- 103 Brassington K, Selemidis S, Bozinovski S, *et al.* New frontiers in the treatment of comorbid cardiovascular disease in chronic obstructive pulmonary disease. *Clin Sci* 2019;**133**:885–904. doi:10.1042/CS20180316
- 104 Dennett EJ, Janjua S, Stovold E, *et al.* Tailored or adapted interventions for adults with chronic obstructive pulmonary disease and at least one other long-term condition: a mixed methods review. *Cochrane Database Syst Rev* 2021;**7**:CD013384. doi:10.1002/14651858.CD013384.pub2
- 105 Vivodtzev I, Minet C, Wuyam B, *et al.* Significant improvement in arterial stiffness after endurance training in patients with COPD. *Chest* 2010;**137**:585–92. doi:10.1378/chest.09-1437
- 106 Vanfleteren LEGW, Spruit MA, Groenen MTJ, *et al.* Arterial stiffness in patients with COPD: the role of systemic inflammation and the effects of pulmonary rehabilitation. *Eur Respir J* 2014;**43**:1306–15. doi:10.1183/09031936.00169313
- 107 Han MK, Agusti A, Celli BR, *et al.* From GOLD 0 to Pre-COPD. *Am J Respir Crit Care Med* 2021;**203**:414–23. doi:10.1164/rccm.202008-3328PP
- 108 Pinto LM, Alghamdi M, Benedetti A, *et al.* Derivation and validation of clinical phenotypes for COPD: a systematic review. *Respir Res* 2015;**16**:50. doi:10.1186/s12931-015-0208-4
- 109 Patel ARC, Kowlessar BS, Donaldson GC, *et al.* Cardiovascular risk, myocardial injury, and exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;**188**:1091–9. doi:10.1164/rccm.201306-1170OC

- 110 Weng SF, Reps J, Kai J, *et al.* Can machine-learning improve cardiovascular risk prediction using routine clinical data? *PloS One* 2017;**12**:e0174944. doi:10.1371/journal.pone.0174944
- 111 Ruparel M, Quaife SL, Dickson JL, *et al.* Evaluation of cardiovascular risk in a lung cancer screening cohort. *Thorax* 2019;**74**:1140. doi:10.1136/thoraxjnl-2018-212812
- 112 Hurst JR, Sin DD. Chronic Obstructive Pulmonary Disease as a Risk Factor for Cardiovascular Disease. A View from the SUMMIT. *Am J Respir Crit Care Med* 2018;**198**:2–4. doi:10.1164/rccm.201802-0347ED