Defining the relationship between COPD and CVD: what are the implications for clinical practice?

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Abstract: Cardiovascular diseases (CVDs) are arguably the most important comorbidities in chronic obstructive pulmonary disease (COPD). CVDs are common in people with COPD, and their presence is associated with increased risk for hospitalization, longer length of stay and all-cause and CVD-related mortality. The economic burden associated with CVD in this population is considerable and the cumulative cost of treating comorbidities may even exceed that of treating COPD itself.

Our understanding of the biological mechanisms that link COPD and various forms of CVD has improved significantly over the past decade. But despite broad acceptance of the prognostic significance of CVDs in COPD, there remains widespread under-recognition and undertreatment of comorbid CVD in this population. The reasons for this are unclear; however institutional barriers and a lack of evidence-based guidelines for the management of CVD in people with COPD may be contributory factors.

In this review, we summarize current knowledge relating to the prevalence and incidence of CVD in people with COPD and the mechanisms that underlie their coexistence. We discuss the implications for clinical practice and highlight opportunities for improved prevention and treatment of CVD in people with COPD. While we advocate more active assessment for signs of cardiovascular conditions across all age groups and all stages of COPD severity, we suggest targeting those aged under 65 years. Evidence indicates that the increased risks for CVD are particularly pronounced in COPD patients in mid-to-late-middle-age and thus it is in this age group that the benefits of early intervention may prove to be the most effective.

Keywords: COPD, chronic obstructive pulmonary disease, cardiovascular disease comorbidities, cardiovascular disease risk management

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Introduction

Among the long list of comorbid conditions seen in people with chronic obstructive pulmonary disease (COPD), cardiovascular diseases (CVDs) are generally perceived to be the most important. CVDs not only rank among the most common comorbidities in COPD, but are also associated with an increased risk of death.[1] Indeed, the typical COPD patient is just as likely to die from a cardiovascular cause as they are from a respiratory one.[2]

Research findings accumulated over the past decade or so have added significantly to our understanding of the links between COPD and CVD.[3–6]

While smoking remains an important shared risk factor for both diseases, it is becoming more widely accepted that responses to smoking are not the sole reason for the observed association between COPD and CVD. Increased awareness of the role of other risk factors for COPD, in particular those that influence its natural history, has led to the realization that COPD and CVD are more closely intertwined mechanistically than was previously thought. At the same time, our perceptions of COPD as a disease have changed. No longer 'just a disease of the lungs', COPD has recently been described as the pulmonary component of systematic endothelial disease whereby a range of 'inflam-mageing' processes simultaneously affect multiple

organs giving rise to a state multimorbidity, without any clear indication as to which disease came first.[7,8]

From a clinical practice standpoint, however, fewer advances have been made. There remains an unmet need to target CVDs in the COPD population in order to improve symptom burden and quality of life, as well as to reduce the number of premature deaths in this patient group. In this review, we summarize current knowledge regarding the COPD–CVD relationship, focusing on the prevalence and incidence of CVDs in people with COPD and the mechanisms that underlie their coexistence. Finally, we discuss the implications of this knowledge for clinical practice and highlight the barriers to and opportunities for managing CVD more aggressively in this population.

Epidemiological evidence

The burden of cardiovascular disease in COPD
Prevalence. COPD is a common disease in most developed countries with a tradition of tobacco use, and increasingly so in many developing countries. According to recently published estimates there were 384 million cases of COPD in 2010, which equates to a global prevalence of 11.7% [95% confidence interval (CI); 8.4–15.0%].[9] Estimates for individual regions and countries are however highly variable; COPD prevalence in the UK adult population is estimated to be around 3%[10] but in some low-to-middle-income countries, prevalence rates in excess of 10% are not uncommon.[11]

Given that COPD and some CVDs are roughly equally prevalent and share the same risk factors, it is not at all surprising that these diseases are frequently seen in the same individual. Indeed, multimorbidity (defined as the coexistence of two or more chronic diseases) is increasingly recognized as a problem worldwide. According to this definition, more than 70% of people aged over 65 years can be described as multimorbid, and in a substantial proportion of cases at least one of the diseases is cardiovascular in nature.[12,13]

Despite the growing appreciation of the importance of CVDs in COPD,[14] there is still considerable ambiguity about their prevalence and impact, especially in the general COPD population. Much of the epidemiological evidence has come from studies conducted in highly selected patient groups, typically those presenting in secondary care with more advanced disease.[15,16] The majority find evidence of a much-increased prevalence of CVD in people with COPD relative to the general (age-matched) population. A meta-analysis of observational studies supports a two-fold increase in the odds of having any CVD in people with COPD relative to COPD-free patients [odds ratio (OR) = 2.46; 96% CI; 2.02–3.00], and ORs in the range 2–5 for ischaemic heart disease (IHD), arrhythmias, heart failure and diseases of the arterial circulation.[17]

IHD, heart failure and cardiac arrhythmias are among the most commonly observed CVDs seen in people with COPD. Estimates of the prevalence of IHD in people with COPD vary from less than 20% to over 60%, depending on the characteristics of the study population.[5,17–19] Heart failure prevalence estimates lie in the range 10–30%, with estimates for primary care and community-based populations lying towards the lower end of this range. Prevalence estimates for arrhythmias also exhibit a degree of variability, but are typically between 10% and 15%.[5,17–19] Stroke prevalence in community or primary care COPD populations is generally less than 10% but can be as high as 20% in hospital-based cohorts.[17,20,21] Peripheral arterial disease (PAD) was found in about 9% of COSYCONET study participants who had a diagnosis of COPD.[22]

Several studies have investigated whether CVDs are more prevalent in certain subtypes of COPD patients. To date, studies of this type, including cluster analyses, have yet to provide definitive answers to this question.[13,23] What has emerged is that CVD comorbidity is not confined to those with more advanced airflow obstruction, but occurs across the spectrum of COPD disease severity. There is some suggestion that the prevalence of CVDs (in particular IHD and PAD) may be higher in those with higher body mass index (BMI) and a predominantly small airways form of COPD (chronic bronchitis).[24] This resonates with the observation that in the Japanese COPD population, which is dominated by patients who present with symptoms consistent with emphysema, the prevalence of CVD comorbidities is relatively low compared with that typically seen in Europe and North America.[25]

Observational studies have also established the reverse association, namely that COPD is common

in people presenting with various forms of CVD. In heart failure patients, for example, the prevalence of COPD varies between 13% and 39% and in the case of atrial fibrillation, while most estimates lie in the range 10–15%, some studies report prevalence rates in excess of 20%.[5] COPD is also extremely common in those with established IHD; typically up to a third of people with IHD also have COPD.[5] A recent study conducted by Franssen and colleagues[26] found airflow limitation in 30.5% of patients attending 15 cardiovascular outpatient clinics in nine European countries. Of these, 11.3% had mild, 15.8% had moderate and 3.4% had severe or very severe airflow obstruction. More significantly, more than 70% of those with airflow limitation had not previously had spirometry or been diagnosed with pulmonary disease.

Incidence. Longitudinal studies add considerable weight to the case for a causal association between COPD and CVD.[3, 27–30] Earlier studies were predominantly conducted in secondary care settings but these have been complemented in more recent years by a series of larger-scale, prospective population-based studies. These generally find in favour of increased risk for CVDs in COPD, both as a composite outcome (any CVD) and for individual diseases. Attention has focused on acute events, namely myocardial infarction (MI) and stroke, for which an increased risk in COPD is now well established.[28,31,32] It is generally accepted that having a diagnosis of COPD approximately doubles the risk of an MI; the risk for stroke is likely to be more modest.[32] However, given the difficulties in adjusting for smoking in observational studies, it is unclear at the present time to what extent this association can be attributed to smoking.[30]

Despite a relative paucity of studies, evidence is accumulating that COPD is linked to increased risks for CVD outcomes other than MI and stroke. Furthermore, the indications are that the magnitude of the increased risk associated with COPD for outcomes such as heart failure, angina and cardiac arrhythmias, as well as diseases of the arterial circulation, is even greater than that for MI and stroke. Curkendall and colleagues[33] for instance estimated an age-adjusted risk ratio for heart failure of 4.5 (95% CI: 2.8–6.2) in a Canadian cohort, while Agarwal and colleagues[34] in their longitudinal study of a United States (US) cohort of patients aged 45–64 years found that the incidence of heart failure increased with

decreased forced expiratory volume in 1 sec (FEV_1), even after adjustment for age, smoking and other cardiovascular risk factors. Several studies have shown that the presence and severity of COPD is associated with an increased likelihood of atrial fibrillation,[35] while others have reported higher P-wave dispersion (a surrogate for atrial fibrillation) in patients with COPD relative to those without.[27]

The heterogeneity in the magnitude of the relative risk for individual CVD outcomes is interesting but not altogether surprising, and hints at the complexity of the biological mechanisms that underpin the COPD–CVD association. However, the fact that these heterogeneity patterns are broadly similar to those reported for the association between smoking and the initial (first) presentation of specific CVD outcomes by Pujades-Rodriguez and colleagues,[36] serves to underscore the important role of smoking in the aetiology of both diseases.

A clear inverse relationship between relative risk and increasing age is a defining feature of those studies which have estimated age-specific relative risks for CVDs in COPD. Studies conducted using UK primary care data in particular have demonstrated that the relative risk of developing CVD associated with COPD is greatest in those in late-to-middle-age.[28] Although studies have on the whole failed to find convincing evidence that frequent exacerbators [typically defined as individuals who experience two or more acute exacerbations of COPD (AECOPD) per year] are at greater risk for acute CVD outcomes (MI and stroke) than people who rarely experience an exacerbation of their symptoms, the period immediately after an AECOPD has been shown to be a period of high risk for such events.[31] A more rapid rate of decline in lung function (FEV_1) has also been associated with an increased cardiovascular risk.[37,38] The CVD event rate among a cohort of smokers from Malmo, Sweden was for example greatest in those in the highest tertile of lung function decline.[37]

Impacts of concomitant CVD morbidity in COPD
The presence of cardiovascular comorbidities in people with COPD is associated with a range of unfavourable outcomes, which range from reduced quality of life, a greater number of hospitalizations and increased risk for all-cause and CVD mortality.

Hospitalization and healthcare utilization. Cardiovascular events are a leading cause of hospitalization in people with COPD and contribute significantly to the cost burden of this disease. Analysis of data collected as part of the US Lung Health Study revealed that CVD accounted for up to 50% of hospital admissions in smokers with mild-to-moderate COPD.[39] In a study of over 45,000 patients with COPD, heart failure was the leading cause of hospitalization, followed by MI and stroke.[40]

A recent study which draws on Canadian administrative health data for over 7 million people highlights the scale of the healthcare burden posed by COPD comorbidities. According to this analysis, 13% of patients with COPD were responsible for a fifth of all ambulatory care visits, emergency department visits and hospitalizations for psychiatric, musculoskeletal and diabetic-related conditions. COPD patients also accounted for a third of all such interactions for lower respiratory tract infections and CVD, and over half of all lung cancer healthcare interactions. Overall, people with COPD had more health service claims for their comorbid disease than for COPD itself.[41]

Among patients with COPD, coexisting CVDs have consistently been linked to higher rates of hospitalization, in-hospital mortality and 30 days re-admission, as well as increased length of stay (post an index admission for COPD).[29] It has also been suggested that the presence of CVD prolongs the course of an exacerbation of COPD.[42] Other outcomes that have been repeatedly associated with the presence of CVDs in people with COPD include physical inactivity and low scores for quality of life measures.[42]

Mortality. Cardiac diseases account for a substantial proportion of deaths among people with a diagnosis of COPD. Estimates vary between 12% and 60%, depending on the study population.[2,43,44] However, on average, between a quarter and one third of people with COPD die as a result of CVD, a proportion that rises to 40% in those with a cardiovascular history.[45] Several studies have reported a shift in the distribution of cause of death with increasing COPD disease severity: in patients with mild COPD, the main causes are cardiac disease and lung cancer but as severity increases, deaths due to respiratory disease become increasingly common.[2]

Not only is CVD a common cause of death in COPD, but its presence has also been identified as a prognostic factor for a range of negative outcomes in people with COPD, including mortality. Mannino and colleagues[45] reported that COPD patients with hypertension, diabetes or CVD had an increased risk of mortality compared with subjects with similar lung function impairment but without comorbidity. Furthermore, a diagnosis of COPD is associated with a worse prognosis in those who suffer an acute cardiac event, such a MI or stroke.[46]

Pathophysiology of the COPD–CVD relationship

Traditionally, COPD and CVD have been viewed as two distinct conditions. Combined evidence from epidemiological, clinical and experimental studies has since firmly dispelled this notion, and in its place comes a growing understanding of the complexity of biological pathways and interactions that link these two diseases. 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 in the same individual. The question that has preoccupied many researchers is whether the two conditions are linked in any way beyond this, and more specifically whether there are any mechanistic pathways which act to increase the likelihood of developing a CVD or worsen an existing CVD in COPD, and vice versa. Epidemiological studies, described in the preceding section, imply that this is likely the case, with several studies suggesting that COPD is an independent risk factor for a range of cardiovascular outcomes, both acute and chronic.

In this section, we briefly explore some of the mechanisms that are believed to underlie the association between COPD and CVD, focusing on those we consider to be of greatest clinical significance (Figure 1).

Shared risk factors and common pathophysiological mechanisms

Among the risk factors that are common to COPD and CVD, smoking is undeniably the most important. Smoking and COPD are inextricably linked, while smoking is also well established as a major risk factor for atherosclerotic
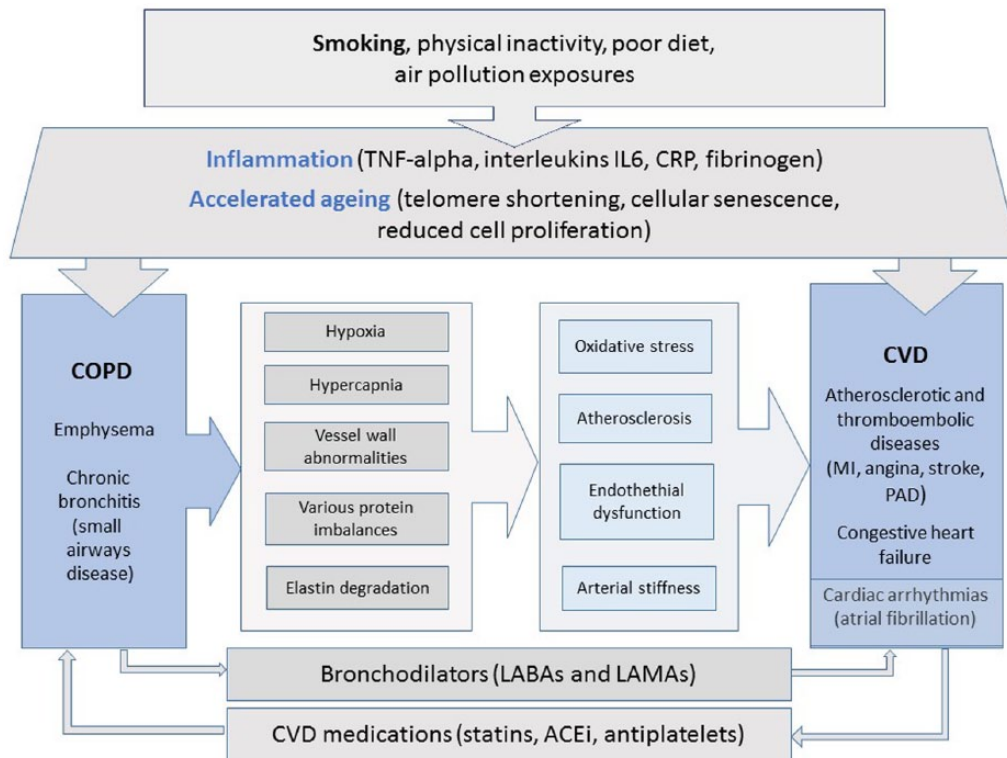
Figure 1. Biological pathways and mechanisms linking COPD and CVD.
ACEi, angiotensin-converting enzyme inhibitor; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; IL6, interleukin-6; LABAs, long-acting beta agonists; LAMAs, long-acting muscarinic antagonists; MI, myocardial infarction; PAD, peripheral arterial disease; TNF, tumour necrosis factor.

disease. Other shared risk factors include physical inactivity and air pollution exposure (Figure 1). Additional known risk factors for CVD, notably diabetes and hypertension, are highly prevalent in COPD cohorts, especially in patients with more severe disease.[45,47]

Smoking and inflammation. Smoking induces a variety of inflammatory responses in susceptible individuals. It contributes directly to chronic, systemic inflammation, which in turn has been implicated in the initiation, development and rupture of atherosclerotic plaques[48] and thus the development of coronary heart disease as well as heart failure.[49] COPD is considered to be a consequence of a heightened inflammatory response to inhaled cigarette smoke (and other noxious particles), leading to disruption of normal lung defence and repair mechanisms, narrowing and remodelling of the small airways, and destruction of the lung parenchyma (emphysema). There is also compelling evidence for a sustained (primary and/or secondary) systemic inflammatory response in COPD,[50] which appears to increase with disease severity[51] and is further amplified during an exacerbation.[52]

The systemic inflammatory response associated with COPD has been proposed as a possible mechanism that links COPD and an increased risk for CVD.[6,53] According to this hypothesis, COPD-related chronic inflammation contributes to atherosclerotic plaque formation and progression, which during periods of acute inflammatory stimulation such as a respiratory tract infection or an AECOPD, induces plaque rupture and a subsequent acute cardiovascular event. Several studies have shown that patients with stable COPD and comorbid CVD have higher levels of several systemic inflammatory biomarkers, including fibrinogen, compared with COPD patients without comorbid CVD.[54] Furthermore, circulating levels of the inflammatory biomarker C-reactive protein (CRP) have been linked with increased mortality among patients with COPD and in the general population.[55] More significantly, levels of inflammatory biomarkers appear to be heightened during and immediately after an exacerbation when the risk of acute

vascular events (acute coronary syndromes and stroke) is at its highest.[56] Finally, it has been shown that COPD is associated with increased carotid intimal medial thickness (CIMT), a measure of atherosclerotic plaque burden, and that among those with COPD, CIMT is associated with higher cardiovascular mortality.[4]

However, other lines of evidence suggest that this may not be the whole story and for some patients, in particular the more elderly and those with more advanced emphysematous disease, other mechanisms involving arterial stiffness may be more important. For instance, data from the ECLISPE study have demonstrated that sustained systemic inflammation only occurs in a proportion of COPD patients. Moreover, frequent exacerbators do not appear at significantly greater CVD risk than infrequent exacerbators and treatments to reduce systemic inflammation in COPD (e.g. statins) have yet to demonstrate convincing and universal benefits.[57,58]

Ageing. The processes related to accelerated ageing (telomere shortening, cell senescence of endothelial cells and diminished cell proliferation) provide another possible mechanistic link between COPD and CVD,[59] although this is probably less important among those under 65 years of age. Age-related telomere shortening,[60] cellular senescence,[61] and diminished cell proliferation[62] have all been reported in patients with COPD, in particular those with emphysema.[4] Mechanisms linked to accelerated ageing are also considered to be involved in the pathogenesis of atherosclerosis. Shortened leukocyte telomere length has been associated with increased arterial stiffness,[63] a predictor of future coronary disease events. Cellular senescence of endothelial cells is believed to play a role in endothelial dysfunction and atherogenesis.[64]

Among patients with a more emphysematous form of COPD, pronounced age-related degradation in lung, skin and arterial elastin has been identified.[65] Resulting loss of lung elastic recoil may additionally contribute to the development of pulmonary arterial hypertension (PAH) and right ventricular dysfunction in COPD,[66] though contradictory reports also exist.[67]

In recent years, evidence has emerged that accelerated ageing of the lungs may be linked to the defective function of certain anti-ageing molecules, such as sirtuin 1 and FOXO proteins, probably caused by increased oxidative stress in the lung, in a pathway that involves phosphoinositide 3-kinase. Sirtuin 1 has also been found to play a critical role in endothelial cell homeostasis and may protect against vascular senescence and atherosclerosis.[68] These shared molecular pathways may provide suitable therapeutic targets to help prevent progression of both COPD and its associated CVD comorbidities.

Other mechanisms. There are a number of other mechanisms that provide a putative link between COPD and CVD and which may also be driving CVD risks in COPD.[69] The observation that arterial stiffness is more pronounced in patients with COPD compared with controls matched for age and smoking status[47,69] has led to the hypothesis that COPD is associated with elastin degradation both in the lung (where it results emphysema) and in the vasculature (systemic elastin degradation) where it results in increased arterial stiffness. Arterial stiffness is considered a surrogate indicator of coronary, cerebrovascular and PAD and is assessed by measuring aortic pulse wave velocity. This measure is strongly associated with cardiovascular mortality in the general population,[70] and is of potential interest as a predictive marker of CVD risk in COPD.[71]

The precise cause of the degradation of elastin in arterial walls is unclear but it is thought to involve protease/antiprotease imbalances (Figure 1). Several extracellular matrix metalloproteinases (MMPs), MMP-2 and MMP-9 in particular, have been implicated in the pathogenesis of both COPD and atherosclerosis, and it is possible therefore that the upregulation of these proteases may also help explain the increased CVD risk in COPD. As arterial stiffness is also a feature of ageing (see Ageing), it is possible that this pathway to increased cardiovascular risk is more important in older patients, and especially in those whose COPD is predominantly emphysematous.

Increased oxidative stress (both local and systemic), is another key feature in COPD which has also been associated with IHD. Although studies have demonstrated that reactive oxygen species are involved in the development of atherosclerosis and heightened inflammatory responses, there is little direct evidence that increased oxidative stress in COPD contributes to an increased risk for IHD.[4] However, some have speculated that oxidative stress is a driver of cerebral vascular

dysfunction (and thus vascular deficiency) and through this pathway may independently increase stroke risk in COPD.[72]

Other factors that may worsen CVD in COPD
Other factors that may be contributing or worsening CVD risks in people with COPD include hypoxia and air pollution. Certain medications routinely prescribed for COPD are thought to have cardiac side effects and may well also be playing a part. While exposure to ambient air pollution, in particular to small particles ($PM_{2.5}$) and ozone, has been linked to deleterious effects in both the lung and heart as well as increased mortality due to cardiovascular and respiratory causes[73] and may well exacerbate pre-existing heart and lung disease, little is known about how air pollutants may mediate CVD risks in COPD and vice versa. For this reason, we have confined our discussion to the roles of hypoxia and COPD medications.

Hypoxia. Patients with COPD are subject to sustained or intermittent hypoxia. Hypoxia is known to induce increased systemic inflammation, oxidative stress, foam cell production and upregulation of cellular adhesion molecules in endothelial cells, which may all contribute to progression of atherosclerosis, and thus cardiovascular disease (Figure 1). Chronic hypoxia also induces pulmonary vascular remodelling (intimal and medial thickening)[74] and pulmonary artery endothelial dysfunction,[75] which may be exacerbated by the presence of local inflammatory cells. Gas trapping during exercise can lead to compression of the pulmonary arteries (dynamic hyperinflation), giving rise to exercise-induced pulmonary hypertension.[76]

COPD medications. Bronchodilators, principally long-acting muscarinic antagonists (LAMAs) and long-acting beta agonists (LABAs) have long been the mainstay pharmacological treatment of COPD, despite some evidence that their use may worsen existing underlying CVD or even increase the risk of developing CVD.[3,77] The main concern relates to beta-adrenergic therapy which can increase activation of the sympathetic nervous system[78] leading to cardiac rhythm disturbances, although there is a propensity for LABAs to be beta 2 selective. Inhaled corticosteroids (ICSs) are commonly used in combination with LABAs in patients who are at higher risk of exacerbations. While ICSs are thought to reduce cardiovascular

mortality in COPD, they too may worsen atrial fibrillation, ventricular arrhythmias and heart failure.[77] Among the oral options, caution with theophylline therapy is certainly warranted in patients with COPD given a widely recognized risk of tachyarrhythmias, particularly atrial fibrillation (see Table 1).[77,79–81]

Accumulated evidence from clinical trials suggests that inhaled COPD therapies do not pose a significant CVD risk, at least in people free from cardiovascular comorbidities.[77] However, a number of observational studies have raised cardiovascular safety signals (see Table 1). One study found that cardiovascular risk (as measured by hospital admission or emergency room attendance for CVD) was increased in new LABA and LAMA users [OR = 1.31 (1.12–1.52) and OR = 1.14 (1.01–1.28), respectively].[82] It is possible therefore that people with COPD and a history of heart disease might be at increased risk of atrial fibrillation and other cardiac diseases (Figure 1).

The evidence is muddied somewhat by what some have called the 'COPD trial paradox'. Randomized controlled trials (RCTs) have traditionally excluded people with underlying CVD, and thus the very individuals in whom adverse cardiac events are most likely. On the other hand, while observational studies provide a more 'real-life' context for the assessment of the safety of COPD medications, they are prone to biases and residual confounding.

More recent trial designs have sought to address these recognized shortcomings. The SUMMIT trial, which included 16,000 people with moderate COPD at increased risk for or with a history of CVD, was designed to allow stratification to assess cardiac effects of LABA treatment in these groups.[83] The trial is ongoing, but interim results suggest that while use of a LABA either alone or in combination with an ICS may reduce the rate of FEV_1 decline, the benefits of therapy appear to be confined to the respiratory system, that is to say no effect on mortality or a composite CVD outcome was observed.[84,85]

Clinical implication
It is evident from the preceding discussion that CVDs are common in people with COPD, and that there is good mechanistic data to suggest that the presence of obstructive lung disease increases

Table 1. Cardiac safety of COPD treatments: an overview.

Therapy	Respiratory effects	Cardiac effects	Evidence for cardiac effects
Bronchodilators			
LABAs	Improve airflow obstruction Decrease static and dynamic hyperinflation Decrease functional dyspnoea Increase exercise endurance	Potential cardiac effects include ischaemia, arrhythmias, and QT prolongation in the ECG	Collectively, the results of RCTs suggest that LABA use is not associated with adverse cardiac outcomes. Formoterol and indacaterol carry the highest potential for cardiac effects. One trial involving arformoterol reported a numerically higher but statistically insignificant number of cardiac adverse events in active treatment arms relative to placebo.[79] A total of 9 of 15 observational studies reported increased rates of adverse cardiac outcomes (e.g. hospitalization, visit to A&E, arrhythmias) in either new LABA users or those with a history of heart failure (relative to nonuse).[77]
LAMAs	Decrease functional dyspnoea Decrease exacerbations Increase exercise endurance	Cardiac arrhythmias Less frequently reported cardiac effects include tachycardia, heart failure and MI	While LAMAs have been associated with arrhythmias and higher mortality rates in both observational studies and RCTs, the evidence is weak, and overall the cardiac safety profile is good. While the vast majority of RCTs found no safety signals, one pooled analysis of 35 trials[80] and a meta-analysis of 42 trials[81] reported increased risk for fatal events in users of tiotropium (soft mist inhaler, Respimat). However, the methodology of these meta-analyses has been questioned and a subsequent trial, TIOSPIR, reported that Respimat has a similar safety profile to other tiotropium inhalers.[77]
ICS and LABA combinations	Improve airflow obstruction Decrease functional dyspnoea Decrease static and dynamic hyperinflation Decrease CD8+ lymphocytes in airway biopsy Decrease exacerbations Increase exercise endurance	Inhaled steroids may worsen existing heart failure but may be protective against MI	Several small studies have suggested that use of ICSs in people with heart failure may worsen underlying cardiac failure but further work is needed in this area.[77] Some studies have suggested that ICS use in people with COPD may have a protective effect on the risk of acute myocardial infarction.[77]
Oral maintenance treatments			
Theophylline (nonselective phosphodiesterase inhibitor)	Bronchodilator	Cardiac arrhythmias	At high doses theophylline has been shown to cause cardiac arrhythmias. More recent studies have demonstrated similar effects, in particular ectopic beats and sinus tachycardia even at low therapeutic doses.[77]
Roflumilast (phosphodiesterase-4 inhibitor)	Improves lung function Prevents AECOPD	Cardiac arrhythmias, including atrial fibrillation	Pooled safety analyses have not reported any significant differences in the proportion of patients reporting cardiovascular adverse events, including atrial fibrillation, between roflumilast and placebo.[77]

Table 1. (Continued)

Therapy	Respiratory effects	Cardiac effects	Evidence for cardiac effects
Azithromycin (a macrolide antibiotic)	Improves QoL Prevents AECOPD	Known to cause repolarization disturbances, and may cause torsade des pointes, ventricular arrhythmias, and sudden cardiac death Contraindicated in people with congenital long QT syndrome	While macrolide antibiotics are contraindicated in people with congenital long QT syndrome, other contraindications in terms of long-term use in COPD have yet to be established.[77]

A&E, accident and emergency department; AECOPD, acute exacerbations of COPD; COPD, chronic obstructive pulmonary disease; ECG, echocardiogram; ICS, inhaled corticosteroid; LABAs, long-acting beta agonists; LAMAs, long-acting muscarinic antagonists; MI, myocardial infarction; QoL, quality of life; RCT, randomized controlled trial.

CVD risk. While the magnitude of these risks is reasonably well quantified for acute cardiovascular events, in particular MI, for other outcomes the risks are less certain but appear to be high for a spectrum of CVDs including arrhythmias and heart failure as well as PAD. Epidemiological evidence also points to especially high risks in younger age groups, that is, those aged under 65 years. Smoking accounts for some but probably not all of the association, with physical inactivity, air pollution and possibly low maximally-attained adult lung volume also playing a role.[86]

The biological mechanisms that underpin this association have been shown to be complex and multifaceted, and have yet to be fully elucidated. It is highly unlikely that just one mechanism is at work. A more likely scenario is that, even within the same individual, a multiplicity of factors are operating, the relative importance of which probably vary over time. While unpicking the intricacies of the COPD–CVD relationship remains a highly laudable and necessary goal, not least because increased knowledge and understanding of the biological pathways that link the two will lead to the discovery of sorely-needed novel targets for therapy, from the perspective of dealing with the comorbid patient in clinical practice this knowledge is perhaps not necessarily of paramount importance. Precisely how a patient came to have comorbid COPD and CVD is not the most pressing concern of the treating physician but how to deal with that patient is.

The presence of comorbid CVD inevitably complicates the management of COPD. The task is not made any easier by the lack of dedicated clinical guidelines for the management of CVD in patients with COPD. Current recommendations state that CVD should be treated in people with COPD as if they did not have COPD,[14] which means that pulmonary clinicians are at present guided by general recommendations for the management of CVD. This is in direct contrast to the situation for several other conditions, for example, inflammatory arthritis, kidney disease and diabetes, for which respective guideline committees have made more specific recommendations about screening and treatment of comorbid CVD.[87]

Despite broad acceptance that they are important in people with COPD, underdiagnosis and undertreatment of CVDs in COPD, and also of COPD in CVD, remains commonplace, if not endemic. Heart failure is one of the most underdiagnosed comorbidities in COPD, second only to depression and anxiety. It has been shown that patients with COPD receive less guideline-recommended treatment for CVD, such as revascularization, than patients with CVD but without COPD,[46] and less secondary prevention for MI and heart failure. This is particularly evident in the case of β-blockers.[88] In spite of the unequivocal morbidity and mortality benefits of β-blockers, in many COPD patients with a history of MI they remain underused and are frequently withdrawn in heart

failure patients with concomitant COPD due to fear of precipitating bronchospasm.[89]

The current underdiagnosis and undertreatment of CVD in COPD can be attributed to a number of factors, among them the above-mentioned lack of appropriate guidelines for the management of comorbidities in people with COPD. In a review of international guidelines for the management of COPD, Bakke notes that while guidelines do indeed acknowledge the existence of comorbidities, they do not offer any detailed guidance on when and how to screen for comorbid CVD, how to assess comorbid CVD, or whether certain diseases need particular treatment when they happen to occur alongside COPD.[90] Several authors have highlighted this obvious gap and as part of calls for routine cardiovascular check-ups in people with COPD have suggested a range of diagnostic tests and procedures that may be performed.[5,29,91–93] We have summarized these and grouped them according to the principal points of contact of the COPD patient with healthcare services (see Table 2).

The situation is not helped by the fact that COPD shares the same symptomology as some CVDs, in particular heart failure. Alveolar and interstitial oedema due to acute decompensated heart failure may lead to airways compression and breathlessness and reduced exercise intolerance, characteristic of COPD. Although additional signs and symptoms (e.g. orthopnoea, paroxysmal nocturnal dyspnoea, peripheral oedema, irregular pulse, heart murmur) signify a greater likelihood of heart failure, and the presence of elevated serum natriuretic peptides usually confirms the heart failure diagnosis (Table 2), there may be a degree of reluctance on the part of the physician having come to one diagnosis that explains the presenting symptoms to pursue other options. This may stem from an under-appreciation of just how closely related the two conditions are.

At the present time, there is no convincing evidence to guard against a more aggressive approach to the management and treatment of CVD in people with COPD. On the contrary, although appropriately-designed clinical studies have yet to be conducted, there are some suggestions that the use of cardiovascular medications may improve longer-term outcomes (all-cause and CVD mortality) in some COPD patients.[3,4,91] Antiplatelet therapy, vitamin K antagonists excepting,[94] may

yet be demonstrated as being of additional preventive value after an exacerbation when increased platelet activation heightens cardiovascular risk.[91] Analysis of data from the Multi-ethnic Study of Atherosclerosis lung study,[95] coupled with evidence from experimental studies,[96] indicates that ACE-inhibitors may have a role in limiting emphysema progression and lung function decline in patients whose COPD is characterized by endothelial dysfunction,[97] and a recent meta-analysis of 10 trials which examined the clinical efficacy of statin therapy in COPD concluded that statins may well benefit COPD patients with overt CVD.[98]

In sum, we advocate heightened vigilance and comprehensive investigation of patients with COPD who also present with symptoms suggestive of CVD, especially in the under 65s in whom the benefits of early intervention may prove to be the most effective. In terms of the management of the COPD–CVD patient, smoking cessation remains a core strategy and for the time being at least, pharmacological therapies should be utilized for the same CVD indications and treatment targets as patients without COPD.

Conclusions: where next?

Given available evidence which supports the case for a more aggressive and integrated approach to the management of CVD in people with COPD, we should be actively seeking opportunities for better CVD primary prevention, be this with screening in primary care settings or with cross-collaboration in specialist clinics. Current barriers to the implementation of a more integrated management approach are largely institutional[99] and are a consequence of a tendency towards over-specialization and vertical disease-programming. Strategies to overcome these barriers include further education and the development of shared evidence-based treatment guidelines which promote greater integration of care. Certainly, the new NICE guidance on multimorbidity points us in the right direction.[100] However, guideline writers need high-quality evidence on which to base their recommendations which can only stem from dedicated and inclusive clinical trials (which do not exclude individuals with comorbid conditions) and continued research into the natural history, clinical presentation and shared mechanisms of disease in comorbid patient populations.

Table 2. Diagnostic techniques for the identification of CVD comorbidities in COPD.

Cardiovascular comorbidity	Suggested investigation/ diagnostic technique	Additional comments
Primary care settings: a minimal cardiovascular check-up		
Atherosclerosis/ ischaemic heart disease Heart failure Arrhythmias Angina PAD	To include: A medical history [dyspnoea, nocturia, weight changes, oedema, exertional chest pain, leg pain (intermittent claudication)] A physical examination (irregular heartbeats, abnormal breath sounds, fluid homoeostasis, vascular pulsations) BMI Blood pressure Blood testing (cholesterol; blood sugar and low-density lipoproteins) Ankle brachial index Exercise tolerance test Cardiovascular risk score	A routine basic cardiovascular check-up on initial diagnosis, followed by regular check-ups thereafter might identify early signs of concomitant cardiovascular disease in patients with COPD Conversely, lung function testing (spirometry) in patients presenting with symptoms consistent with cardiovascular disease may help to identify latent cases of COPD
Secondary care settings (outpatient): referrals for further investigation		
Atherosclerosis/ischaemic heart disease/angina	ECG Radiography of the chest CT scan Coronary angiography or ultrasonography Exercise stress test or nuclear stress test	A resting ECG might show evidence of a previous ischaemia
Heart failure	BNP	A biomarker of left ventricular dysfunction; associated with increased 30-day mortality
	HF echocardiography (if indicated by symptoms)	Noninvasive, widely available: provides exam of right and left ventricular structure and function, assesses valve disease and pulmonary artery pressures
	MRI	Helpful for those patients in whom chest hyper-expansion and pulmonary hyperinflation results in suboptimal ECG images
Arrhythmias, including atrial fibrillation	12-lead or prolonged ambulatory ECG	The gold standard technique for the diagnosis and quantification of arrhythmias
Stroke	CT imaging MRI	Assesses the presence of small vessel disease and white matter lesions in the brain
PAH	Right heart catheterization	The gold standard for diagnosis and quantification of PAH

(Continued)

Table 2. (Continued)

Cardiovascular comorbidity	Suggested investigation/ diagnostic technique	Additional comments
Secondary care settings (inpatient): on admission for AECOPD		
MI	Troponin	Elevated troponin suggests myocardial damage and is predictive for increased mortality
	ECG	An ECG may identify cardiac injury but is often less useful in an exacerbating patient as a high proportion of tests are unsatisfactory
Heart failure	BNP/NT-proBNP	BNP testing may help to distinguish cardiac and pulmonary causes of breathlessness: an elevated serum BNP is indicative of heart failure
	ECG	An ECG may also help to distinguish acute heart failure and AECOPD
	Chest X-ray	A chest X-ray identifies pulmonary oedema

Sources: based on references 5, 29, 91–93.
AECOPD, acute exacerbations of COPD; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CVD, cardiovascular disease; ECG, echocardiogram; HF, heart failure; MI, myocardial infarction; MRI, magnetic resonance imaging; NT-proBNP, N-terminal proB-type natriuretic peptide; PAD, peripheral arterial disease; PAH, pulmonary arterial hypertension.

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