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CLINICAL REVIEW

Is Airway Inflammation in Chronic Obstructive Pulmonary Disease (COPD) a Risk Factor for Cardiovascular Events?

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ABSTRACT

Cardiovascular disease (CVD) is a very common cause of death in patients with chronic obstructive pulmonary disease (COPD). Smoking is a well-described risk factor for both COPD and CVD, but CVD in patients with COPD is likely to be due to other factors in addition to smoking. Inflammation may be an important common etiological link between COPD and CVD, being well described in both diseases. It is hypothesized that in COPD a "spill-over" of local airway inflammation into the systemic circulation could contribute to increased CVD in these patients. Inhaled corticosteroids (ICS) have well-documented anti-inflammatory effects and are commonly used for the treatment of COPD, but their effects on cardiovascular endpoints and all-cause mortality have only just started to be examined. A recent meta-analysis has suggested that ICS may reduce all-cause mortality in COPD by around 25%. A case-controlled study specifically examined the effects of ICS on myocardial infarction and suggested that ICS may decrease the incidence of MI by as much as 32%. A large multicenter prospective randomized trial (Towards a Revolution in COPD Health [TORCH]) is now ongoing and will examine the effect of fluticasone propionate in combination with salmeterol on all-cause mortality.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) causes substantial disability and increases the risk of premature death not only in the developed countries of Western Europe and North America but in many developing economies around the world. This problem is set to increase in size and scope over the next 15 years (1–4). COPD is the third commonest cause of death in the UK (5) and is projected to become the fourth most common cause of death in Europe as a whole (6), as it is in the United States (7). U.S. data suggest that COPD cost the healthcare system $32.1 billion ($18.0 billion direct costs and $14.1 billion indirect costs) in 2002.

We now have more information about the socioeconomic impact of COPD, its effect on the patient's life (8) and the impact of COPD exacerbations on health status (9–11). The more dramatic and potentially robust endpoint of patient mortality has been tactfully avoided yet remains of immense importance to patients and their care providers. The common assumption is that COPD patients will normally die as a result of their disease. A moment's reflection makes this seem improbable. Cigarette smoking is certainly a major risk factor for COPD mortality in the general population, with smokers having higher COPD morbidity and mortality rates than non-smokers (3). Likewise, exposure to atmospheric pollution, another COPD risk factor, is significantly more likely to trigger a cardiac event (12, 13). However, the major risk factor for COPD, tobacco exposure, is a significant cause of ischemic heart disease.

Epidemiological studies have demonstrated that both active cigarette smoking and passive smoking increase the risk of coronary heart disease (14, 15). A meta-analysis of 19 epidemiological studies of exposure to environmental tobacco smoke (passive smoking) and ischemic heart disease estimated that the risk of

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ischemic heart disease was 30% greater in non-smokers who lived with smokers than in non-smokers living with non-smokers (15). Unsurprisingly, the risk of active smoking was even worse compared with non-smokers; smoking at a rate of one cigarette per day increased the risk of ischemic heart disease by 39%. Thus there is an increased chance of COPD patients dying of a cardiovascular cause simply because of their past and/or continuing tobacco exposure.

Although cigarette smoking has generally been thought to be the confounding factor central to the association between reduced forced expiratory volume in 1 second (FEV_1) and cardiovascular disease, a recent study has indicated that, regardless of smoking status, the relationship between reduced FEV_1 and cardiovascular disease was dose-dependent, and FEV_1 remains an important factor after correcting for smoking exposure (16).

These findings suggest that factors other than cigarette smoking are also important in the development of cardiovascular events in COPD. Furthermore, this raises two issues that are central to this review. First, what is the evidence that COPD patients die from cardiovascular causes and if they do, are they more likely to do so than others with comparable tobacco exposure? Second, if cardiovascular disease is more prevalent among COPD patients, what factors might operate to explain this and can we modify these with our existing COPD therapy?

Evidence of an association between COPD and cardiovascular disease

Several studies have suggested that there is an independent association between COPD and cardiovascular disease, and that COPD is a predictor of cardiovascular mortality. An assessment of all-cause mortality in patients where obstructive airways disease was mentioned on the death certificate found that the underlying cause of death was reported as being cardiovascular in 42% of cases, compared with pulmonary in 26% of cases and malignancy in 9% of cases (17). Hansell and colleagues undertook a descriptive analysis of all conditions mentioned on the death certificates of all decedents in England and Wales between 1993 and 1999, where COPD was mentioned but not as the immediate cause of death (18). They found that found that ischemic heart disease, lung cancer and bronchopneumonia were the major certified causes of death in this group. However, it should be remembered that death certificate records are not very tightly controlled data and therefore may not represent the best source of information. More accurate data can be obtained from clinical trials which include an independent committee adjudicating the primary cause of death using a range of information including clinical records and site investigator reports as well as death certificates. The **TO**wards a **R**evolution in **C**OPD **H**ealth (TORCH) study was a 3-year investigation of over 6,000 patients with COPD randomized to salmeterol/fluticasone propionate (50/500 μg), salmeterol (50 μg), fluticasone propionate (500 μg), or placebo. In TORCH, the primary causes of death were adjudicated to be respiratory 36%, cancer 22%, cardiovascular 27%, other causes 10%, and unknown 7% (19).

There is now strong evidence linking COPD to cardiovascular mortality. Huiart et al. (20) examined a population of 5,648 patients with COPD. Cardiovascular morbidity and mortality were 1.9- and 2-fold higher in the COPD patients than in a matched population without COPD. Heart failure was the most frequent cause of hospitalisation due to cardiovascular disease in these patients. In a study of 11,493 patients with COPD, Curkendall et al. (21) found that cardiovascular mortality was 2.07-fold greater than individuals without COPD. Odds ratios for cardiovascular outcomes were: congestive heart failure 3.84 (95% confidence intervals [CI] 3.56–4.14), arrhythmia 1.76 (95% CI 1.64–1.89), angina 1.61 (95% CI 1.47–1.76), acute myocardial infarction 1.61 (95% CI 1.43–1.81), stroke 1.11 (95% CI 1.02–1.21), and pulmonary embolism 5.46 (95% CI 4.25–7.02). Sidney et al. (22) studied a very large cohort of 45,966 patients with COPD. They found that the risk of hospitalisation due to cardiovascular disease was 2.09-fold higher and cardiovascular mortality was 1.68-fold higher, in patients with COPD compared with patients without the disease. Of all cardiovascular outcomes measured, mortality as a result of congestive heart failure was the most associated with COPD compared with individuals without COPD (odds ratio 3.75 [95% CI 3.39–4.15]). In a study of the incidence and causes of cardiac and non-cardiac mortality in a cohort of 15,000 Israelis with coronary heart disease, where 57.4% of all the deaths were cardiac, COPD was the second most significant predictor of cardiac mortality (odds ratio = 1.67 [95% CI 1.29–2.16]) after the effect of increasing age (odds ratio = 1.75 [95% CI 1.59–1.94]) (23). In comparison, current smoking was the third most significant predictor (odds ratio = 1.29 [95% CI 1.08–1.55]).

Large population-based studies have investigated the association between pulmonary function and mortality from cardiovascular disease. They have prospectively demonstrated that the lowest quintile of the FEV_1 percentage predicted (24, 25) and the lowest quartile of the forced vital capacity (FVC) (26) are important risk factors, associated with an increased incidence of myocardial infarction and cardiac mortality in men and women. Rather surprisingly, FEV_1 turns out to be a better predictor than diastolic blood pressure, social class and serum cholesterol concentration for all-cause mortality, and is just as important a predictor as social class and serum cholesterol concentration for ischemic heart disease (Figure 1) (24). However, some caution needs to be exercised in interpreting these data because FEV_1 is influenced by both obstructive and restrictive lung disease, which can occur during lung development in childhood and by destructive insults to lung tissues during adult life (27).

More support for this association comes from data about the development of congestive cardiac failure and the subsequent prognosis of 6,669 patients recently admitted to hospital with acute myocardial infarction (28). Diagnosis of COPD was made in 765 patients (11.5%) and this group had a significantly worse survival compared with patients without pulmonary disease (relative risk of dying 1.44). Patients with COPD were significantly more likely to develop congestive heart failure (65.9%) compared with those without COPD (52%).

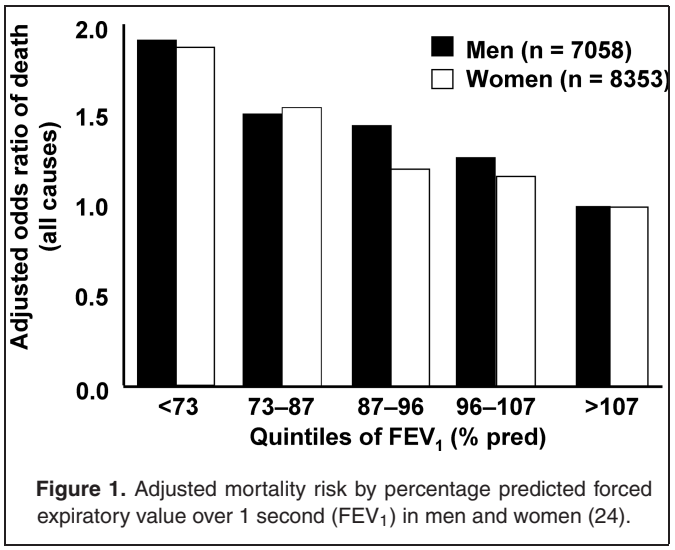

Figure 1. Adjusted mortality risk by percentage predicted forced expiratory value over 1 second (FEV_1) in men and women (24).

More prospective data come from the extended follow-up of the original Lung Health Study cohort (29), in which patients identified as having mild COPD (predominantly GOLD stage 1) were randomised to intensive smoking cessation therapy or usual care. During the subsequent follow-up, more cardiovascular than respiratory-related deaths were reported but lung cancer was the principal cause of death in this cohort. This reflects the exclusion of cardiovascular co-morbidities in the original cohort and emphasises the need to follow up unselected patient populations if potentially misleading conclusions about the importance of specific causes of death are to be avoided.

Thus, a range of studies in the general population of patients known to have cardiovascular disease and those with COPD without an initial cardiac diagnosis suggests that having COPD is associated with a greater likelihood of cardiovascular death than can be accounted for by the known association of COPD and tobacco smoking. One important issue, particularly in primary care, is diagnostic uncertainty. COPD and heart failure have many overlapping signs and symptoms as well as overlapping risk factors such as smoking. Echocardiology is required to definitively diagnose heart failure, but access to this facility may be limited in primary care (30, 31). In one cross-sectional study including 405 patients $\geq$ 65 years of age with a diagnosis of COPD from their primary care physician but without a confirmaed diagnosis of heart failure, 20.5% of patients were found to have previously unrecognised heart failure (32). Thus it is very important to have close co-operation between primary care physicians, pulmonologists, and cardiologists to improve diagnosis of heart failure in patients with COPD.

Accepting that the relationship between COPD and cardiovascular disease is causal rather than simply an epiphenomenon would be helped if a plausible effector mechanism could be identified. There is increasing interest in the association between inflammation and both cardiovascular disease and COPD. The remainder of this review considers how these inflammatory processes might interact and whether treatment of COPD could influence cardiovascular mortality.

POSSIBLE MECHANISMS UNDERLYING THE LINK BETWEEN COPD AND INCREASED CARDIOVASCULAR DISEASE

The role of inflammation

COPD as an inflammatory disease. There are substantial data indicating that chronic lung inflammation (involving increased numbers of several inflammatory cells and a variety of pro-inflammatory mediators) is a characteristic finding in all stages of COPD and this increases in intensity as the disease worsens, as elegantly demonstrated in a data from lung resection specimens in patients with mild to severe disease (33, 34). This inflammatory process is not confined to the airway wall but involved the adjacent glandular structures in the large airways, the adventitia around the airway and extended into areas of emphysema where inflammation can, proportionate to the tissue available, be intense. During exacerbations there are more inflammatory cells and cytokines detectable in bronchoalveolar lavage fluid or in induced sputum (34–39), although the time course of these changes and their relationship to disease progression remain to be determined. Rather similar changes are seen in the vessel wall (33, 40).

Systemic markers of inflammation, particularly C-reactive protein (CRP) detected by a high sensitivity assay, fibrinogen and tumour necrosis factor-alpha (TNFα), have been shown to be significantly increased in the plasma of stable COPD, compared with healthy individuals (41, 42). There is some evidence that systemic fibrinogen (an important marker of cardiovascular risk) and interleukin (IL)-6 rise acutely during a COPD exacerbation and that the increase in fibrinogen was greater when the exacerbation was associated with purulent sputum, increased cough, and symptoms of an upper respiratory tract infection (43). This suggests that infection may be involved in this increase in fibrinogen in COPD. However the increase in systemic markers of inflammation in COPD appears to be related only weakly to smoking status and is more evident in patients with more severe disease (44) (Figure 2).

Cardiovascular disease and inflammation. Increased concentrations of circulating inflammatory mediators are also seen in cardiovascular disease. High sensitivity assay CRP, IL-6, IL-18, TNFα, serum amyloid A protein, and lipoprotein-associated phospholipase A_2 have been identified as independent risk factors for cardiovascular disease, and are particularly associated with acute coronary syndromes and mortality (45–51).

Of these markers, CRP, an acute phase reactant produced in the liver in response to IL-6, has been the most intensively investigated. Several large-scale prospective trials have identified elevated CRP concentrations as a predictor of future cardiovascular risk and mortality in apparently healthy individuals, patients undergoing elective revascularization procedures, patients presenting with acute coronary syndromes, and patients with troponin-negative acute coronary syndromes (46, 47). A study of nearly 28,000 apparently healthy American women found that the adjusted relative risk of cardiovascular events was higher in women with high CRP and low low-density

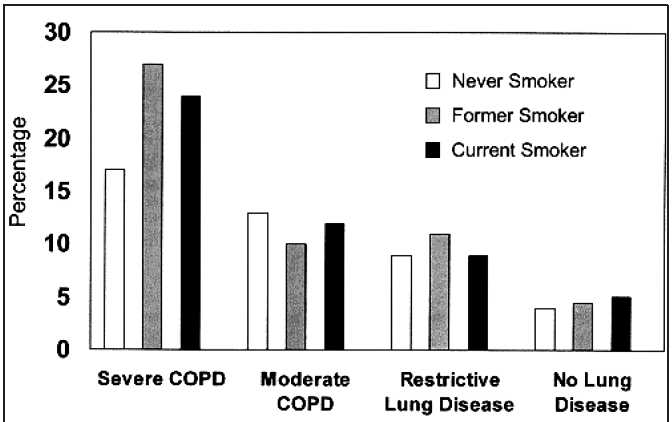

Figure 2. Percentages of individuals with C-reactive protein ≥10.0 mg/L, stratified by smoking status and lung function category (44). Reprinted from Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and markers of inflammation: data from the Third National Health and Nutrition Examination. Am J Med, 114, 758–762, Copyright (2003), with permission from Exerpta Medica Inc.

lipoprotein (LDL)-cholesterol concentrations, compared with low CRP and high LDL-cholesterol concentrations, suggesting that CRP was a stronger predictor of cardiovascular events than LDL-cholesterol (52) (Figure 3). These findings have been challenged by data suggesting that increased levels of CRP are associated with only a moderately increased risk of cardiovascular disease (53).

The validity of the interpretation of the newer data has been questioned, particularly since the odds ratios reported for CRP after adjustment for age, sex, period and risk factors for coronary heart disease were similar to those associated with hypertension and smoking, and the 10-year risk estimate was in accordance with the findings from other studies (54). Taking the published literature into account, it appears that there is stronger evidence for an association with CVD mortality than with morbidity, which is not at odds with the data from Danesh (2004) (53).

There is reasonable evidence that higher concentrations of the various systemic markers of inflammation are associated with atherosclerosis and its complications (47, 55). Mechanistic studies have suggested that CRP may be directly involved in atherogenesis (47, 56, 57). It remains unclear whether CRP is a surrogate marker or plays a causative role in this disorder, although a direct effect of CRP in accelerating atherosclerotic

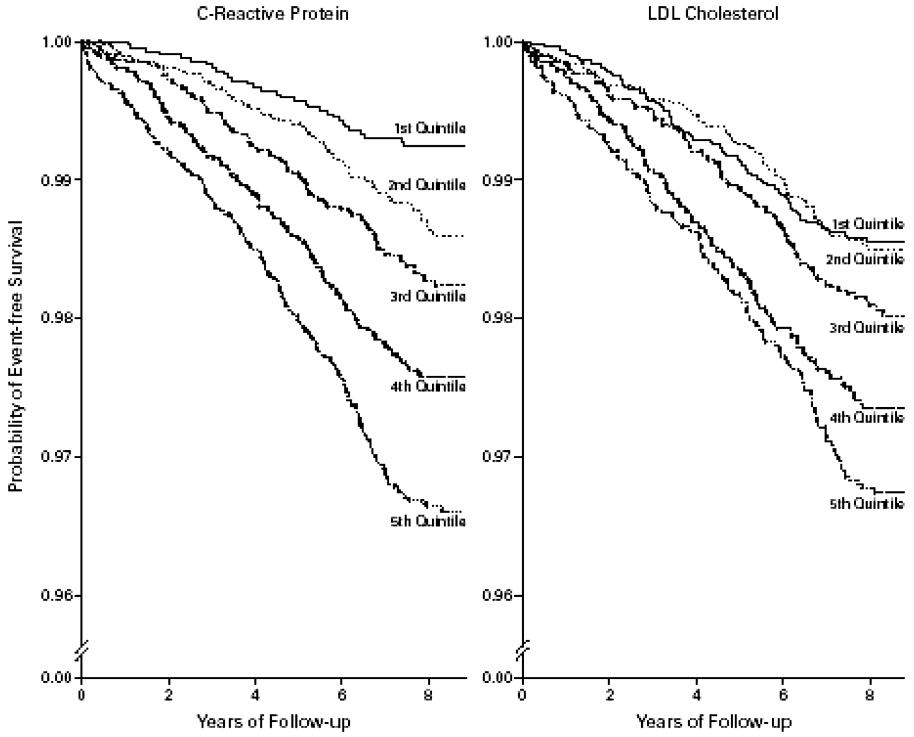

Figure 3. Cardiovascular event-free survival according to base-line quintiles of C-reactive protein and LDL-cholesterol. (The values for C-reactive protein for first quintile = ≤0.49 mg/litre; second quintile = >0.49 to 1.08 mg/liter; third quintile = >1.08 to 2.09 mg/litre, fourth quintile = >2.09 to 4.19 mg/liter and fifth quintile = >4.19 mg/litre. The values for LDL-cholesterol for first quintile = ≤97.6 mg/deciliter, second quintile = >97.6 to 115.4 mg/deciliter, third quintile = >115.4 to 132.2 mg/deciliter, fourth quintile = >132.2 to 153.9 mg/deciliter and fifth quintile = >153.9 mg/deciliter) (52). [Reproduced with permission from Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. N Engl J Med 2002; 347:1557–1565. Copyright © 2002 Massachusetts Medical Society. All rights reserved.]

progression has been proposed (47). In this model, CRP deposits directly in the arterial wall during atherogenesis and interacts with other inflammatory mediators to create foam cells, which serve as building blocks of atherosclerotic plaques (58). Indeed, CRP has been shown to induce the expression and synthesis of several pro-inflammatory cytokines (IL-1α, IL-1β, IL-6 and TNFα) in human peripheral blood mononuclear cells and alveolar macrophages (59), and intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and plasminogen activator inhibitor-1 in endothelial cells (60, 61). Collectively, these inflammatory changes might bias the vascular equilibrium towards a proinflammatory, prothrombotic and vasoconstrictive state (47).

Thus, it is possible that in COPD a "spill-over" of increased local airway inflammation into the systemic circulation might increase concentrations of specific systemic inflammatory markers and lead to cardiovascular disease over time. Whether this process explains the observed epidemiological associations remains to be determined. However, COPD is not the only chronic inflammatory disease to be linked to cardiovascular disease.

Increased risk of cardiovascular disease in other inflammatory conditions. There is evidence of an increased risk of cardiovascular disease in a range of disorders, such as rheumatoid arthritis (62, 63), renal disease (64), dental disease (65, 66), and type 2 diabetes (67, 68), where chronic low-grade inflammation is a prominent feature. For example, patients with rheumatoid arthritis have a nearly four-fold higher incidence of cardiovascular events relative to the general population (62), while in patients with end-stage renal disease cardiac mortality is 100-fold greater than in the general population (64). Studies have demonstrated that rheumatoid arthritis and atherosclerosis have many common inflammatory mechanisms (including increased concentrations of IL-1β, IL-6, IL-18, TNFα, ICAM-1, VCAM-1 and CRP, and increased activation of monocytes, mast cells, T and B-cells, and endothelial cells) (62, 69, 70). Indeed, levels of IL-1β, IL-6, IL-8, TNFα and CRP, which are all known to be associated with cardiovascular disease, have also been shown to be significantly higher in patients with acute renal failure, dental disease and type 2 diabetes (68, 71–73).

What else might contribute?

Role of cigarette smoke. Despite the overwhelming epidemiological evidence linking cigarette smoking with COPD and cardiovascular disease, the precise components of cigarette smoke and the mechanisms by which they exert their effects in these conditions have not been fully elucidated (74, 75). Limited information from some recent mechanistic studies suggests that common pathways may operate, since cigarette smoke exposure leads to inflammation, oxidative stress and arterial endothelial dysfunction in both conditions (74–78). The effects on endothelial cell function may be of particular importance because there is some information which suggests that cigarette smoke may attenuate the angiogenesis of pulmonary artery endothelial cells in COPD (78) and lead to cell injury and remodelling in cardiovascular disease (77, 79); effects which predispose the individual to atherogenic and thrombotic problems. However, additional mechanisms, other than those associated with cigarette smoke-induced inflammation in the lung and in the cardiac vessels, are likely to be involved in the development of cardiovascular disease in patients with COPD.

Role of infections. Exacerbations of COPD are associated with increased systemic oxidative stress (80), although the relationship of this potentially important process to co-existing bacterial or viral infection is unclear. Likewise, we remain uncertain about the systemic burden of persistent lower respiratory tract colonisation in COPD, a process now identified as contributing to exacerbations and perhaps accelerated lung function decline (43, 81).

There is comparatively little information about the role of infections in the aetiology of cardiovascular disease, although the role of oxidative stress in ventricular remodelling is well described (82). The data that are available suggest that viral (cytomegalovirus and herpes simplex virus type 1) and bacterial (*Helicobacter pylori, Chlamydia pneumoniae* and dental infections) pathogens may be associated with the inflammatory changes in atherosclerosis (83, 84). The evidence is strongest for the respiratory bacterium *Chlamydia pneumoniae* (84). However, in a recent randomised controlled clinical trial involving 2012 patients with stable coronary artery disease randomised to receive azithromycin (600 mg) or placebo weekly for 1 year with a mean follow up of 3.9 years, the risk of cardiac events (a composite endpoint of death due to coronary heart disease, nonfatal myocardial infarction, coronary revascularization, or hospitalization for unstable angina) was similar in the active treatment and placebo group (occurring in 446 and 449 patients, respectively). Furthermore, there was no significant difference between groups when patients were stratified according to *Chlamydia pneumoniae* serological status at baseline (85). Thus in this secondary prevention population, the role of this organism remains uncertain. Remarkably, a recent study demonstrated that in current smokers and ex-smokers, the risk of atherosclerosis was increased only in the presence of chronic infections (86). Furthermore, exposure to environmental tobacco smoke in the presence of chronic infections may also increase the risk of atherosclerosis in individuals vulnerable to the manifestation of chronic infection (86).

Insulin resistance. A review of studies of glucose metabolism in COPD has led to the hypothesis that intermittent hypoxia, a characteristic feature of COPD at least in its more severe form, may affect glucose metabolism by influencing peripheral insulin sensitivity in COPD (87). In contrast, studies in chronic heart failure patients have demonstrated that whole-body insulin resistance is prevalent in chronic heart failure patients with either ischemic heart failure or idiopathic dilated cardiomyopathy, likely as a consequence of impaired insulin-stimulated glucose uptake in the skeletal muscle (88). Collectively these studies suggest that insulin resistance could be a potential mechanism of cardiovascular disease in COPD, although this needs to be explored further. Careful control for differences in lean body mass will be needed to establish the importance of this mechanism.

Physical inactivity. Patients with COPD often have a significant degree of physical disability, preventing them from taking regular physical exercise. This physical inactivity has been proposed as another potential cause of raised levels of coronary heart disease in this patient population (89).

Can we do anything about this?

Role of anti-inflammatory therapy. Anti-inflammatory therapy plays a role in the mangement of both COPD and cardiocascular disease, although in the latter case it is other actions of the therapy which have received most attention. Statins reduce all cardiovascular events and total mortality, and have consistently been shown to have specific properties (including anti-inflammatory, anti-proliferative, anti-thrombogenic, and anti-proteolytic properties), which inhibit atherogenesis and improve plaque stability (90). In patients with stable angina and acute coronary syndromes, statins can reduce CRP, LDL-cholesterol and oxidant stress, and inhibit pro-inflammatory cell-to-cell interactions (56).

Data from studies of the thiazolidinedione rosiglitazone maleate, have suggested that this agent may also have cardiovascular benefits in patients with type 2 diabetes, because it results in the formation of more buoyant LDL and the reduction of CRP levels (71, 91), effects which could potentially lead to the stabilisation of atherosclerotic plaques and delay/inhibition of further plaque development (71, 92). The indications for adding an inhaled corticosteroid to maintenance bronchodilator therapy in COPD patients have now been clarified following guidance from the 'Global initiative for chronic Obstructive Lung Disease' (GOLD) (3) and the National Institute of Health and Clinical Excellence (NICE) in the UK (93). However recent studies have indicated that inhaled corticosteroids can reduce the levels of inflammatory markers in the circulation of patients with COPD and, therefore, may have the potential for improving cardiovascular outcomes in COPD.

One study investigated the effect of inhaled fluticasone propionate (500 μg twice daily) or oral prednisone (30 mg/day) for 2 weeks on serum markers of inflammation in patients with stable COPD (94). This study demonstrated that fluticasone propionate and prednisone significantly decreased the concentrations of CRP by 50% and 63%, respectively, from baseline, compared with the placebo group in which CRP decreased by only 8%. An additional week of fluticasone was associated with CRP levels that were lower than baseline levels. Fluticasone propionate, but not prednisone, also significantly reduced the levels of IL-6 by 26% compared with baseline, although this effect was less marked than for CRP. This study is challenging and requires further prospective validation in a larger patient population (95).

Observational data from another prospective study suggest that inhaled corticosteroids are associated with lower CRP levels in patients with COPD, although any effects of corticosteroid treatment on mortality were not evaluated (96). Barnes et al. (97) examined the anti-inflammatory effects of combination therapy with fluticasone propionate plus the long-acting beta 2 agonist salmeterol (50/500 μg twice daily) with placebo in 140 patients with COPD. This regimen induced a broad spectrum of anti-inflammatory effects, including reduced $CD8^+$ cell counts in bronchial biopsies (decreased by 36% compared with placebo [$p = 0.001$]); significantly reduced numbers of $CD45^+$, $CD4^+$ TNF-α and interferon-γ mRNA+ cells in bronchial biopsies; and decreased sputum neutrophil and eosinophil counts ($p \leq 0.04$ for all). Novel therapies directed against specific cytokines, cell adhesion molecules, nuclear factor-kappa-beta ($NF\kappa_\beta$), p38 and other mediators which influence the activity of inflammatory cells and markers found in COPD are also in development (98).

Mortality outcomes in COPD. Until recently most large longer term studies of anti-inlammatory therapy in COPD have looked at the rate of decline of FEV_1 over time as their main outcome (99–103). A systematic review and one meta-analysis have reported that treatment with inhaled corticosteroids for $\geq$6 months reduces the rates of COPD exacerbations (104) and slows the rate of lung function decline in COPD (105). Treatment with the anti-oxidant N acetyl cysteine reduced the exacerbation rate in patients not treated with inhaled coticosteroids but was not effective in those who received this therapy (103). Some epidemiological studies have also provided evidence of an association between the use of inhaled corticosteroids and reduced re-hospitalisation or mortality in COPD patients (106–109), this has not been found to be the case in other studies (110–112). However, the effect of inhaled corticosteroids on mortality in COPD has only recently been explored in the Inhaled Steroid Effects Evaluation in COPD (ISEEC) study—a meta-analysis of seven placebo-controlled studies involving 5085 patients treated with triamcinolone, budesonide, or fluticasone (16). Two-hundred-and-one patients (4%) died during these studies. Patients receiving inhaled corticosteroids (n = 2543) had a 27% reduced risk of all-cause mortality compared with patients receiving placebo (n = 2542) (mortality = 1.57 and 2.10 per 100 patient years for inhaled corticosteroid and placebo groups, respectively). This effect was seen with death from cardiovascular as well as pulmonary causes but the number of events remains too small for such a small difference to be considered as definitive.

Epidemiological and clinical studies of inhaled corticosteroids in combination with long-acting beta 2 agonists suggest there may be a greater effect with the combination compared with the components alone. Clinical studies show a significant additional effect on pulmonary function and a reduction in symptoms in those receiving combination therapy compared with its components (113–117), while pharmacoepidemiological studies show that the combination was associated with a greater reduction in mortality and hospitalisations than inhaled corticosteroids alone (108, 109).

In a recent case-controled study, 371 COPD patients with first acute myocardial infarction were compared with a matched cohort of 1,864 patients with COPD but without infarction. 12.7% of the patients with myocardial infarction, compared with 17.6% without, were found to have been exposed to inhaled corticosteroids at a dose equivalent to 50–200 μg/day beclomethasone over the previous 12 months. This represents a significant 32% reduced risk of this coronary event (118). The limitations of

studies like this are well known (112) but the study does provide some rationale for a proper prospective trial which will address this issue. Such a large scale multicenter trial (TORCH) is currently in progress. This study is investigating the effect of fluticasone propionate and salmeterol administered individually and in combination on all-cause mortality, the ultimate clinical endpoint, and may in part address this issue (119).

CONCLUSIONS

There is now substantial evidence for an association between COPD and cardiovascular disease, with several studies demonstrating that cigarette smoke and airflow limitation are independent risk factors for cardiovascular disease and mortality.

There is a growing body of data that supports an inflammatory basis for both conditions with the possibility of "cross-talk" between the lungs and circulation that may be detrimental to cardiovascular health. More detail is needed about the nature of the cardiovascular events that lead to death in those with COPD before we can understand how these mechanisms might interact at the cellular or physiological level.

However, drugs that modify inflammation may provide us with the tools to begin to unravel these processes. We know that while many patients die of COPD, even more die with COPD. For the first time, we have evidence that the cause of death may not be random in these patients and that their pulmonary disorder may directly contribute to death from a non-pulmonary mechanism. Preventing this unexpected problem poses an important challenge for the future.

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