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REVIEW

Mortality in COPD: role of comorbidities

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) represents an increasing burden throughout the world. COPD-related mortality is probably underestimated because of the difficulties associated with identifying the precise cause of death. Respiratory failure is considered the major cause of death in advanced COPD. Comorbidities such as cardiovascular disease and lung cancer are also major causes and, in mild-to-moderate COPD, are the leading causes of mortality.

The links between COPD and these conditions are not fully understood. However, a link through the inflammation pathway has been suggested, as persistent low-grade pulmonary and systemic inflammation, both known risk factors for cardiovascular disease and cancer, are present in COPD independent of cigarette smoking.

Lung-specific measurements, such as forced expiratory volume in one second (FEV_1), predict mortality in COPD and in the general population. However, composite tools, such as health-status measurements (*e.g.* St George's Respiratory Questionnaire) and the BODE index, which incorporates Body mass index, lung function (airflow Obstruction), Dyspnoea and Exercise capacity, predict mortality better than FEV_1 alone. These multidimensional tools may be more valuable because, unlike predictive approaches based on single parameters, they can reflect the range of comorbidities and the complexity of underlying mechanisms associated with COPD.

The current paper reviews the role of comorbidities in chronic obstructive pulmonary disease mortality, the putative underlying pathogenic link between chronic obstructive pulmonary disease and comorbid conditions (*i.e.* inflammation), and the tools used to predict chronic obstructive pulmonary disease mortality.

KEYWORDS: Chronic obstructive pulmonary disease, comorbidities, inflammation, mortality

Chronic obstructive pulmonary disease (COPD) represents an increasing burden worldwide, reported to be the sixth leading cause of death in 1990 [1] and the fourth in 2000 [2]. Discouragingly, it is projected to jump to third place by the year 2020 [1].

To date, only smoking cessation [3] (fig. 1) and supplementary oxygen therapy in selected patients with severe hypoxaemia [4–7] increase survival in patients with COPD. While these therapies undoubtedly reduce mortality from respiratory failure, they have beneficial effects that extend beyond COPD-specific mortality. Smoking cessation, for instance, has a major impact in reducing lung cancer rates and deaths from cardiovascular diseases. Supplemental oxygen reduces the risk for sudden deaths, and deaths from arrhythmias and ischaemia [5]. In contrast, so far, no pharmacological therapy has been shown to reduce mortality in randomised controlled trials in COPD; indeed mortality has not been a primary end-point in currently published studies.

Traditionally, studies investigating the therapeutic benefit of a pharmacotherapy have relied on COPD-specific end-points, such as forced expiratory volume in one second (FEV_1) or exacerbations. However, with the increased recognition of the role of comorbidities in COPD, all-cause mortality has become a paramount end-point for the evaluation of novel therapies. Two such clinical trials, TOwards a Revolution in COPD Health (TORCH) [8] and Understanding the Potential Long-term Impacts on Function with Tiotropium (UPLIFT) [9], are examples of how COPD studies are changing because of comorbidities. TORCH may help to clarify the true impact of inhaled corticosteroids and long-acting β_2-agonists on all-cause (and not just COPD-specific) mortality in patients with COPD. Results

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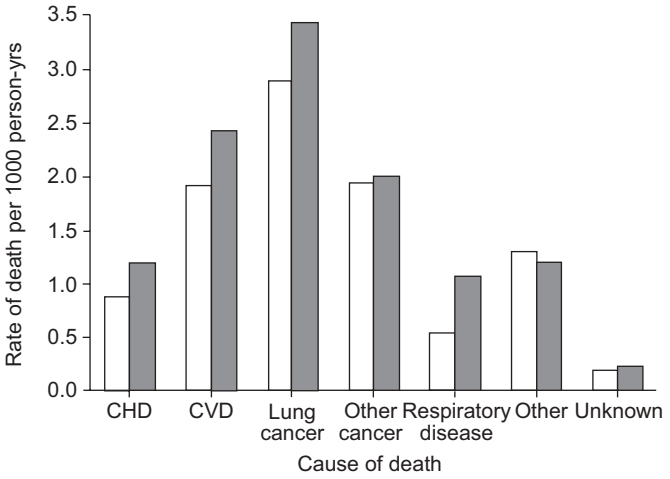

FIGURE 1. Mortality rates by specific cause of death in patients with asymptomatic airway obstruction followed for up to 14.5 yrs after randomisation. Special intervention refers to a 10-week smoking cessation programme. CHD: coronary heart disease; CVD: cardiovascular disease. □: special intervention; ■: usual care. Reproduced with permission [3].

are expected in 2006. The ongoing UPLIFT study will also provide some information on mortality and the results are expected in 2008.

The present review paper, based on discussions of a round-table meeting of respiratory specialists held in December 2004 in Montreal (Canada), explores the causes of death in COPD, the potential role of comorbidities in the health outcomes of COPD patients, and the pathogenic factors (*e.g.* inflammation) that may link COPD and comorbid conditions. The material discussed herein is based on literature searches, participation in various expert roundtable meetings, and many years of research in the subject. A systematic Medline search was performed until March 2006 for articles in English or with English abstracts with the following keywords: COPD, mortality, death, prognosis, comorbidities, inflammation, cardiovascular disease, lung cancer, and health status. Additional relevant references were identified from the reference lists of selected papers.

CASE DEFINITION OF COMORBIDITY

Unfortunately, there is no universally accepted definition of comorbidity. Traditionally, comorbidity has been defined as a disease coexisting with the primary disease of interest, though there are a plethora of examples where this definition has been significantly modified or ignored. In COPD, the definition becomes even more problematic as certain coexisting illnesses may be a consequence of the patients' underlying COPD. Examples of these ''comorbid'' conditions include cardiovascular diseases, lung cancer and osteoporosis. For the purposes of the current review, comorbidities are defined as the following: 1) the presence of one or more distinct disorders (or diseases) in addition to COPD, regardless of whether the comorbid conditions are or are not directly related to COPD; and 2) a distinct disorder or disease that is not part of the spectrum of the natural history of COPD (*e.g.* respiratory infection resulting in a COPD exacerbation). Within this case definition, conditions such as ischaemic heart disease, cancer and osteoporosis would qualify as comorbid conditions of COPD.

MEASUREMENTS OF COMORBIDITIES IN COPD

Patient data from the UK General Practice Research Database were analysed to quantify baseline rates of comorbidities in 2,699 patients with COPD (46% were current smokers) compared with age-, sex-, practice- and time-matched controls (21% were current smokers) [10]. Angina, cataracts and osteoporosis all had a frequency of >1% within the first year after COPD diagnosis. Furthermore, compared with controls, COPD patients had a significantly increased risk of comorbidities and other medical events (fig. 2). The authors concluded that COPD is associated with many comorbidities, particularly those related to cardiovascular-, bone- and other smoking-related conditions, that previously had not been systematically documented. Comorbidities were also assessed in a chart review study of 200 COPD patients compared with 200 matched controls [11]. Patients with COPD were randomly selected from a total of 1,522 COPD patients who enrolled in a health maintenance organisation in 1997. Compared with controls, patients with COPD had a longer smoking history (49.5 *versus* 34.9 pack-yrs; $p=0.002$). This chart review revealed that patients with COPD had a higher prevalence of certain comorbid conditions, including coronary artery disease, congestive heart disease, other cardiovascular disease, local malignant neoplasm (which includes any history of nonmetastatic cancer except basal cell and squamous cell skin carcinoma), neurological disease other than stroke with hemiplegia, ulcers and gastritis. Patients in the COPD cohort had an average of 3.7 chronic medical conditions (including lung disease), compared with 1.8 chronic medical conditions for the controls ($p<0.001$) [11].

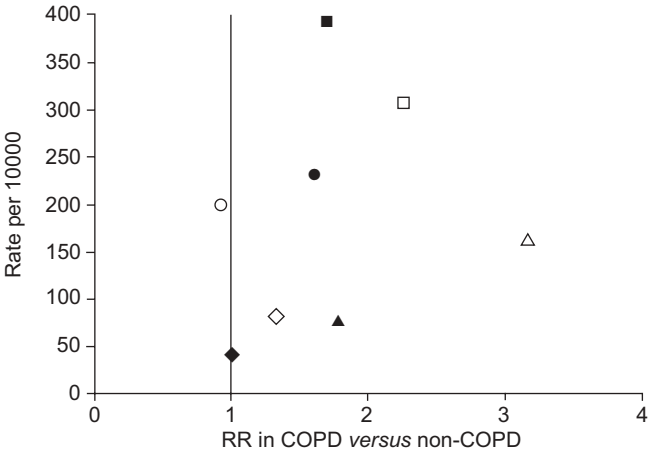

FIGURE 2. Relationship between rate per 10,000 of selected medical events and their relative risk (RR) in chronic obstructive pulmonary disease (COPD) *versus* non-COPD. Data were obtained from the United Kingdom General Practice Research Database 1998. ■: angina 1.67; □: respiratory infection 2.24; ●: fractures 1.58; ○: cataracts 0.90; ▲: myocardial infarction 1.75; △: osteoporosis 3.14; ◆: skin bruises 1.00; ◇: glaucoma 1.29. The RR for pneumonia was 16. Reproduced with permission [10].

The Charlson Index is an automated method designed to quantify, for analytical purposes, the comorbid conditions that might alter the risk of mortality in hospitalised patients [12]. A prospective study of 171 COPD patients, hospitalised for acute exacerbation of COPD, included comorbidities in its assessment of risk factors for 1-yr mortality [13]. More than two-thirds of patients had at least one comorbid illness and the mean Charlson Index score was 1.55 ± 0.90. Although the relative risk (RR) of death was significantly associated with the Charlson Index (RR=1.38; 95% confidence interval (CI) 1.06–1.80; p=0.016), a multivariate Cox analysis (adjusting for age, number of hospitalisation days, FEV_1, arterial level of CO_2, and oral corticosteroid use) failed to demonstrate an independent relationship (RR adjusted=1.22; 95% CI 0.92–1.62; p=0.177). An important limitation of this analysis was that the relationship between the Charlson Index and mortality was assumed to be linear. This assumption is unlikely to be valid, as the impact of the Charlson Index on mortality is probably exponential.

A study of 135 patients hospitalised with acute exacerbation of COPD identified comorbidity as an independent predictor of mortality [14]. The study showed that the Charlson Index was associated with reduced survival ($p<0.001$). Chronic heart failure was the most common comorbidity observed in the decedents (odds ratio (OR)=2.3; 95% CI 1.39–2.83; $p<0.001$; bivariate analysis). Multivariate analysis, which adjusted for a variety of different factors including FEV_1, revealed that patients who had a Charlson Index score of three or more (equivalent to two chronic diseases or one severe disease apart from COPD) were more than twice as likely to die compared with those individuals with lower burden of comorbidities (OR=2.2; 95% CI 1.26–3.84; p=0.005).

A major limitation of the Charlson Index is the complexity of weights that are used to calculate the scores. As such, most automated database studies currently use a modified Charlson Comorbidity Index, which uses weights that are more easily calculable and more intuitive. The Deyo-modified Charlson Index is one such scoring system and is commonly used for research involving hospital administrative databases, International Classification of Diseases (ICD)-9 diagnoses and procedural codes [15]. PATIL *et al.* [16] used administrative databases to estimate in-hospital mortality and to identify predictors of mortality in 71,130 patients admitted to a hospital with acute COPD exacerbation. This cohort included data from the 1996 Nationwide Inpatient Sample for all hospitalisations in a 20% sample of all non-federal USA hospitals. The overall in-hospital mortality was found to be 2.5%. Deyo-Charlson Index scores were significantly associated with mortality: individuals with a score of five or more (indicating at least four comorbidities) were over five times as likely to die in hospital compared with COPD patients without comorbidities, adjusted for a wide range of confounders including age and sex (adjusted OR=5.70; 99% CI 4.08–7.89).

Perhaps one of the most important studies to demonstrate the impact and prognostic role of comorbidities in COPD was carried out by ANTONELLI-INCALZI *et al.* [17] in their analysis of data from a cohort of 270 COPD patients discharged from hospital after an acute exacerbation of COPD. The researchers found that the most common comorbid conditions were hypertension (28%), diabetes mellitus (14%) and ischaemic heart disease (10%). The median survival was 3.1 yrs and 228 out of the 270 patients died during the 5-yr follow-up period. The 5-yr mortality was predicted by FEV_1 <590 mL (hazard ratio (HR)=1.49; 95% CI 0.97–2.27), age (HR=1.04; 95% CI 1.02–1.05), electrocardiogram (ECG) signs of right ventricular hypertrophy (HR=1.76; 95% CI 1.3–2.38), chronic renal failure (HR=1.79; 95% CI 1.05–3.02) and ECG signs of myocardial infarction or ischoemia (HR=1.42; 95% CI 1.02–1.96) with an overall sensitivity and specificity of 63 and 77%, respectively.

A separate study aimed to identify factors affecting short-term prognosis by retrospectively analysing the records of 590 patients hospitalised for acutely exacerbated COPD from 1981 to 1990 [18]. In this study, increased age (OR=1.07; 95% CI 1.04–1.11), alveolar–arterial oxygen gradient of >5.45 kPa (OR=2.33; 95% CI 1.39–3.90), the presence of ventricular arrhythmias (OR=1.91; 95% CI 1.10–3.31) and atrial fibrillation (OR=2.27, 95% CI 1.14–4.51) were independent predictors of 1-yr mortality. These data suggest that indicators of heart dysfunction are particularly important predictors of increased risk of death in patients with COPD and indicate the importance of cardiovascular disease as a factor contributing to COPD mortality. In a separate study, the estimated risk of dying within 1 yr, increased almost two-fold (RR=1.94; 95% CI 1.17–3.24) for patients with COPD and pulmonary embolism compared with those without pulmonary embolism [19].

A recent evaluation [20] of the USA National Hospital Discharge Survey analysed more than 47 million hospital discharges for COPD (8.5% of all hospitalisations) that occurred in the USA from 1979 to 2001 in adults >25 yrs of age. The prevalence and in-hospital mortality of many conditions were greater in hospital discharges with any mention of COPD *versus* those that did not mention COPD. Of interest, a hospital diagnosis of COPD was associated with a higher rate of age-adjusted, in-hospital mortality for pneumonia, hypertension, heart failure, ventilatory failure and thoracic malignancies (fig. 3). In contrast, a hospital diagnosis of COPD was not associated with a greater prevalence of hospitalisation or in-hospital mortality for acute and chronic renal failure, HIV, gastrointestinal haemorrhage and cerebrovascular disease [20].

THE TWO MOST IMPORTANT COMORBIDITIES IN COPD MORTALITY: CANCER AND CARDIOVASCULAR DISEASES

The predominant causes of death in COPD patients vary as a function of the underlying severity of airflow obstruction (table 1, fig. 4). In the 1990s, ZIELINSKI and colleagues [21, 22] from the World Health Organization (WHO) reviewed deaths in a multicentre study of patients with COPD. They collected data from 215 severe COPD patients with chronic respiratory failure (arterial oxygen tension <7.78 kPa) who died following treatment with long-term oxygen therapy [21]. Three-quarters of patients died in the hospital. In this very sick group of COPD patients, respiratory failure was the leading cause of death, but, overall, accounted for only one-third of the total number of deaths. Cardiovascular causes, pulmonary infection, pulmonary embolism, lung cancer and other cancers accounted for the remaining two-thirds of the deaths, reinforcing the likely importance of comorbidities in COPD-related mortality. In a more recent report, the Lung Health Study

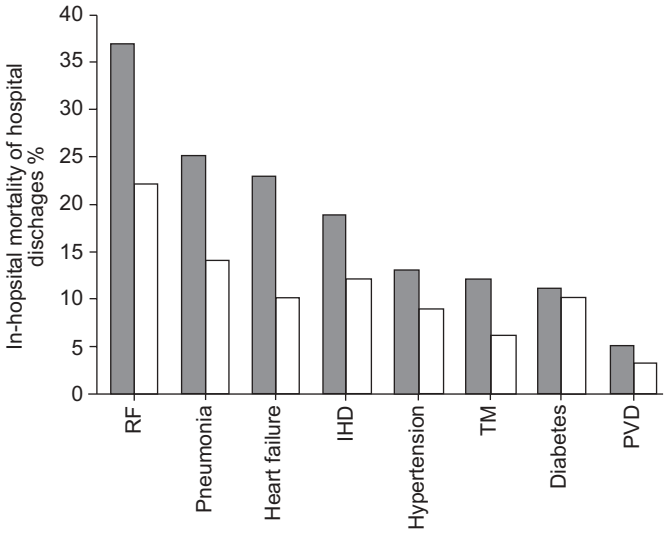

FIGURE 3. Estimated age-adjusted mortality of hospital discharges associated with selected comorbid conditions in patients with (■) and without (□) chronic obstructive pulmonary disease mentioned as discharge diagnosis. Data are from the National Hospital Discharge Survey 1979–2001. RF: respiratory failure; IHD: ischaemic heart disease; TM: thoracic malignancy; PVD: pulmonary vascular disease. Reproduced with permission [20].

investigators showed that in this cohort of patients with mild COPD, lung cancer and cardiovascular complications accounted for nearly two-thirds of all deaths during follow-up (fig. 1) [3]. The specific causes of death reported in different series of COPD patients are summarised in table 1 and figure 4 [3, 21, 23–27]. In summary, the main causes of death in mild or moderate COPD are lung cancer and cardiovascular diseases, while in more advanced COPD (<60% FEV_1), respiratory failure becomes the predominant cause. Addressing the potential link between COPD and comorbidities, such as cancer and cardiovascular diseases, may be of paramount importance in modifying the morbidity and mortality associated with COPD across the full spectrum of COPD severity from Global Initiative for Chronic Obstructive Lung Disease stage 0 to 4.

In patients with very advanced COPD, respiratory failure is the leading cause of mortality. Even in this subgroup of COPD patients, comorbidities play a salient role in altering clinical outcomes. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) included data from 9,105 seriously ill patients (47% died within 6 months) [29]. An ancillary study, the Hospitalized Elderly Longitudinal Project, reported data for 1,286 hospitalised patients aged ⩾80 yrs (25% died within 6 months) [29]. In the SUPPORT cohort [29], 39% of the COPD patients had three or more comorbidities or other medical events, including respiratory infection (47%) and cardiac problems (30%). Approximately two-thirds of patients suffered from dyspnoea and one-quarter reported serious pain in the 6-month period prior to death. These comorbid factors had such a serious impact on their life expectancy and activities of daily living that many patients had ''do not resuscitate'' orders (40% at 3–6 months prior to death; 77% within 1 month of death) [30]. Further analysis of data for these 1,016 patients revealed that survival time was independently and significantly related to a number of factors, including severity of illness, body mass index (BMI), age, prior functional status, congestive heart failure as a cause of exacerbation, serum albumin concentration and the presence of cor pulmonale [31], suggesting that comorbidities play a major role even in ''COPD-specific'' deaths among patients with very advanced COPD.

LIMITATIONS IN ATTRIBUTING CAUSES OF DEATH IN COPD PATIENTS

One of the major limitations of accurately ascertaining causes of death in COPD cohorts is the difficulty in differentiating between various causes of deaths in clinical settings. For example, there may be diagnostic problems separating sudden deaths related to cardiac arrhythmias from mortality related to acute massive pulmonary embolism, or separating deaths from heart failure secondary to cardiac ischaemia from those related to cor pulmonale.

Clearly, many patients with COPD have multiple comorbid conditions and accurate coding of cause(s) of death is necessary, yet challenging. The complexity of the issue was illustrated by HANSELL *et al.* [32], who analysed death certificate records for England and Wales for 1993–1999. In cases where death was attributed to obstructive lung disease (OLD) the underlying causes included bronchitis, unspecified (ICD-490), chronic bronchitis (ICD-491), emphysema (ICD-492), asthma (ICD-493) and chronic airways obstruction not otherwise classified (ICD-496). However, in the remaining group of patients where OLD was mentioned on the death certificate, but was not considered to be the underlying cause of death, important questions arose. For example, if a COPD patient also had lung cancer or suffered a cardiovascular event, such as acute myocardial infarction, was death more likely to be attributed to COPD or to the other, perhaps more easily defined, condition? In both cases, it was possible that COPD may be a contributing cause but, dependent on how consistently the ICD codes were applied, the potential importance of COPD was not reflected as an underlying cause in the death certificate; this latter point was notable as death certificates were often used as the only source of data to analyse national and international death mortality trends in COPD. This is a difficult issue that does not help to clarify the true role of COPD on mortality.

The difficulties of accurately representing the total burden of COPD mortality are reflected in the literature describing national and global mortality statistics. For example, analysis of 31 million USA death certificates from 1979 to 1993 indicated that 8% of all decedents had recorded COPD in the death certificate [33]. However, only 43% of the death certificates that listed COPD also identified it as the primary underlying cause of death. Furthermore, inconsistent use of ICD codes may omit large categories of patients with COPD by focusing only on chronic bronchitis and emphysema (ICD codes 491–492). For example, chronic airways obstruction (ICD-496) represents one of the largest categories of COPD mortality, but has previously not been consistently included in WHO estimates of COPD mortality, leading to significant underestimation of COPD deaths in France, Germany, Ireland and the UK [34].

TABLE 1 Summary of underlying causes of death reported for patients with chronic obstructive pulmonary disease (COPD)

First author [ref.]	Total sample size	Mean age yrs	Mean FEV_1 L and/or % pred	Mean follow-up yrs	Total deaths	Causes of death	Proportion of deaths %
Zielinski [21]	215	66	0.72 L[#] (pre- or post-BD not stated)	Not reported	215	Chronic respiratory failure	38
						Heart failure	13
						Pulmonary infection	11
						Pulmonary embolism	10
						Cardiac arrhythmia	8
						Lung cancer	7
						Myocardial infarction	6
						Other	7
Garcia-Aymerich [23]	340	69	36% (pre- or post-BD not stated)	1.1	98	Respiratory causes	74
						Cardiovascular causes	12
						Lung cancer	5
						Other cancer	2
						Other	6
Waterhouse [24]	751	64	1.4 L; 50% (post-BD)	2.8	103	Respiratory	49
						Cardiac	22
						Lung cancer	11
						Other cancer	10
						Other	8
Keistinen [25]	2727	50–54	Not reported	8.5	973	Coronary ischemia, stroke and other circulatory diseases	37
						COPD	22
						Lung cancer	13
						Other cancer	8
						Other pulmonary disease (including asthma)	4
						Other	16
Vilkman [26]	2237	67	Not reported	Not reported	1070	Coronary heart disease and other circulatory causes	37
						COPD	30
						Lung cancer	12
						Other cancer	8
						Other	13
Anthonisen [27][¶]	5887	48	2.7 L; 75% (post-BD)	5.0	149	Lung cancer	38
						Cardiovascular disease	25
						Other	37
Anthonisen [3] [¶]	5887	48	2.7 L; 78% (post-BD)	14.5	731	Lung cancer	33
						Cardiovascular disease (including coronary heart disease)	22
						Other cancer	21
						Respiratory causes other than lung cancer	8
						Other or unknown	16
Celli [28]	625	64–67[+]	39–47% (post-BD)[+]	2.3	162	Respiratory failure	61
						Myocardial infarction	14
						Lung cancer	12
						Other	13

Data are presented as n or as a range, unless otherwise stated. FEV_1: forced expiratory volume in one second; % pred: % predicted; BD: bronchodilator. [#]: measurement taken at a median of 10 months before death; [¶]: both studies report data from the Lung Health Study, but at 5-yr [27] and 14.5-yr [3] follow-up; [+]: range across three patient cohorts.

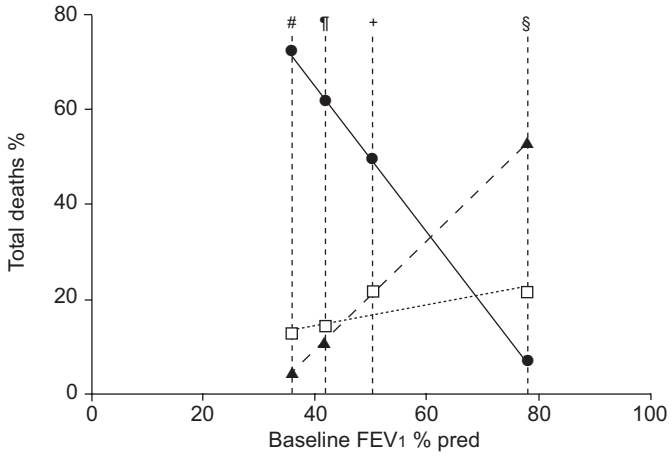

FIGURE 4. The relationship between baseline lung function and percentage of total deaths from cardiovascular diseases (CVD; □), cancer (▲) and respiratory failure (●) in large cohort studies of chronic obstructive pulmonary disease (COPD) patients. The four cohort studies were as follows. #: Estudi dels Factors de Risc d'Agudització de la MPOC (Risk Factors of COPD Exacerbation) Study [23]; ¶: Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity [28]; +: Inhaled Steroids in Obstructive Lung Disease in Europe study [24]; §: Lung Health Study-3 [3]. FEV1: forced expiratory volume in one second.

SYSTEMIC AND PULMONARY INFLAMMATION: THE MECHANISTIC LINK BETWEEN COPD AND CANCER AND CARDIOVASCULAR DISEASE?

The mechanistic link between COPD and comorbidities is far from certain. Recently, some evidence has implicated systemic and pulmonary inflammation as the common link between COPD and certain comorbid conditions, such as lung cancer, cardiovascular disease and cachexia [35, 36]. COPD is characterised by an abnormal/excessive inflammatory response of the lung parenchyma to inhaled irritants and toxins, mostly but not exclusively tobacco smoking [37], and by the presence of systemic inflammation. A systematic review identified 14 studies investigating the relationship between stable COPD (of any severity), FEV1 or forced expiratory vital capacity and levels of systemic inflammatory markers, including C-reactive protein (CRP), fibrinogen, circulating leukocytes and the pro-inflammatory cytokine tumour necrosis factor (TNF)-α [36]. The levels of all these systemic inflammatory markers were elevated for patients with stable COPD compared with controls. The authors suggested a link between COPD and systemic complications such as cachexia, osteoporosis and cardiovascular disease, while acknowledging the need for studies to determine whether attenuation of the systemic inflammatory process is able to modify such risks.

RELATIONSHIP BETWEEN COPD AND LUNG CANCER

COPD is an independent risk factor for lung cancer, with chronic bronchitis and/or emphysema increasing lung cancer risk two- to five-fold, compared with incidence rates in smokers without COPD [38–42]. An inverse correlation between the degree of airflow obstruction and lung cancer risk was clearly demonstrated in an analysis of 22-yr follow-up data for 5,402 participants from the first National Health and Nutrition Examination Survey (NHANES I), including a total of 113 cases of lung cancer (fig. 5) [41].

There is also a growing recognition that chronic inflammation may play a salient role in the pathogenesis of lung cancer as a tumour promoter, an idea that was first proposed by VIRCHOW [43] in the 1860s. There are examples elsewhere in the body where chronic inflammation plays a relevant role in cancer. Examples include inflammatory bowel disease and colon cancer [44], chronic hepatitis and hepatoma [45], chronic pancreatitis and pancreatic cancer [46], and Barrett's oesophagus and oesophageal cancer [47]. Experimental findings suggest that cigarette smoke upregulates the production of cytokines such as interleukin (IL)-1β, and other cytokines, which in turn increase cyclooxygenase (COX)-2 enzymatic activity. COX-2 products can promote an inflammatory response by the lymphocytes, leading to the over-production of cytokines such as IL-6, IL-8, IL-10 [48–50]. Some of these cytokines can inhibit apoptosis, interfere with cellular repair and promote angiogenesis [48]. Chronic inflammation may thus be instrumental in amplifying the initial mutagenic damage and promoting tumour growth and metastasis [48]. IL-8, for example, has been demonstrated to upregulate pro-oncogenes such as B-cell leukaemia/lymphoma 2 gene product (Bcl-2) and downregulate suppressor oncogenes such as p53, thereby inhibiting apoptosis and inducing cell transformation [48, 49]. These cytokines also create a pro-angiogenic environment, which promotes tumour growth [50, 51]. Interestingly, these cytokines have also been implicated in COPD progression. There is a clear link between COPD and lung cancer independently of active smoking [52]. Even after patients with COPD stop smoking, the risk of lung cancer remains elevated, though the risk is lower than that of continued smokers [3]. Some have suggested that the missing link between reduced FEV1 and lung cancer is chronic airway inflammation, which is evident in the airways of COPD patients, even years after smoking cessation.

At the molecular level, activation of nuclear factor (NF)-κB transcription factor may have major relevance for cancer and

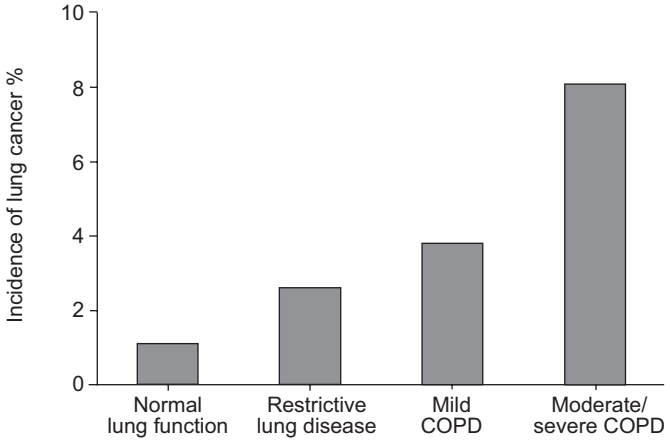

FIGURE 5. Inverse relationship between degree of lung function obstruction and incidence of lung cancer [41]. Normal lung function (n=4,002); restrictive lung disease=forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ⩾70% and FVC <80% (n=501); mild chronic obstructive disease (COPD)=FEV1/FVC <70% and FVC ⩾80% (n=423); moderate/severe COPD=FEV1/FVC <70% and FVC <80% (n=476).

COPD [53]. Although the precise role of NF-κB in COPD remains speculative, chronic airway inflammation in COPD has been associated with activation of NF-κB in macrophages and epithelial cells. Furthermore, it has been suggested that the synergistic effects of latent infection and cigarette smoking cause chronic airway inflammation through enhanced expression of cytokines and adhesion molecules, possibly through NF-κB-mediated activation [53, 54].

Links between NF-κB and lung cancer have also been reported, including resistance to chemotherapy and regulation of pro-metastatic, pro-angiogenic and anti-apoptotic genes [53]. Altered expression of the p50 subunit of NF-κB was investigated in paired normal and nonsmall cell lung cancer (NSCLC) tissues [55]. Of NSCLC tissues, >80% expressed two- to 20-fold higher levels of the p50 subunit of NF-κB than normal lung tissue. Furthermore, 13 NSCLC cell lines exhibited high levels of p50. MUKHOPADHYAY *et al.* [55] suggested that alterations in the normal NF-κB regulation pathway may play a role in the development of NSCLC.

A number of additional experimental studies indicate that NF-κB may be essential for promoting inflammation-associated cancers [56, 57]. Evidence from these studies suggests that NF-κB activation in the airways of COPD patients causes chronic inflammation and increases risk of lung tumour development. Furthermore, COPD patients have impaired mucociliary clearance [58], so it is not unreasonable to suggest that reduced clearance of carcinogens from the lungs may also contribute to the increase in cancer risk.

RELATIONSHIP BETWEEN COPD AND CARDIOVASCULAR DISEASE

A number of studies report increased risk of death in cardiovascular patients with COPD, compared with those without COPD. The 3-yr follow-up of 4,284 patients who received hospital treatment for coronary heart disease reported mortality rates of 21% for patients diagnosed with COPD *versus* 9% in those without COPD ($p<0.001$) [59]. Furthermore, COPD was independently associated with a two-fold increase in the risk of long-term mortality (HR=2.146; 95% CI 1.525–3.021; $p<0.001$) [59]. A separate healthcare database cohort study [60], including 11,493 COPD patients, reported an approximately two- to four-fold increased risk of death at 3-yr follow-up due to cardiovascular diseases (RR=2.07; CI 1.82–2.36), compared with age- and sex-matched controls without COPD. Specifically, patients with COPD had a significantly higher risk of congestive heart failure (RR=4.09), arrhythmia (RR=2.81) and acute myocardial infarction (RR=1.51) [60].

Cardiovascular disease also leads to hospitalisation of COPD patients. For example, in the Lung Health Study [27], cardiovascular causes accounted for 42% of first hospitalisations and 44% of second hospitalisations of patients with relatively mild COPD. In comparison, respiratory causes accounted for only 14% of hospitalisations. A study of patients with chronic airway obstruction admitted to hospital with acute respiratory failure found that arrhythmias were associated with 70% in-hospital mortality and no survival at 2.4 yrs [61]. In another study, hospital mortality was 31% in patients with severe COPD and arrhythmia, compared with 8% in patients without arrhythmias [62].

Strong epidemiological evidence points to reduced FEV_1 as a marker for cardiovascular mortality. A longitudinal, population-based study, including 1,861 participants from NHANES I, reported that patients with poor lung function (lowest quintile of FEV_1) had the highest risk of cardiovascular mortality (RR=3.36; 95% CI 1.54–7.34), more than double that for patients in the highest FEV_1 quintile and independent of smoking status [63]. Furthermore, the risk of death from ischaemic heart disease was more than five-fold higher for the lowest *versus* highest lung function quintiles (RR=5.65; 95% CI 2.26–14.13). Similar reports of increased cardiovascular mortality with decreased lung function are found in numerous other studies, including the Framingham Heart Study and Copenhagen City Heart Study [64–67]. The authors of the NHANES I analysis also performed a systematic review of the literature and meta-analysis that included >80,000 patients and identified an almost two-fold risk of increased cardiovascular mortality in patients in the lowest *versus* highest lung function quintiles (pooled RR=1.77; 95% CI 1.56–1.97). STAVEM *et al.* [68] also assessed the role of lung function on cardiovascular mortality, controlling for physical fitness and smoking status, in a 26-yr follow-up of 1,623 healthy males aged 40–59 yrs at baseline. Of the 615 deaths during follow-up, 50% were from cardiovascular causes and FEV_1 was a predictor of all-cause mortality (RR=1.10 per 10% reduction in FEV_1). The RRs for cardiovascular causes and respiratory death were 1.07 and 1.34, respectively. Furthermore, a prospective, general population study investigated the impact of reduced lung function on various causes of mortality in 7,058 males and 8,353 females in Scotland, aged 45–64 yrs at baseline [69]. A total of 2,545 males and 1,894 females died during 15 yrs of follow-up and poor lung function accounted for approximately one-quarter of the attributable mortality risk related to ischaemic heart disease.

Although COPD may be an important risk factor for atherosclerosis, ischaemic heart disease, stroke and sudden cardiac death [69–73], the underlying mechanisms are not fully understood [74]. The pathogenesis of atherosclerosis is complex and multifactorial. Persistent low-grade systemic inflammation is believed to be one of the centrepiece events leading to plaque formation [75]. There are compelling epidemiological data linking systemic inflammation to atherosclerosis, ischaemic heart disease, strokes and coronary deaths [76–78]. Under normal physiological conditions (and without external insults), the human endothelium does not support leukocyte adhesion, which is the building block of plaque genesis [79]. However, in an inflammatory state (such as diabetes, COPD or obesity), the endothelium begins to over express surface adhesion molecules, such as vascular cell adhesion molecule-1, that allow circulating white blood cells to adhere to damaged endothelial surfaces [80, 81]. Once the white cells become adherent to the endothelium, they trigger a whole series of inflammatory reactions.

Certain molecules can promote (or amplify) this inflammatory process. The most studied of these molecules is CRP. It is an acute phase protein that responds to infectious or inflammatory stress. When released into the systemic circulation, CRP can upregulate production of other inflammatory cytokines, activate the complement system, promote uptake of low-density lipoproteins (LDL) by macrophages, and foster

leukocyte adhesion to vascular endothelium, thereby amplifying the inflammatory cascade. CRP can also upregulate the expression of adhesion molecules and monocyte chemotactic protein-1, promote macrophage uptake of LDL and interact with endothelial cells to stimulate the production of IL-6 and endothelin-1 [80–83]. Other acute phase proteins released by the liver, such as plasma fibrinogen, can also be used to predict future cardiovascular events [76].

If systemic inflammation is a key mechanism for atherosclerosis, patients suffering from conditions associated with systemic inflammation should have an excess risk of cardiovascular morbidity and mortality. Indeed, this appears to be the case. There is compelling epidemiological evidence that patients with rheumatoid arthritis, for example, have an elevated risk of cardiovascular disease. A recently published meta-analysis evaluating this relationship indicated that rheumatoid arthritis increases mortality rates by 70%; nearly half of this excess risk is directly attributable to cardiovascular causes [84]. Treating rheumatoid arthritis with disease-modifying agents appears to mitigate this risk. In a recent report by CHOI *et al.* [85], therapy with methotrexate reduced the overall mortality by 60%, primarily by reducing cardiovascular deaths. Methotrexate had little impact on other causes of mortality. Similar associations have been observed with systemic lupus erythematosis, another systemic inflammatory disorder [86].

COPD is characterised by persistent systemic inflammation. Data were analysed for 6,629 patients from the third NHANES (NHANES III) to determine whether systemic inflammatory markers, including CRP, were present in patients with COPD and to assess the possible link with cardiovascular injury [74]. The 2,070 patients with COPD were grouped by degree of airflow obstruction. The group of patients with severe COPD had significantly higher circulating leukocyte, platelet and fibrinogen levels and were 2.2-times more likely to have elevated CRP levels, compared with subjects without airflow obstruction [74]. Patients with moderate COPD also showed significant, albeit smaller, increases in these inflammatory markers, indicating that systemic inflammation is not solely associated with severe COPD.

The link between COPD and plasma fibrinogen level (another nonspecific marker of systemic inflammation and an independent risk factor for coronary heart disease) was investigated in 93 patients with COPD [87]. Plasma fibrinogen levels were elevated in stable patients with COPD. Exacerbation of COPD increased serum IL-6 levels, which was associated with rises in plasma fibrinogen. Multiple regression analyses showed that the increase in fibrinogen was significantly greater when exacerbations were associated with purulent sputum, increased cough and symptomatic colds. The authors concluded that increases in plasma fibrinogen, associated with rises in IL-6 in patients with COPD exacerbation, may contribute to increased cardiovascular mortality [87].

By no means, however, are cardiovascular diseases and cancer the only comorbid conditions that may bear some relationship to the abnormal pulmonary and systemic inflammatory responses that characterise COPD. For example, unexplained weight loss is common in COPD and TNF-α has been linked with cachexia in laboratory animals. Serum levels of TNF-α were measured in a prospective study of 30 male patients with stable COPD, half of whom were below normal weight levels [88]. Serum TNF-α concentrations were significantly elevated in the group of underweight COPD patients, but not in those with stable body weight, even though both groups had similar pulmonary function. The authors concluded that increased TNF-α production is a likely cause of weight loss in patients with COPD, suggesting a systemic inflammatory component even in clinically stable COPD. An additional systemic complication of COPD, insulin resistance [89], appears related to elevated levels of TNF-α and IL-6, and may lead to a greater risk of diabetes and cardiovascular disease [90].

COMORBIDITIES AND COPD MORTALITY: CAUSE OR EFFECT?

A key issue that must be considered when measuring the role of comorbidities in COPD mortality is causation. For example, do comorbidities make patients more susceptible to the consequences of COPD, does COPD increase their susceptibility to these comorbidities, or is it a combination of both? Unfortunately, the exact nature of these causal pathways is unknown. However, there is good evidence that COPD is a risk factor for lung cancer [52], and that COPD precedes cardiovascular mortality [63]. The possibility of reverse causation is also possible in certain patients for cardiovascular disease, but not for lung cancer. Clearly more work is required to establish the potential mechanisms and causal pathways that link comorbid conditions and COPD mortality.

PREDICTING MORTALITY IN PATIENTS WITH COPD

Identification of validated markers to help predict COPD mortality is clearly desirable, but not necessarily straightforward, probably reflecting the range of comorbidities, causes of death and complexity of underlying mechanisms associated with COPD. The most widely used prognostic factor in COPD has been FEV_1 [63, 68, 73]. However, it is becoming increasingly clear that prognostic tools that better capture comorbidities demonstrate superior performance than does FEV_1 alone. The BODE Index (Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity) is a recent example of a multidimensional instrument that shows great promise in predicting prognosis of COPD patients. The BODE Index was designed to show that it is important to consider a range of factors (rather than just a single component such as lung function) when assessing COPD prognosis [29]. The BODE Index is derived from BMI, FEV_1, a modified Medical Research Council dyspnoea score and the 6-min walk distance. The index was validated in 625 patients with respiratory and all-cause mortality as its end-points [28]. One-point increase in the BODE Index was associated with a 34% increase in all-cause mortality (HR=1.34; 95% CI 1.26–1.42; $p<0.001$) and 62% increase in respiratory mortality (HR=1.62; 95% CI 1.48–1.77; $p<0.001$). Overall, the BODE Index was more effective than FEV_1 alone at predicting risk of all-cause or respiratory mortality [28].

Health status instruments provide incremental prognostic information beyond FEV_1, in part because they reflect the burden imposed by comorbidities. One possible reason why these health status indices do better than just FEV_1 in predicting mortality in COPD is that they capture, to a certain

extent, underlying comorbidities (which may be subclinical at the time of assessment). In particular, domains such as exercise tolerance and dyspnoea provide an assessment of the nutritional and cardiovascular status, as well as the fitness level of the COPD patient, which will impact on their prognosis. The hypothesis that health-status measurements capture underlying comorbidities better than other prognostic tools is supported by a study involving 381 patients with COPD of any severity [91]. The presence of comorbidities was associated with higher scores on St George's Respiratory Questionnaire (SGRQ) impacts (β coefficient=0.137; p=0.02) and SGRQ total (β=0.115; p=0.05). In another analysis of 381 consecutive patients, patients with comorbid conditions had worse health-related quality of life (fig. 6) [92]. In a 3-yr follow-up study that included 312 males with COPD, both SGRQ and Short Form-36 Physical Component scores (PCS-36) were independently associated with mortality after adjustment for age, FEV_1 and BMI [93]. In the final adjusted model, poorer SGRQ (standard HR=1.30) and PCS-36 (standard HR=1.32) scores were associated with ~30% increased mortality and post-bronchodilator FEV_1 (standard HR=1.60) was associated with 60% increased mortality. Furthermore, SGRQ and PCS-36 were independently associated with mortality attributed specifically to respiratory causes. In addition, many of these approaches used to help predict COPD mortality are also associated with the inflammatory marker CRP, further strengthening the link between systemic inflammation and COPD. For example, in a study involving 102 COPD patients [94], those with elevated CRP had a lower SGRQ symptom score (p=0.003) as well as lower maximal (p=0.040) and submaximal (p=0.017) exercise capacity, and 6-min walking distance (p=0.014).

Peak exercise capacity is another integrated measure of the cardiopulmonary performance of COPD subjects. In one study [95], the authors analysed the relationship between exercise capacity, health status and mortality in 150 males with COPD, followed-up for 5 yrs. Univariate analysis showed that SGRQ activity (p=0.0001), impact (p=0.0023) and total (p=0.0017) scores were significantly correlated with mortality, whereas only the Chronic Respiratory Disease Questionnaire (CRQ) dyspnoea domain, but not total CRQ, was significantly predictive (p=0.0047). Multivariate analysis showed that SGRQ total score (RR=1.035; 95% CI 1.008–1.063; p=0.012) and peak oxygen uptake ($V'_{O_2,max}$; RR=0.995; 95% CI 0.993–0.998; p<0.0001) were predictive of mortality independently of age and FEV_1. Most importantly, a stepwise Cox analysis found $V'_{O_2,max}$ to be the most significant predictor of mortality (RR=0.994; 95% CI 0.992–0.996; p<0.0001). Collectively, these data suggest that tools that evaluate both the cardiopulmonary performance of COPD patients (*e.g.* $V'_{O_2,max}$) provide incremental prognostic information beyond just FEV_1 and, in certain settings, perform better than tools that reflect only the ventilatory status of COPD subjects.

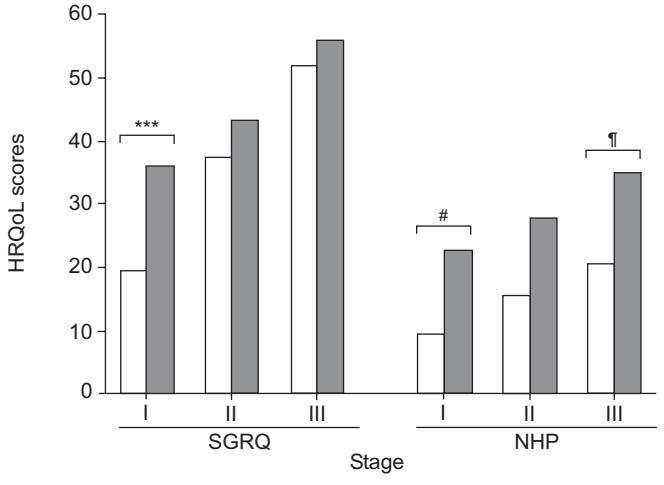

FIGURE 6. Health-related quality of life (HRQoL), as assessed by total St. George's Respiratory Questionnaire (SGRQ) score or total Nottingham Health Profile (NHP) score, in patients without (□; n=52) or with (■; n=269) comorbid conditions [92]. HRQoL scores range from 0 (best) to 100 (worst). #: p=0.004; ¶: p=0.016; ***: p=0.001.

IMPLICATIONS FOR FUTURE RESEARCH

There are several important implications of these observations. First, there needs to be a concerted effort to standardise reporting of cause(s) of death in COPD. If death certificates are used, it is important to consider and report not just the principal underlying cause of death but also other contributing conditions. As COPD patients frequently die of cardiovascular complications and lung cancer [3, 21], such an approach will minimise the underreporting of COPD as a ''cause of death'' in COPD patients. Secondly, ICD codes for COPD have to be standardised. Dissimilar to asthma, ischoemic heart disease or stroke, there are more than one ICD-9 and ICD-10 codes for capturing COPD. This can pose analytical problems and make comparisons in COPD mortality across jurisdictions and countries difficult, unless standardised protocols are developed and implemented. There should also be intense lobbying of the WHO for the creation of one ICD code specific for COPD in future iterations of the ICD scoring system. Thirdly, the importance of comorbidities in COPD patients, both in life and in death, needs to be appreciated. As summarised in the present review, a number of studies report statistically significant relationships between the type or number of comorbidities and mortality. Therefore, future randomised controlled trials powered for survival in patients with COPD should be careful not to exclude patients inappropriately on the basis of baseline comorbidities. Such an approach is likely to select for a relatively healthy patient population and might lead to underestimates of the true burden of mortality in patients with COPD.

CONCLUSIONS

COPD is a disease associated with high and increasing worldwide mortality. However, COPD-related mortality is probably underestimated because it can be difficult to attribute death to a single cause, even when the patient dies in a clinical setting. Contrary to common opinion, respiratory failure is not the only major cause of death in end-stage COPD; moreover, cardiovascular disease and lung cancer are common causes of death earlier in the disease progression of COPD. Although the underlying mechanisms are not fully understood, cardiovascular disease and lung cancer are clearly associated with COPD, possibly due to chronic systemic and pulmonary inflammation. While all of these diseases are smoking related, and therefore should be associated with each other, the

presence of airways obstruction (and possibly inflammation) imposes additional risk.

Although no single approach has been adopted as the standard for predicting mortality in patients with COPD, health status appears to be an independent predictor of mortality. The SGRQ appears to be a more consistent predictor than the CRQ, and the BODE Index is also predictive of mortality. These multicomponent approaches may be more useful than approaches that employ single parameters, such as FEV_1, because the former approaches are more likely to capture the health impact of comorbidities in COPD patients.

Due to the presence of comorbidities and associated inaccuracies of cause of death coding, all-cause mortality should be one of the primary end-points for any future studies to evaluate chronic obstructive pulmonary disease therapy. Currently, conclusive data are only available for the use of supplemental oxygen in selected patients and smoking cessation in all patients. However, the ongoing TOwards a Revolution in Chronic obstructive pulmonary disease Health study, which identifies all-cause mortality as its primary end-point, may provide conclusive data for the use of inhaled corticosteroids and long-acting β_2-agonists, either alone or in combination. It is important that future studies consider chronic obstructive pulmonary disease as a multicomponent disease [96] with serious comorbidities, including cardiovascular disease and lung cancer, with pulmonary and systemic inflammation at the heart of the disease. Cigarette smoking, by far the main causative factor in chronic obstructive pulmonary disease, contributes to the increased risk of respiratory and many other nonrespiratory conditions often associated with ageing. Finally, it is important to realise that any clinical trial that attempts to identify ''pure'' chronic obstructive pulmonary disease patients (*i.e.* those without any associated comorbidities) will be likely to explore therapeutic effects in a nonrepresentative group of chronic obstructive pulmonary disease patients.

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