Mortality prevention as the centre of COPD management

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Abstract

COPD is a major healthcare problem and cause of mortality worldwide. COPD patients at increased mortality risk are those who are more symptomatic, have lower lung function and lower diffusing capacity of the lung for carbon monoxide, decreased exercise capacity, belong to the emphysematous phenotype and those who have concomitant bronchiectasis. Mortality risk seems to be greater in patients who experience COPD exacerbations and in those who suffer from concomitant cardiovascular and/or metabolic diseases. To predict the risk of death in COPD patients, several composite scores have been created using different parameters. In previous years, large studies (also called mega-trials) have evaluated the efficacy of different therapies on COPD mortality, but until recently only nonpharmaceutical interventions have proven to be effective. However, recent studies on fixed combinations of triple therapy (long-acting β-agonists, long-acting muscarinic antagonists and inhaled corticosteroids) have provided encouraging results, showing for the first time a reduction in mortality compared to dual therapies. The aim of the present review is to summarise available data regarding mortality risk in COPD patients and to describe pharmacological therapies that have shown effectiveness in reducing mortality.

Introduction

COPD is a major healthcare problem and cause of mortality worldwide [1]. Based on the results of the Burden of Obstructive Lung Diseases programme, which assessed the prevalence of disease globally using standardised methodology, the prevalence of disease worldwide was ∼11.8% in men and ∼8.5% in women [2]. With respect to mortality, COPD is currently the third leading cause of death worldwide following ischaemic heart disease and stroke, causing 3 million deaths annually, which represents ∼4.72% of all deaths [1]. Due to the increased proportion of ageing populations at a global level, which is more pronounced in high-income countries, and the increasing smoking prevalence in developing countries, projections for the number of deaths from COPD and related conditions for 2060 exceed 5.4 million [1]. Data from the Danish registry of COPD have shown the 3-year mortality rate for patients with COPD to range from 10% to 36.9% depending on disease severity, which is up to six times higher than the respective rates in the general population [3, 4].

Historically, several studies have evaluated the efficacy of different therapies on COPD mortality, but until recently only nonpharmaceutical interventions (*i.e.* smoking cessation, long-term oxygen therapy, noninvasive mechanical ventilation (NIMV), lung volume reduction and pulmonary rehabilitation) have proven to be effective [5–12]. However, recent studies on fixed combinations of triple therapy (long-acting β-agonists (LABA), long-acting muscarinic antagonists (LAMA) and inhaled corticosteroids (ICS)) have provided encouraging results, showing for the first time a reduction in mortality compared to dual therapies [13, 14]. The aim of the present review is to summarise available data regarding mortality risk in COPD patients and to describe pharmacological therapies that have shown effectiveness in reducing mortality.

Which COPD patients are at increased risk of death?

Several studies have evaluated mortality in COPD patients, showing that patients who are at increased risk of death are those who are more symptomatic [4, 15, 16], have lower lung function [17] and lower diffusing capacity of the lung for carbon monoxide [18–20], low exercise capacity [21] and/or emphysematous phenotype [20].

One of the major factors influencing mortality in COPD patients is the frequency and severity of exacerbations [22]. Patients experiencing three or more exacerbations per year are at increased risk of death, while severe acute exacerbations of COPD have an independent negative impact on a patient's prognosis. Mortality increases with the frequency of severe exacerbations, particularly if they require hospital admission [22].

To predict mortality risk in COPD patients, several composite scores have been created, which use different parameters such as body mass index (BMI), age, the level of dyspnoea, lung function and exercise capacity. The BODE (body mass index, airway obstruction, dyspnoea and exercise capacity) [23], ADO (age, dyspnoea and obstruction) [24] and DOSE (dyspnoea, obstruction, smoking and exacerbation frequency) [25] index scores have been shown to predict mortality in COPD patients.

As expected, mortality risk is greater as lung function deteriorates, yet comorbidities such as cardiovascular diseases, diabetes mellitus and arterial hypertension also seem to contribute independently to reduced survival [26].

The association between acute exacerbations of COPD and mortality

Most patients with COPD experience exacerbations; yet many (mainly mild) are unreported. Results of the 3-year Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) [27] and Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) [28] studies, as well as results of the 4-year Understanding Potential Long-term Improvements in Function with Tiotropium (UPLIFT) [29] study, indicated that 49–77% of patients with COPD experience at least one moderate or severe exacerbation within a 3-year period. Interestingly, studies from Europe [30] and other geographical settings [30–33] indicated that 40–78% of exacerbations, as assessed with specific criteria, were not reported by the patients to their treating physicians.

COPD exacerbations can have a long-term impact on patients' health and wellbeing [34]. Symptom worsening and incidence of COPD exacerbations have been linked with increased risk of cardiovascular events [35–37], lung function loss [38, 39], decreased physical activity, and deconditioning, leading to deterioration of mental health and quality of life [40, 41], as well as increased risk of further exacerbations [34, 42]. More importantly, exacerbations are associated with an increased risk of hospitalisation or death [42–46]. Based on data from 99 574 patients with COPD from the UK Clinical Practice Research Datalink, with >10 years of follow-up, the risk of death gradually increased with increasing frequency of moderate exacerbations during the first year of follow-up and was highest among patients who had experienced at least one severe exacerbation during the first year of follow-up (hazard ratio (HR) 1.79, 95% CI 1.65–1.94) [46]. According to an adjusted model, considering the 12-month period before death, patients who had experienced two moderate exacerbations had 80% higher risk of death compared with those who had not experienced any acute COPD exacerbation during that time [46]. Accordingly, identifying patients at risk of exacerbations might be a key to optimising their management and increase their survival. Factors that could potentially serve as predictors of future exacerbations include a history of COPD exacerbations [27, 47], increased dyspnoea and productive cough [47, 48], as well as raised eosinophil counts when not receiving ICS [49].

Comorbidities and mortality in patients with COPD

The interaction between COPD and comorbidities is complex, and in practice it is extremely difficult to dissect the cause of death in patients with comorbidities. Accumulating evidence indicates that the negative impact of exacerbations on patients' health extends beyond the lungs. Patients with comorbidities or uncontrolled comorbid conditions may experience more frequent exacerbations, while frequent exacerbators may also be at increased risk of comorbidities [50, 51].

Cardiovascular diseases (including coronary disease, atrial fibrillation, arterial hypertension, chronic heart failure, myocardial infarction and stroke) are among the commonest and most important comorbidities in COPD patients [50, 52]. COPD patients have an ~4.5 higher risk to develop cardiovascular comorbidities [53]. A case-series study in 25 857 patients with COPD estimated that the risk of myocardial infarction increased two-fold within 5 days ($p=0.03$) of a moderate COPD exacerbation and returned to baseline over time,

while the risk of stroke increased by 40%, although not statistically significantly, on days 6–10 following such an exacerbation [35]. Similarly, another study showed that in patients with COPD who either have cardiovascular disease or have risk factors for cardiovascular disease, the risk of cardiovascular events persisted for up to 1 year following an exacerbation [36]. The risk of such events, which included cardiovascular death, myocardial infarction, stroke, unstable angina and transient ischaemic attack, was particularly elevated (HR 3.8, 95% CI 2.7–5.5) in the first 30 days after an exacerbation and was almost two-fold between 31 and 90 days after the exacerbation onset [36]. The risk of cardiovascular events was even higher in COPD patients hospitalised for acute exacerbations, with the corresponding 30-day hazard ratio being 9.9 (95% CI 6.6–14.9) [36]. If no new acute COPD exacerbation occurred, the risk of cardiovascular events was no longer increased 1 year after the exacerbation [36].

In addition, the relationship between cardiovascular events and mortality in COPD has been examined from a different perspective, analysing the effect of cardiovascular comorbidities on the risk of death in these patients. Individuals with COPD seem to have a greater risk of suffering from cardiovascular disease than those without COPD [54]. Coexistence of moderate-to-very-severe COPD and cardiovascular disease is associated with increased dyspnoea and worse quality of life, while coexistence of mild-to-very-severe COPD is associated with greater risk of hospitalisation than either condition alone [26, 55]. The presence of cardiovascular comorbidities increases mortality risk in COPD patients [56]. In particular, among patients with COPD who also have ischaemic heart disease, atrial fibrillation, diabetes or heart failure, the risk of death is increased by 27–50%, 56%, 54–70% and 30–90%, respectively, *versus* patients having COPD alone [56].

The contribution of cardiovascular disease to mortality in COPD patients is substantial, even among those who suffer from moderate disease. The proportion of deaths attributed to cardiovascular disease ranged from 22% to 44% across the Lung Health Study III [5], the Towards a Revolution in COPD Health (TORCH) [57], the Informing the Pathway of Chronic Obstructive Pulmonary Disease Treatment (IMPACT) [58] and the Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) [14] studies. Focusing on patients with moderate COPD (Global Initiative for Chronic Obstructive Lung Disease stage II), the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study indicated that only ∼4% of deaths were related to respiratory causes, while 25% were due to lung cancer and 28% were due to cardiovascular events [16].

Despite the strong association between COPD and cardiovascular diseases, the actual components and biological processes underlying this interplay remain poorly understood. The proposed mechanisms that mediate the functional interaction between COPD and cardiovascular disease generally involve shared risk factors and common pathophysiological pathways such as smoking, physical inactivity, poor diet and air pollution [56]. The effect(s) of the aforementioned factors to COPD and cardiovascular disease could be mediated by inflammatory and accelerated-ageing mechanisms [59]. Another hypothesis proposes that COPD, emphysema and chronic bronchitis/bronchiolitis (small airways disease) are associated with hypoxia, hypercapnia, vessel wall abnormalities, imbalances of various proteins and elastin degradation, which in turn can lead to oxidative stress, spilling into the systemic circulation and thence to atherosclerosis, endothelial dysfunction and arterial stiffness, eventually causing atherosclerotic and thromboembolic diseases such as myocardial infarction, angina, stroke, peripheral artery disease, congestive heart failure and cardiac arrhythmias (atrial fibrillation) [59, 60].

In some cases, the interaction between COPD and various comorbidities remains unclear. Treatments perceived as beneficial for COPD may have detrimental impact on the management of a coexisting comorbid condition; the reverse is also theoretically possible, while in other cases a particular treatment administered for one condition may also benefit a comorbidity. Some studies have suggested that treatment with LABA and LAMA leads to increased cardiovascular risk [61]. Along the same line, β_2-agonists, despite their safety claims, may cause unwanted effects in a patient who has uncontrolled supraventricular tachycardia, particularly if the patient also suffers from heart failure or atherosclerosis, as the β_2-agonist-induced tachycardia may further increase cardiovascular risk [62]. In contrast, some cardiovascular medications may also have a beneficial impact on COPD, even though there have been concerns about nonselective β-blockers that may adversely affect the respiratory system [63]. Similarly, there are treatments for COPD, such as ICS, that may reduce nonrespiratory (mainly cardiovascular) mortality, although this is still debatable.

In COPD patients with lung cancer, death often occurs from the coexistence of the two diseases (COPD and lung cancer), thus is often difficult to attribute COPD mortality in these patients to either disease.

Furthermore, COPD patients with lung cancer are often unable to undergo curable surgical interventions due to severe lung function impairment, which finally leads to death from lung cancer.

Prevention of mortality in COPD patients: is it feasible?

Regarding the fact that the main risk factor for the development of COPD in Western countries is cigarette smoking, the most drastic prevention measure would be to ban cigarette smoking globally. Existing data from the United States of America show the effect of banning public cigarette smoking on reducing cancer incidence [64]. Undoubtedly, a public smoking ban would reduce deaths among COPD patients, but would not reduce the numbers of patients who already have COPD.

A crucial, inadequately investigated question is whether very early aggressive pharmaceutical intervention can change the natural course of the disease. This may sound reasonable, but it remains speculative, as no study has been conducted to address this. One study examined the effect of administration of tiotropium to treatment-naïve patients with stage II COPD showing a beneficial effect on lung function and patient-reported outcomes, suggesting benefits in initiating maintenance therapy early [65]. The recent Redefining Therapy in Early COPD (RETHINC) trial, in which a LABA/LAMA combination was administered in symptomatic smokers without COPD, did not show any beneficial effect [66], yet this is a different setting, given that we do not know whether and which symptomatic patients would develop COPD.

To reduce mortality in COPD, it is essential to first diagnose patients and then implement the appropriate management plan. Besides pharmacological treatment, patients should quit smoking and follow any additional nonpharmacological COPD management interventions that are recommended. Although COPD remains the third cause of death worldwide, over recent years, mortality in COPD has decreased from 15% to 5%, probably due to medical and pharmaceutical advances combined with public smoking bans. Potential long-term effects on COPD prevalence could become apparent in the future. In the real-life setting, any effects on mortality are mainly attributed to the different and proper management of both stable disease and exacerbations compared to previous years [67, 68]. Interestingly, during the coronavirus disease 2019 pandemic, the number of hospital admissions among patients with COPD dramatically decreased [69] suggesting that measures like social distancing, protection by their relatives, self-isolation, vaccination and the use of face masks had a very strong impact on decreasing exacerbations in COPD patients (50% reduction over the first and second waves of the pandemic).

Nonpharmacological interventions to reduce mortality in COPD patients

Several nonpharmacological interventions have been shown to be effective in reducing mortality in patients with COPD. The first recognised intervention related to mortality reduction in COPD is smoking cessation. The greatest benefit occurs when smoking cessation takes place early in life, reaching up to 90% reduction of tobacco-attributable death in smokers who quit before the age of 40 years. However, the risk of mortality decreases significantly even when smoking cessation is achieved after the age of 60 years [5, 70, 71]. Long-term oxygen therapy has been recognised to be beneficial in increasing survival in patients with respiratory failure, especially those with a resting partial arterial oxygen pressure $\leqslant$55 mmHg [8, 9]. This reduction in mortality has been shown to be as great as 35% in patients who received supplementary oxygen for $\geqslant$15 h·day^{-1}, but not in patients who received supplemental oxygen for shorter periods. Furthermore, oxygen supplementation did not result in any reduction in mortality in patients who suffered from moderate hypoxaemia [72, 73], those with hypoxaemia only on exertion [74] or patients with only nocturnal hypoxaemia [75].

NIMV has been used in the treatment of stable COPD in selected patients. Several studies have shown beneficial effects of the use of NIMV in the survival of COPD patients [10, 11, 76]. COPD patients treated with both oxygen supplementation and NIMV had a better survival compared to those treated with long-term oxygen therapy alone [68]. Several years ago, lung volume reduction surgery was shown to increase survival in COPD patients with emphysematous lesions with upper lobe predominance [12]. Nowadays, interventional bronchoscopic methods are used to perform lung volume reduction in patients with severe emphysema, leading to survival benefits [77–79], yet these studies lack proper design for the drawing of conclusions. Finally, pulmonary rehabilitation has been shown to lead to improvements in survival of COPD patients [6, 7].

Pharmacological interventions to reduce mortality in COPD patients

Mortality data overview of COPD mega-trials (TORCH, UPLIFT and SUMMIT)

In previous years, the effect of pharmacotherapy on mortality in COPD patients was mainly studied in three large randomised double-blind placebo-controlled trials [57, 80, 81]. The first, the TORCH study [57] was conducted in 444 centres and included >6000 patients. The study duration was 3 years and

patients were randomised to treatment with the combination of salmeterol (50 µg dose) and fluticasone propionate (500 µg dose) or salmeterol alone (50 µg dose), fluticasone propionate alone (500 µg dose) or placebo. The primary end-point of the study was the time to death from any cause by 3 years of treatment initiation. Although a clear numerical difference was observed in the proportions of deaths from any cause at 3 years between groups (12.6% in the combination therapy group, 13.5% in the salmeterol group, 16.0% in the fluticasone group and 15.2% in the placebo group), which led to an absolute risk reduction of 2.6% in the combination therapy group compared to the placebo group (HR 0.825, 95% CI 0.681–1.002), the p-value was 0.052, just failing to reach statistical significance. Thus, although the combination therapy had shown a 17.5% (95% CI −0.2–31.9%) reduction in the risk of death from any cause during the 3-year observation period compared to placebo, the study was characterised as negative, not proving that treatment with fluticasone propionate and salmeterol led to mortality reduction in COPD patients.

Possible explanations for the lack of significant mortality reduction in the TORCH study (as conventionally determined by the p-value of 0.052, which exceeded the 0.05 threshold by 0.002) despite improvements in lung function and respiratory symptoms, might be that mortality is mainly influenced by unknown factors that do not interfere as much with the measured symptoms and lung function parameters. Furthermore, the study might have been underpowered to detect a potential effect of treatment on mortality, as it was initially powered to detect an effect on overall mortality that was expected to be almost double (4.3%) that actually identified (2.6%). This, along with the increased threshold for statistical significance that was introduced by the second interim analysis, may have contributed to the failure of finally reaching significance in mortality, as stated by the authors of the study [57]. Additionally, the 3-year observation period might not be sufficient to allow for any differences to reach significance, while even with the given sample size, a statistically significant effect on mortality might had been observed after a longer observation period. Finally, the high withdrawal rate, especially among placebo-treated patients (44.2%), who were free to subsequently receive active therapy, probably also resulted in an underestimation of the effect of the combination regimen on the risk of death, which is a well-known phenomenon in trials using the intention-to-treat analysis. Yet, it should be emphasised that the statistical threshold of $p \leqslant 0.05$ is rather arbitrary. In fact, p is the probability that the reduction in mortality found in TORCH was not real, but was due to chance. Thus, p=0.052 means that this probability is 5.2%, whereas a p-value of 0.049 (which would have declared the finding statistically significant) would have meant that the probability that the mortality reduction is not real but is due to chance was 4.9%, a 0.3% difference in probability. Furthermore, this p-value might change with a slight change in the date that the study was terminated. This is clearly illustrated in the mortality analysis of the UPLIFT study, which took place 2 years later [80].

The UPLIFT study [80] which was conducted in 487 sites and lasted for 4 years, compared treatment with 18 µg tiotropium once daily with placebo. The primary objective was pre-bronchodilator and post-bronchodilator pulmonary function, but analyses of exacerbations and mortality were also performed. It is important to point out that in the UPLIFT trial, participants were receiving tiotropium or placebo as add-on therapy to their usual respiratory treatment, which could include any medication, only excluding other inhaled anticholinergic drugs. Regarding mortality rates, the UPLIFT trial showed a reduction in the proportion of deaths in the tiotropium group (14.4%) compared to placebo (16.3%), corresponding to a hazard ratio of 0.87 (95% CI 0.76–0.99). The main criticism of these findings was that, as stated earlier, many of the patients randomised to the tiotropium arm were also receiving additional treatment for COPD, while many of them were receiving ICS/LABA combinations [80, 82]. However, an alternative view could be that maximising therapy in COPD (*i.e.* the addition of tiotropium to whatever therapy the patient was receiving) can lead to reduction in mortality. Furthermore, mortality was not the primary end-point of the UPLIFT trial. On a temporal analysis of mortality during the study, mortality in the arm receiving the active treatment was consistently lower over time, while confidence limits indicate significance on most of the period, although at particular time points significance was lost [83] (figure 1).

This observation leads to the conclusion that when performing a mortality analysis, the outcome should rather be examined over an entire period of time, and no pre-defined time point should be used. This is important to keep in mind when analysing the mortality reduction in TORCH.

Following a *post hoc* analysis of the TORCH trial showing a significant reduction of cardiovascular mortality in the ICS/LABA combination [84] the Study to Understand Mortality and Morbidity (SUMMIT) [81] trial was designed. The study was conducted in 1368 centres and included >16 000 COPD patients who either suffered from cardiovascular comorbidities or were at increased risk of cardiovascular death. Patients were randomised into four treatment arms to receive a fixed-dose combination of fluticasone furoate and vilanterol, fluticasone furoate, vilanterol or placebo. The primary end-point of the study was the time to death from any cause. Although SUMMIT was an event-driven trial,

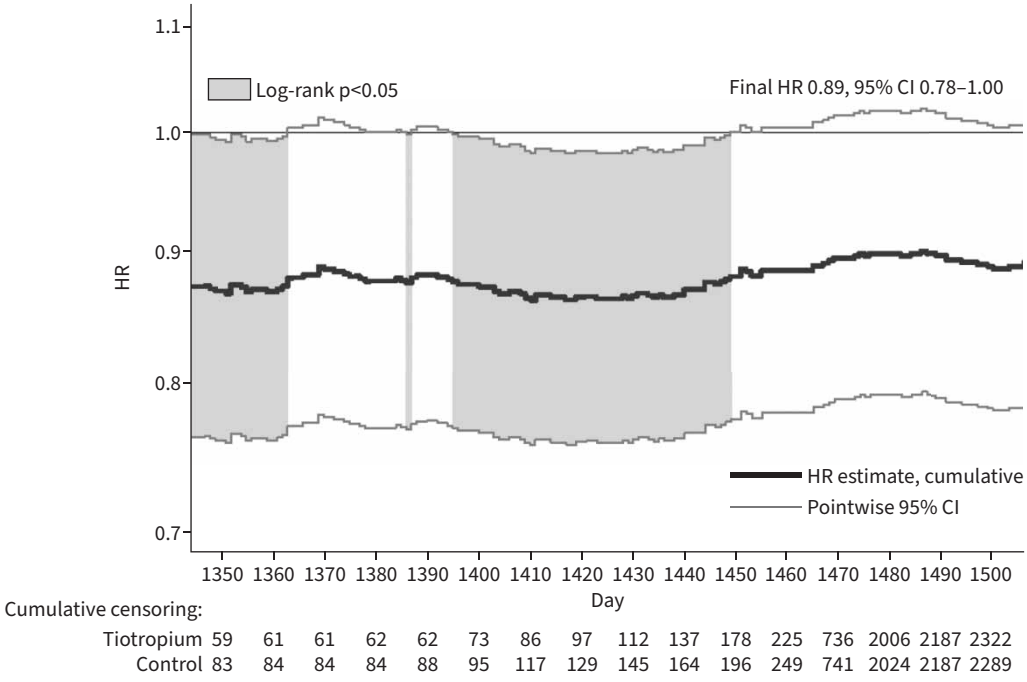

FIGURE 1 Hazard ratios (HR) (tiotropium/control) and 95% confidence intervals for mortality including data from prematurely discontinued patients from day 1340 to day 1510. Cumulative censoring represents the total number of censored patients up to each time point. Reproduced and modified from [84] with permission.

completed after the occurrence of 1000 deaths, it failed to show any difference in mortality rates between study groups, showing a proportion of death from any cause of 6.7% in the placebo group, 6.1% in the fluticasone furoate group, 6.4% in the vilanterol group and 6.0% in the combination therapy group, with no significant effect of combination therapy or its components on the risk of all-cause mortality compared to placebo [81]. Although SUMMIT probably included the largest COPD cohort, it used a very ambitious primary end-point. We must state that the inclusion criterion regarding forced expiratory volume in 1 s (FEV_1) in SUMMIT [81] was 50–70%, and <60% in TORCH [57], and since greater lung function impairment is associated with increased risk of death, the expected mortality in TORCH was greater compared to SUMMIT.

Studies of triple (ICS/LABA/LAMA) combinations for COPD treatment

The first major studies examining the efficacy of triple combinations on COPD patients were the TRILOGY, TRINITY and TRIBUTE studies. All three studies were designed to compare the triple extra-fine combination regimen (beclomethasone dipropionate (BDP)/formoterol furoate (FF)/glycopyrronium (GLY)) with dual combinations of ICS/LABA or LABA/LAMA and with tiotropium. In TRILOGY, the triple combination was compared with ICS/LABA; in TRINITY it was compared with LAMA, but the study also included an open triple combination of ICS/LABA and LAMA (tiotropium); and in TRIBUTE, the triple combination was compared with LABA/LAMA (indacaterol (IND)/glycopyrronium). All three studies lasted for 52 weeks, and their primary end-point was the analysis of moderate or severe exacerbations during the observation period. Although none of these studies was designed to assess mortality, death from any cause was studied as a safety outcome. Using data from these trials, a pooled analysis was conducted to address mortality, comparing the pool of the arms receiving extra-fine ICS combinations *versus* the pooled arms receiving ICS-free regimens [85]. Comparison of the pooled groups receiving BDP/FF/GLY, BDP/FF and BDP/FF+tiotropium (n=3745) *versus* patients receiving tiotropium, IND/glycopyrronium bromide (GB) (n=1844) showed a numerical (2.0% *versus* 2.7%) difference in mortality, which was close to but did not attain statistical significance (HR 0.71, 95% CI 0.50–1.02; p=0.066). Similarly, comparison of the 2.0% mortality rate in BDP/FF/GLY (n=2528) with the 2.7% rate in tiotropium, IND/GB (n=1844) did not yield statistically significant results (HR 0.72, 95% CI 0.49–1.06; p=0.096). However, comparison of the 1.5% mortality rate of BDP/FF/GLY, BDP/FF, BDP/FF+tiotropium (n=3745) *versus* the 2.2% rate in tiotropium, IND/GB (n=1844) yielded a statistically significant (p=0.037), hazard ratio of 0.65 (95% CI 0.43–0.97) [85]. When examining mortality rates in

triple therapy *versus* LABA/LAMA, in the BDP/FF/GLY pool (n=2582), 51 (2%) deaths were recorded *versus* 21 (2.7%) deaths recorded in the group receiving IND/GLY (n=768) in TRIBUTE. Moreover, when including both patients receiving open (BDP/FF+tiotropium in TRINITY) and patients receiving closed (BDP/FF/GLY in TRILOGY, TRINITY and TRIBUTE) triple therapy (n=3065), the number of deaths was 59 (1.9%) *versus* 21 (2.7%) deaths in the LABA/LAMA (IND/GLY in TRIBUTE; n=768). This observation leads to the hypothesis that there is a potential for mortality reduction with the use of triple combinations compared to dual and/or single bronchodilation.

However, this pooled analysis had a main limitation, which was that none of the individual included trials were designed to evaluate mortality. Thus, there are methodological gaps when making any comparisons between groups. Additionally, the duration of the observation period (52 weeks) was too short for a mortality analysis. In the context of safety analysis, patients were followed-up for only 2 weeks (which is a time period significantly shorter than the usually applied 30-day follow-up period) after the last study drug intake. Furthermore, there is a lack of an off-treatment analysis, which adds an additional limitation. Finally, given that the frequency of fatal cardiovascular events during and after exacerbations is known to be elevated, the reduction in the number of observed deaths from nonrespiratory causes could be related to the decrease in exacerbations [35, 36].

Some years later, the IMPACT [13] study was the first study on a triple combination to include all-cause mortality as a pre-specified end-point. IMPACT was a phase 3, randomised, double-blind parallel-group trial which included >10 000 participants and compared triple therapy of the inhaled glucocorticoid fluticasone furoate (100 µg), the LAMA umeclidinium (UME) (62.5 µg) and the LABA vilanterol (VI) (25 µg) with dual combinations.

With respect to mortality, a total of 50 (1%) patients died during the study in the triple-therapy group, *versus* 49 (1%) patients in the FF/VI and 39 (2%) patients in the UME/VI group (which was half the size of the first two groups), corresponding to a significantly lower all-cause mortality rate in the regimens including FF compared to the UME/VI group. The estimated hazard ratio of triple therapy *versus* UME/VI was 0.58 (95% CI 0.38–0.88, 42% difference; unadjusted p=0.01). However, in this original analysis of mortality of the IMPACT study, 574 individuals were censored, as their vital status at week 52 was not recorded following discontinuation of study treatment or participation. To more accurately evaluate the effect of the aforementioned treatments on mortality, a secondary analysis was conducted, following the collection of additional data regarding the patient's vital status at week 52, reaching an evaluable sample of 99.6% of the intention-to-treat population [58]. Based on this revised and expanded dataset, the numbers of deaths in the FF/UMEC/VI, FF/VI and UMEC/VI treatment groups were 98 (2.36%), 109 (2.64%) and 66 (3.19%), respectively. Moreover, this *post hoc* time to all-cause death, including events that occurred off-treatment, demonstrated a hazard ratio of 0.72 for patients treated with FF/UMEC/VI *versus* UMEC/VI (95% CI 0.53–0.99; p=0.042), which was close to the 0.71 (95% CI 0.51–0.99; p=0.043) ratio estimated without the follow-up vital status data.

When analysed by prior ICS use, the benefit of regimens containing ICS in terms of reduction of mortality risk with ICS/LAMA/LABA *versus* LAMA/LABA was only observed among patients who received an ICS-containing regimen before entering the study. In particular, among patients receiving ICS prior to randomisation, the hazard ratio for on-treatment all-cause mortality was 0.44 (95% CI 0.27–0.71; p<0.001) for those randomised to triple therapy *versus* UMEC/VI, while the respective hazard ratio including off-treatment data and additional vital status follow-up was 0.63 (95% CI 0.44–0.89; p=0.009). Upon randomisation, ∼40% of patients who were using a triple therapy (ICS/LAMA/LABA) prior to study entry remained on triple therapy, while 40% were stepped down to an ICS/LABA and 20% to a LAMA/LABA regimen. Furthermore, although not statistically significant, a reduced risk of on-/off-treatment death was observed for patients who remained on triple therapy following randomisation, *versus* those who were stepped down from triple to dual therapy (HR 0.71, 95% CI 0.46–1.10; p=0.124 for ICS/LABA and HR 0.62, 95% CI 0.38–1.00; p=0.051 for LAMA/LABA).

The IMPACT study had been criticised because patients with a history of asthma were not excluded from study participation, provided they did not currently suffer from asthma [86]. In both TRIBUTE and IMPACT, prior ICS treatment was withdrawn at the time of randomisation in the group of patients who were assigned to non-ICS-containing regimens, which might have affected the study outcomes. The potential effect could be considerable, as most of the patients in both trials were on previous ICS treatment at study entry.

To address the pattern of exacerbation over time, Suissa and Ariel [87] converted cumulative moderate or severe exacerbation incidence curves from the TRIBUTE and IMPACT trials into monthly rates of

exacerbation. Based on this analysis, they suggested that both in the IMPACT and TRIBUTE trials, the favourable effect of triple therapy on reducing the rate of exacerbations compared to dual LAMA/LABA therapy is statistically significant only during the first month of treatment, and that the differences between the two groups are attenuated afterwards. This transient effect was attributed to ICS discontinuation and was also observed in a similar conversion of mortality data from the IMPACT study. In the analysis of monthly mortality rate, the difference between the LAMA/LABA/ICS and LAMA/LABA groups is prominent during the first 4 months of treatment, following which the difference between the two groups is lost. The authors went on to highlight the similarity of the observed mortality rate pattern with that reported in a study of asthma following discontinuation of ICS treatment, where the risk of asthma death rate is increased over four-fold in the first 3 months since ICS discontinuation. Even if this *post hoc* analysis were accepted, a clear conclusion is that ICS should not be withdrawn from COPD patients receiving LABA/LAMA who need them. Thus, more research in this field is needed to identify these patients.

The first study of fixed triple combination which included mortality as a secondary end-point was the ETHOS trial [14], in which triple therapy with budesonide (320 µg or 160 µg), glycopyrrolate (18 µg) and formoterol fumarate (9.6 µg) was compared to dual therapies (glycopyrrolate 18 µg and formoterol fumarate 9.6 µg or budesonide 320 µg and formoterol fumarate 9.6 µg).

In the context of mortality assessment in the ETHOS trial, the total number of deaths from any cause over the 52-week study observation period was 28 (1.3%) and 39 (1.8%) in the 320 µg and 160 µg budesonide triple therapy groups, respectively; 49 (2.3%) in the glycopyrrolate/formoterol group; and 34 (1.6%) in the budesonide/formoterol group. Based on time-to-event analysis over this period, the risk of death from any cause in the 320 µg budesonide triple therapy group was 46% lower than that in the glycopyrrolate/formoterol group (HR 0.54, 95% CI 0.34–0.87). However, this finding was interpreted cautiously, as the analysis was performed with vital status at week 52 missing for 384 out of 8509 patients. To increase the robustness of the finding, the mortality analysis was revisited following additional data retrieval, which achieved to include vital status data for 99.6% of the intention-to-treat population [88]. Besides the pre-specified end-point of time to death from any cause, which was assessed in the intention-to-treat population and regardless of whether the patients continued their assigned treatment or not, the time to death was also examined with the final dataset for on-treatment deaths only, as well as for and on- and off-treatment deaths by subgroups according to prior exacerbation history, FEV_1 % predicted and prior medications. In addition, tipping-point analyses applying different imputation approaches of missing vital status data for patients in the 320 µg budesonide triple therapy and glycopyrrolate/formoterol groups were conducted to explore the robustness of the findings. The possible impact of ICS withdrawal on the time to death was also examined, while the incidence of death was also analysed by subgroup according to baseline eosinophil count. Lastly, the relationship between COPD exacerbations and mortality was addressed through analysis of moderate or severe and severe exacerbations according to vital status and by measuring the time elapsed from exacerbation to death.

Consistent with the original findings, the secondary analysis of ETHOS showed a significant 49% reduction of risk of death from any cause in the subgroup receiving 320 µg budesonide triple therapy compared to LABA/LAMA (HR 0.51, 95% CI 0.33–0.80; unadjusted p=0.0035), equivalent to a number needed to treat of 80 (95% CI 58–198). The respective on-treatment hazard ratio was 0.50 (95% CI 0.30–0.81; p=0.0056), while no statistically significant differences were found in any of the other pairwise comparisons between the study treatment groups either. Finally, it is worth mentioning that the reduction in the risk of death in the 320 µg budesonide triple therapy compared to the budesonide/formoterol group was 28% (HR 0.72, 95% CI 0.44–1.16; p=0.1721).

In the analysis of the incidence of death according to baseline eosinophil count, the results derived with the final dataset showed that the benefit of 320 µg budesonide triple therapy compared to budesonide/formoterol generally increased with the baseline eosinophil count at the range above ~200 cells·µL^{-1} [88].

At baseline, ~70% of participants had at least one cardiovascular risk factor, with a similar distribution across the four treatment groups. Overall, 202 on- and off-treatment deaths were reported in the final dataset; of these, 67 were attributed to cardiovascular causes. The numbers (and incidence) of deaths were 11 (0.5%) and 16 (0.8%) in the 320 µg and 160 µg budesonide triple therapy groups, respectively; 29 (1.4%) in the glycopyrrolate/formoterol group; and 11 (0.5%) in the budesonide/formoterol group.

Further analysis in the subgroup of patients who were receiving ICS at study entry showed that the benefit of 320 µg budesonide triple therapy *versus* glycopyrrolate/formoterol in terms of reducing mortality was

not driven by an early period of acute withdrawal effects, as the corresponding hazard ratio remained consistently <1 throughout the 1-year observation period [88]. Thus, the *post hoc* analysis of IMPACT by Suissa and Ariel [87] was not replicated in the ETHOS trial, which clearly cast doubts about the conclusions drawn by Suissa and Ariel.

Looking into the characteristics of the patients who died and of those who survived in ETHOS, it can be derived that among the former, the mean age at baseline (67.7 *versus* 64.6 years), the proportion of male patients (70.6% *versus* 59.5%) and the proportion of patients who were using ICS when they entered the study (84.7% *versus* 80.4%) were numerically higher, but not statistically different in the former group than in the latter group, while the mean FEV_1 (40.1% pred *versus* 43.4% pred) and percentage reversibility (13.0% *versus* 15.5%) were lower among patients who died than among those who survived during the study. Interestingly, the proportion of patients who had experienced two or more exacerbations was lower among patients who died than among those who survived (50.6% *versus* 56.6%). Analysis of baseline characteristics of patients who died by assigned regimen further showed that across all treatment groups, patients who died during the 52-week study observation were predominantly male, not frequent exacerbators, used ICS at screening, had high symptom burden and did not show reversibility to bronchodilation [88].

Finally, in the context of the analysis of the relationship between COPD exacerbations and mortality, the annual rate of moderate or severe exacerbations was 2.20 among patients who died and 1.11 among patients who survived, while the respective rates of severe exacerbations were 0.80 and 0.16. Thus, of patients who died, 42.4% had not experienced any moderate or severe exacerbation during the study, implicating other factors in the observed mortality [88].

Data on triple therapy in COPD patients at low risk of COPD exacerbations

Since the effect of triple therapy on the reduction of all-cause mortality in COPD patients resulted from studies which included patients at high risk of COPD exacerbations, the use of triple therapy in patients of low exacerbation risk remains poorly studied. A pooled analysis was recently performed by Miravitlles *et al.* [89] using data from the randomised controlled trials TOnado 1, TOnado 2, DYNAGITO, WISDOM, UPLIFT and TIOSPIR to compare time to all-cause mortality with LAMA/LABA *versus* LAMA/LABA/ICS in patients with mild-to-very-severe COPD and low risk of exacerbation. The study was performed using data on treatment with LAMA/LABA (n=3156) and LAMA/LABA/ICS (n=11 891), censored at 52 weeks. Patients between the two groups were propensity-score matched, with age, sex, geographical region, smoking status, post-bronchodilator FEV_1 % predicted, exacerbation history in previous year, BMI and time since diagnosis serving as selected variables. Following propensity-score matching, baseline characteristics were well balanced across the two arms. The proportion of patients who had two or more COPD exacerbations over the year prior to study entry was 19.0% in the overall study population, 19.1% in the LAMA/LABA group and 19.0% in the LAMA/LABA/ICS group. The incidence of on-treatment death was 1.3% (41 deaths) in the LAMA/LABA group and 1.4% (45 deaths) in the LAMA/LABA/ICS group, with no statistically significant difference in the risk of death between the two groups (HR 1.06, 95% CI 0.68–1.64; p=0.806) identified by either the main or any of the three additional sensitivity analyses performed. Similarly, no difference was observed between the two groups with respect to both on-treatment and off-treatment deaths prior to 52 weeks (74 (2.4%) deaths in the LAMA/LABA arm and 66 (2.1%) deaths in the LAMA/LABA/ICS arm), with the corresponding hazard ratio being 1.19 (95% CI 0.84–1.68; p=0.338). In addition, no difference in the cause of death was observed between the two groups, including deaths attributable to respiratory, cancer, cardiac and other causes. In particular, the proportions of on-treatment deaths attributed to respiratory causes were 22% (nine out of 41) in the LAMA/LABA arm and 24% (11 out of 45) in the LAMA/LABA/ICS arm.

Discussion

Although the results from the megatrials regarding pharmacological interventions for the reduction of mortality in COPD were definitely not enthusiastic, recent studies on fixed-dose triple ICS/LABA/LAMA combinations have provided more encouraging results. It must be acknowledged that the survival of COPD patients has improved in recent years, mainly due to the wealth of available treatments and improvements in the management of the disease. This improvement in survival is observed both in routine clinical practice and in randomised controlled trials, in which the number of deaths has decreased dramatically compared to the past. However, the frequency of comorbidities which are also associated to an increased rate of deaths make the study of COPD mortality challenging. The numbers needed to benefit and to harm for the different pharmacological and nonpharmacological interventions for COPD are shown in table 1.

TABLE 1 Number needed to benefit (NNTB) and number needed to harm (NNTH) for the different pharmacological and nonpharmacological interventions

	NNTB	NNTH[#]	References
Smoking cessation	21 (in 10 years)	NA	[90]
LTOT	5 in 5 years 6 in 2 years	NA	[91]
NIMV	7.7 in 1 year	NA	[92]
LVRS	246 in 5 years (NETT) 7 in 5 years in patients with predominantly upper lobe disease and low exercise capacity	NA	[12, 93]
Rehabilitation	6 in 2 years[+]	NA	[94]
Triple therapy[¶] (ICS/LABA/LAMA)	120 (FF/UMEC/VI *versus* UMEC/VI) 80 BGF *versus* GFF	33 FF/UMEC/VI *versus* UMEC/VI 58 BGF *versus* GFF	[58, 88, 95]

LTOT: long-term oxygen therapy; NIMV: noninvasive mechanical ventilation; LVRS: lung volume reduction surgery; ICS: inhaled corticosteroids; LABA: long-acting β-agonists; LAMA: long-acting muscarinic antagonists; NA: not applicable/not available; NETT: National Emphysema Treatment Trial; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; BGF: budesonide/glycopyrrolate/formoterol; GFF: glycopyrrolate/formoterol fumarate. [#]: for pneumonia risk; [¶]: for pharmaceutical studies, effect on mortality was not a primary outcome; [+]: the quality of evidence in this study was low, there was a high heterogeneity, and any significant effect of rehabilitation on mortality remains controversial.

TORCH, SUMMIT and UPLIFT were all performed in years where clinical practice regarding COPD treatment was different to current practice in some way. In contrast, the IMPACT and the ETHOS studies reflect current clinical practice, which mainly includes triple-therapy regimens. However, it should be emphasised that TORCH was the only longitudinal study having mortality as the primary outcome (although SUMMIT had mortality as a primary outcome, it had a pragmatic design). Thus, TORCH was a pioneer and landmark study in COPD, which set a difficult outcome and challenged the existing knowledge at the time. The inclusion of a "true" placebo group was also a very strong feature of the design of this study, even though it raised criticism whether it was ethical to leave patients without treatment. However, considering that recent studies compare triple therapy with other active treatments (which are known to be effective) and not a placebo arm makes the comparison extremely challenging.

TORCH had a 3-year duration and had additional important end-points such as loss of lung function and exacerbation reduction, demonstrating that patients often died from causes others than COPD. IMPACT and ETHOS had one common element: during the study, exacerbations were decreased and the occurrence of even one exacerbation probably reflected increased disease severity. All of which suggest that the number of exacerbations does not solely determine outcome. In fact, a significant number of patients who died did not experience exacerbations during the studies (thus the beneficial effect of triple therapy on mortality cannot be attributed to exacerbation reduction). The beneficial effect of triple therapy seems to be even more pronounced in patients with high blood eosinophil levels. Accordingly, the main issue for the clinician is to identify COPD patients who would mostly benefit from triple therapy.

Looking at the data, it is obvious that in the UPLIFT study a large proportion of patients received tiotropium in addition to an ICS/LABA combination. These patients have shown better outcomes.

TORCH has slightly failed to prove a statistically significant decrease in mortality by providing a p-value just above the level of 0.05. However, one can hypothesise that a longer duration of the study would probably reveal a formal statistically significant difference between ICS/LABA and placebo. Recent studies on triple therapies differ methodologically from the megatrials, since they have been designed to be completed in a shorter period of time and they lack a placebo comparator, while, in contrast, including potent comparator arms. Despite this, mortality seems to be reduced with triple therapy. However, it must be kept in mind that although both IMPACT and ETHOS show the same trend on mortality reduction, ETHOS has the most robust approach, since mortality was a pre-specified secondary outcome. These studies have used different drugs of the same class with different devices; thus, the slight differences noted may be attributable to either the drugs and/or the inhalation delivery devices. The design of head-to-head comparisons would be the only way to provide a definite answer to whether one active combination is superior to another. Of course, similar findings with different drugs of the same class, different devices

and different patient samples provide additional reassurance that the beneficial effect of triple therapy on mortality is real and not due to chance.

It has been suggested that mortality reduction in IMPACT was mainly the result of the deleterious effect of ICS withdrawal in patients who happen to be randomised in the LABA/LAMA arm [87]. In contrast, the difference observed in ETHOS cannot be attributed to ICS withdrawal. In the subgroup analyses, the benefit of 320 µg budesonide/glycopyrrolate/formoterol *versus* dual regimens was observed regardless of ICS use at the time of screening [88]. Triple therapy seemed to be superior to dual regimens mainly in patients with higher numbers of blood eosinophils.

Since mortality in COPD is also affected by several different factors, such as administrative issues, treatment decisions, capacity of the healthcare system, *etc.*, the cause of death is not always clear. Accordingly, mortality rates might be affected by the performance of intubation and intensive care unit (ICU) admission in patients with severe exacerbations. Furthermore, patients experiencing severe COPD exacerbations might die in the ICU due to complications such as infections, septic shock and myocardial infarction. In these cases, a different cause of death would be recorded and the patients would probably be categorised as having died from causes other than COPD. Accordingly, the effect of COPD in the mechanism leading to death might not be recognised. For these reasons COPD-related mortality rates are likely underestimated and relevant statistics should be viewed as approximate rather than precise indicators.

At the moment, there are no sufficient data to support a possible benefit of the triple combination *versus* LABA/LAMA in patients with low risk of exacerbations. The recent pooled analysis examining this hypothesis had several limitations [89], mainly the absence of randomisation, as the addition of an ICS to the LAMA or LAMA/LABA regimen was decided at a patient level by the treating physician, with the exception of patients who participated in the WISDOM study. Moreover, it should be kept in mind that this analysis was performed *post hoc*, and none of the included studies were designed to address the specific outcome under question.

The observed mortality reduction in patients receiving triple combinations might be attributed to several, not mutually exclusive, mechanisms. The ICS component possibly reduces lung inflammation leading to fewer exacerbations [96]. At the same time, LAMA/LABA may decrease airway resistance and reduce lung hyperinflation, improving inspiratory capacity, reducing residual volume and potentially improving cardiac function, while both ICS and bronchodilators may improve ventilation/perfusion matching, increasing blood oxygenation [97–99].

Conclusion

When looking at data from different studies, one can observe that mortality rates decrease over time. Based on the available evidence, even though no dramatic effect can be attributed to a single treatment, over the years, overall mortality reduced, probably due to the fact that the accumulating evidence-based knowledge has led to better-informed clinical management decisions among physicians, resulting in improved patient care.

Exacerbation risk and mortality could be reduced through transforming the COPD care pathway and optimising disease management. Optimal management of COPD requires a combinatorial approach, which comprises four basic components. The first step is the identification of patients with COPD, based on timely diagnosis. The second step is disease assessment and quantification of future risk, based on thorough phenotyping of patients, to identify those most at risk of exacerbations and other conditions. Following disease and risk assessment, early and optimal management with pharmacological and nonpharmacological treatments to prevent exacerbations and decrease risk of mortality is of utmost importance. Lastly, regular patient follow-up to optimise pharmacological and nonpharmacological interventions and to ensure symptom monitoring is required throughout the patient's lifetime [100]. In other words, if we want to reduce the mortality rate in COPD, we must recognise the disease at an early time point, focus on smoking cessation and physical exercise and decrease (ideally eliminate) the rate of exacerbations by combining treatment strategies. Early intervention might need to be considered not only solely based on the grounds of COPD, but also taking into consideration the clinical comorbidome on an individual patient basis [50]. It is quite strange that most pharmaceutical-based studies either failed to show a definite beneficial effect on mortality or select mortality as a *post hoc* analysis outcome. This is a conservative approach. We need long-term studies with representative patients from the real-life setting, receiving the available effective and aggressive treatment strategies. The design of large, randomised controlled trials with long observation periods which will include mortality as a primary end-point is required in order to reach a safe conclusion regarding the benefit of triple therapy regimens for the survival of patients with COPD.

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References

1 Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of COPD. 2023. http://goldcopd.org. Date last accessed: 23 November 2022.

2 Burney P, Patel J, Minelli C, *et al.* Prevalence and population-attributable risk for chronic airflow obstruction in a large multinational study. *Am J Respir Crit Care Med* 2021; 203: 1353–1365.

3 Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. *N Engl J Med* 2019; 381: 1257–1266.

4 Gedebjerg A, Szépligeti SK, Wackerhausen LH, *et al.* Prediction of mortality in patients with chronic obstructive pulmonary disease with the new Global Initiative for Chronic Obstructive Lung Disease 2017 classification: a cohort study. *Lancet Respir Med* 2018; 6: 204–212.

5 Anthonisen NR, Skeans MA, Wise RA, *et al.* The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005; 142: 233–239.

6 Lindenauer PK, Stefan MS, Pekow PS, *et al.* Association between initiation of pulmonary rehabilitation after hospitalization for COPD and 1-year survival among Medicare beneficiaries. *JAMA* 2020; 323: 1813–1823.

7 Ryrsø CK, Godtfredsen NS, Kofod LM, *et al.* Lower mortality after early supervised pulmonary rehabilitation following COPD-exacerbations: a systematic review and meta-analysis. *BMC Pulm Med* 2018; 18: 154.

8 Is 12-hour oxygen as effective as 24-hour oxygen in advanced chronic obstructive pulmonary disease with hypoxemia? (The Nocturnal Oxygen Therapy Trial – NOTT). *Chest* 1980; 78: 419–420.

9 Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981; 1: 681–686.

10 Köhnlein T, Windisch W, Köhler D, *et al.* Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014; 2: 698–705.

11 McEvoy RD, Pierce RJ, Hillman D, *et al.* Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. *Thorax* 2009; 64: 561–566.

12 Fishman A, Martinez F, Naunheim K, *et al.* A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; 348: 2059–2073.

13 Lipson DA, Barnhart F, Brealey N, *et al.* Once-daily single-inhaler triple *versus* dual therapy in patients with COPD. *N Engl J Med* 2018; 378: 1671–1680.

14 Rabe KF, Martinez FJ, Ferguson GT, *et al.* Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med* 2020; 383: 35–48.

15 Cabrera López C, Casanova Macario C, Marín Trigo JM, *et al.* Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease reports. Impact on grouping and outcomes. *Am J Respir Crit Care Med* 2018; 197: 463–469.

16 Mannino DM, Doherty DE, Sonia Buist A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. *Respir Med* 2006; 100: 115–122.

17 Guo C, Yu T, Chang LY, *et al.* Mortality risk attributable to classification of chronic obstructive pulmonary disease and reduced lung function: a 21-year longitudinal cohort study. *Respir Med* 2021; 184: 106471.

18 Boutou AK, Shrikrishna D, Tanner RJ, *et al.* Lung function indices for predicting mortality in COPD. *Eur Respir J* 2013; 42: 616–625.

19 de-Torres JP, O'Donnell DE, Marín JM, *et al.* Clinical and prognostic impact of low diffusing capacity for carbon monoxide values in patients with Global Initiative for Obstructive Lung Disease I COPD. *Chest* 2021; 160: 872–878.

20 Haruna A, Muro S, Nakano Y, *et al.* CT scan findings of emphysema predict mortality in COPD. *Chest* 2010; 138: 635–640.

21 Celli B, Tetzlaff K, Criner G, *et al.* The 6-minute-walk distance test as a chronic obstructive pulmonary disease stratification tool. Insights from the COPD Biomarker Qualification Consortium. *Am J Respir Crit Care Med* 2016; 194: 1483–1493.

22 Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, *et al.* Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; 60: 925–931.

23 Celli BR, Cote CG, Marin JM, *et al.* The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005–1012.

24 Puhan MA, Garcia-Aymerich J, Frey M, *et al.* Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet* 2009; 374: 704–711.

25 Sundh J, Janson C, Lisspers K, *et al.* The Dyspnoea, Obstruction, Smoking, Exacerbation (DOSE) index is predictive of mortality in COPD. *Prim Care Respir J* 2012; 21: 295–301.

26 Mannino DM, Thorn D, Swensen A, *et al.* Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008; 32: 962–969.

27 Hurst JR, Vestbo J, Anzueto A, *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363: 1128–1138.

28 Han MK, Quibrera PM, Carretta EE, *et al.* Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med* 2017; 5: 619–626.

29 Antoniu SA. UPLIFT study: the effects of long-term therapy with inhaled tiotropium in chronic obstructive pulmonary disease. Evaluation of: Tashkin DP, Celli B, Senn S *et al.*: a 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med (2008) 359(15): 1543–1554. *Expert Opin Pharmacother* 2009; 10: 719–722.

30 Leidy NK, Murray LT, Jones P, *et al.* Performance of the EXAcerbations of chronic pulmonary disease tool patient-reported outcome measure in three clinical trials of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2014; 11: 316–325.

31 Langsetmo L, Platt RW, Ernst P, *et al.* Underreporting exacerbation of chronic obstructive pulmonary disease in a longitudinal cohort. *Am J Respir Crit Care Med* 2008; 177: 396–401.

32 Xu W, Collet JP, Shapiro S, *et al.* Negative impacts of unreported COPD exacerbations on health-related quality of life at 1 year. *Eur Respir J* 2010; 35: 1022–1030.

33 Wilkinson TM, Donaldson GC, Hurst JR, *et al.* Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 169: 1298–1303.

34 Hurst JR, Skolnik N, Hansen GJ, *et al.* Understanding the impact of chronic obstructive pulmonary disease exacerbations on patient health and quality of life. *Eur J Intern Med* 2020; 73: 1–6.

35 Donaldson GC, Hurst JR, Smith CJ, *et al.* Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; 137: 1091–1097.

36 Kunisaki KM, Dransfield MT, Anderson JA, *et al.* Exacerbations of chronic obstructive pulmonary disease and cardiac events. A *post hoc* cohort analysis from the SUMMIT randomized clinical trial. *Am J Respir Crit Care Med* 2018; 198: 51–57.

37 Goto T, Shimada YJ, Faridi MK, *et al.* Incidence of acute cardiovascular event after acute exacerbation of COPD. *J Gen Intern Med* 2018; 33: 1461–1468.

38 Watz H, Tetzlaff K, Magnussen H, *et al.* Spirometric changes during exacerbations of COPD: a *post hoc* analysis of the WISDOM trial. *Respir Res* 2018; 19: 251.

39 Dransfield MT, Kunisaki KM, Strand MJ, *et al.* Acute exacerbations and lung function loss in smokers with and without chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017; 195: 324–330.

40 Bourbeau J, Ford G, Zackon H, *et al.* Impact on patients' health status following early identification of a COPD exacerbation. *Eur Respir J* 2007; 30: 907–913.

41 Jones PW, Lamarca R, Chuecos F, *et al.* Characterisation and impact of reported and unreported exacerbations: results from ATTAIN. *Eur Respir J* 2014; 44: 1156–1165.

42 Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012; 67: 957–963.

43 García-Sanz MT, Cánive-Gómez JC, Senín-Rial L, *et al.* One-year and long-term mortality in patients hospitalized for chronic obstructive pulmonary disease. *J Thorac Dis* 2017; 9: 636–645.

44 Ho TW, Tsai YJ, Ruan SY, *et al.* In-hospital and one-year mortality and their predictors in patients hospitalized for first-ever chronic obstructive pulmonary disease exacerbations: a nationwide population-based study. *PLoS One* 2014; 9: e114866.

45 Lindenauer PK, Dharmarajan K, Qin L, *et al.* Risk trajectories of readmission and death in the first year after hospitalization for chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2018; 197: 1009–1017.

46 Rothnie KJ, Müllerová H, Smeeth L, *et al.* Natural history of chronic obstructive pulmonary disease exacerbations in a general practice-based population with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2018; 198: 464–471.

47 Müllerová H, Shukla A, Hawkins A, *et al.* Risk factors for acute exacerbations of COPD in a primary care population: a retrospective observational cohort study. *BMJ Open* 2014; 4: e006171.

48 Lindberg A, Sawalha S, Hedman L, *et al.* Subjects with COPD and productive cough have an increased risk for exacerbations and death. *Respir Med* 2015; 109: 88–95.

49 Bafadhel M, Peterson S, De Blas MA, *et al.* Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a *post-hoc* analysis of three randomised trials. *Lancet Respir Med* 2018; 6: 117–126.

50 Divo M, Cote C, de Torres JP, *et al.* Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 155–161.
51 Westerik JA, Metting EI, van Boven JF, *et al.* Associations between chronic comorbidity and exacerbation risk in primary care patients with COPD. *Respir Res* 2017; 18: 31.
52 Balbirsingh V, Mohammed AS, Turner AM, *et al.* Cardiovascular disease in chronic obstructive pulmonary disease: a narrative review. *Thorax* 2022; 77: 939–945.
53 Curkendall SM, DeLuise C, Jones JK, *et al.* Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada: cardiovascular disease in COPD patients. *Ann Epidemiol* 2006; 16: 63–70.
54 Chen W, Thomas J, Sadatsafavi M, *et al.* Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med* 2015; 3: 631–639.
55 Miller J, Edwards LD, Agustí A, *et al.* Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. *Respir Med* 2013; 107: 1376–1384.
56 Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? *Eur Respir Rev* 2018; 27: 180057.
57 Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
58 Lipson DA, Crim C, Criner GJ, *et al.* Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2020; 201: 1508–1516.
59 Rennard SI. Clinical approach to patients with chronic obstructive pulmonary disease and cardiovascular disease. *Proc Am Thorac Soc* 2005; 2: 94–100.
60 Morgan AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice? *Ther Adv Respir Dis* 2018; 12: 1753465817750524.
61 Wang MT, Liou JT, Lin CW, *et al.* Association of cardiovascular risk with inhaled long-acting bronchodilators in patients with chronic obstructive pulmonary disease: a nested case–control study. *JAMA Intern Med* 2018; 178: 229–238.
62 Wilchesky M, Ernst P, Brophy JM, *et al.* Bronchodilator use and the risk of arrhythmia in COPD: part 1: Saskatchewan cohort study. *Chest* 2012; 142: 298–304.
63 Baker JG, Wilcox RG. β-Blockers, heart disease and COPD: current controversies and uncertainties. *Thorax* 2017; 72: 271–276.
64 Clancy L. Reducing lung cancer and other tobacco-related cancers in Europe: smoking cessation is the key. *Oncologist* 2014; 19: 16–20.
65 Troosters T, Sciurba FC, Decramer M, *et al.* Tiotropium in patients with moderate COPD naive to maintenance therapy: a randomised placebo-controlled trial. *NPJ Prim Care Respir Med* 2014; 24: 14003.
66 Han MK, Ye W, Wang D, *et al.* Bronchodilators in tobacco-exposed persons with symptoms and preserved lung function. *N Engl J Med* 2022; 387: 1173–1184.
67 Brochard L, Mancebo J, Wysocki M, *et al.* Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; 333: 817–822.
68 Murphy PB, Rehal S, Arbane G, *et al.* Effect of home noninvasive ventilation with oxygen therapy *vs* oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA* 2017; 317: 2177–2186.
69 Kyriakopoulos C, Gogali A, Exarchos K, *et al.* Reduction in hospitalizations for respiratory diseases during the first COVID-19 wave in Greece. *Respiration* 2021; 100: 588–593.
70 Jha P. Avoidable global cancer deaths and total deaths from smoking. *Nat Rev Cancer* 2009; 9: 655–664.
71 Rigotti NA. Smoking cessation in patients with respiratory disease: existing treatments and future directions. *Lancet Respir Med* 2013; 1: 241–250.
72 Albert RK, Au DH, Blackford AL, *et al.* A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med* 2016; 375: 1617–1627.
73 Górecka D, Gorzelak K, Sliwiński P, *et al.* Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 1997; 52: 674–679.
74 Garnet BJ, Jean E, Lankenau RD, *et al.* Identification of male COPD patients with exertional hypoxemia who may benefit from long-term oxygen therapy. *PLoS One* 2023; 18: e0283949.
75 Lacasse Y, Sériès F, Maltais F. Randomized trial of nocturnal oxygen in chronic obstructive pulmonary disease. Reply. *N Engl J Med* 2021; 384: 86.
76 Wilson ME, Dobler CC, Morrow AS, *et al.* Association of home noninvasive positive pressure ventilation with clinical outcomes in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 2020; 323: 455–465.
77 Roodenburg SA, Slebos DJ, van Dijk M, *et al.* Improved exercise capacity results in a survival benefit after endobronchial valve treatment. *Respir Med* 2023; 210: 107175.
78 Hartman JE, Welling JBA, Klooster K, *et al.* Survival in COPD patients treated with bronchoscopic lung volume reduction. *Respir Med* 2022; 196: 106825.

79 Turan D, Dogan D, Cortuk M, *et al.* Does bronchoscopic lung volume reduction reduce mortality in patients with severe emphysema? *J Coll Physicians Surg Pak* 2021; 31: 60–64.

80 Tashkin DP, Celli B, Senn S, *et al.* A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543–1554.

81 Vestbo J, Anderson JA, Brook RD, *et al.* Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016; 387: 1817–1826.

82 Tashkin DP, Miravitlles M, Celli BR, *et al.* Concomitant inhaled corticosteroid use and the risk of pneumonia in COPD: a matched-subgroup *post hoc* analysis of the UPLIFT® trial. *Respir Res* 2018; 19: 196.

83 Celli B, Decramer M, Kesten S, *et al.* Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009; 180: 948–955.

84 Calverley PM, Anderson JA, Celli B, *et al.* Cardiovascular events in patients with COPD: TORCH study results. *Thorax* 2010; 65: 719–725.

85 Vestbo J, Fabbri L, Papi A, *et al.* Inhaled corticosteroid containing combinations and mortality in COPD. *Eur Respir J* 2018; 52: 1801230.

86 Suissa S, Drazen JM. Making sense of triple inhaled therapy for COPD. *N Engl J Med* 2018; 378: 1723–1724.

87 Suissa S, Ariel A. Triple therapy trials in COPD: a precision medicine opportunity. *Eur Respir J* 2018; 52: 1801848.

88 Martinez FJ, Rabe KF, Ferguson GT, *et al.* Reduced all-cause mortality in the ETHOS trial of budesonide/glycopyrrolate/formoterol for chronic obstructive pulmonary disease. A randomized, double-blind, multicenter, parallel-group study. *Am J Respir Crit Care Med* 2021; 203: 553–564.

89 Miravitlles M, Verhamme K, Calverley PMA, *et al.* A pooled analysis of mortality in patients with COPD receiving dual bronchodilation with and without additional inhaled corticosteroid. *Int J Chron Obstruct Pulmon Dis* 2022; 17: 545–558.

90 Doo JH, Kim SM, Park YJ, *et al.* Smoking cessation after diagnosis of COPD is associated with lower all-cause and cause-specific mortality: a nationwide population-based cohort study of South Korean men. *BMC Pulm Med* 2023; 23: 237.

91 Lacasse Y, Maltais F. When and when not to prescribe home oxygen in COPD. *Arch Bronconeumol* 2023; 59: 350–351.

92 Frazier W, van Eijndhoven E, Murphy R, *et al.* Noninvasive ventilation at home reduces mortality in COPD with CRF. *Am J Manag Care* 2021; 27: e308–e315.

93 Leung JM, Obeidat M, Sadatsafavi M, *et al.* Introduction to precision medicine in COPD. *Eur Respir J* 2019; 53: 1802460.

94 Puhan M, Scharplatz M, Troosters T, *et al.* Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2009; 1: CD005305.

95 Rabe KF, Martinez FJ, Ferguson GT, *et al.* COPD exacerbation benefits relative to pneumonia risk with budesonide/glycopyrronium/formoterol metered dose inhaler: analyses from ETHOS. *Eur Respir J* 2020; 56: 5230.

96 Celli A, Latorre M, Paggiaro P, *et al.* Chronic obstructive pulmonary disease: moving from symptom relief to mortality reduction. *Ther Adv Chronic Dis* 2021; 14: 20406223211014028.

97 Hwang HJ, Lee SM, Seo JB, *et al.* Assessment of changes in regional xenon-ventilation, perfusion, and ventilation-perfusion mismatch using dual-energy computed tomography after pharmacological treatment in patients with chronic obstructive pulmonary disease: visual and quantitative analysis. *Int J Chron Obstruct Pulmon Dis* 2019; 14: 2195–2203.

98 Singh D, Wild JM, Saralaya D, *et al.* Effect of indacaterol/glycopyrronium on ventilation and perfusion in COPD: a randomized trial. *Respir Res* 2022; 23: 26.

99 Voskrebenzev A, Kaireit TF, Klimeš F, *et al.* PREFUL MRI depicts dual bronchodilator changes in COPD: a retrospective analysis of a randomized controlled trial. *Radiol Cardiothorac Imaging* 2022; 4: e210147.

100 Pullen R, Miravitlles M, Sharma A, *et al.* CONQUEST quality standards: for the collaboration on quality improvement initiative for achieving excellence in standards of COPD care. *Int J Chron Obstruct Pulmon Dis* 2021; 16: 2301–2322.