Early View

Review

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Mortality prevention as the center 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 that are more symptomatic, have lower lung function and lower DLCO, have decreased exercise capacity, belong to the emphysematous phenotype and those who have concomitant bronchiectasis. Also 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 the previous years, large studies (also called Mega-Trials) have evaluated the efficacy of different therapies on COPD mortality, but until recently only non-pharmaceutical interventions have proven to be effective. However, recent studies on fixed combinations of triple therapy (long-acting beta 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 summarize available data regarding mortality risk in COPD patients and to describe pharmacologic 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 (BOLD) program which assessed the prevalence of disease globally using standardized methodology, the prevalence of disease worldwide was approximately 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 ischemic heart disease and stroke, causing approximately 3 million deaths annually which represent approximately 4.72% of all deaths[1]. Due to the increased proportion of aging population 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 millions[3]. 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 rate in the general population [4, 5].

Historically, several studies have evaluated the efficacy of different therapies on COPD mortality, but until recently only non-pharmaceutical interventions (i.e. smoking cessation, long term oxygen therapy, non-invasive mechanical ventilation, lung volume reduction and pulmonary rehabilitation) have proven to be effective[6-13]. However, recent studies on fixed combinations of triple therapy (long acting beta 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[14, 15]. The aim of the present review is to summarize available data regarding mortality risk in COPD patients and to describe pharmacologic 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[5, 16, 17], have lower lung function[18] and lower DLCO [19-21], low exercise capacity [22], and/or emphysematous phenotype [21].

One of the major factors influencing mortality in COPD patients is the frequency and severity of exacerbations [23]. Patients experiencing 3 or more exacerbations per year are at increased risk of death, while severe acute exacerbations of COPD have an independent negative impact on patients’ prognosis. Mortality increases with the frequency of severe exacerbations, particularly if they require admission to the hospital[23].

To predict mortality risk in COPD patients several composite scores have been created which are using different parameters such as body mass index (BMI), age, the level of dyspnea, lung function and exercise capacity. The BODE (Body Mass index, airway obstruction, dyspnea and exercise capacity)[24], ADO (age, dyspnea and obstruction) [25] and DOSE (Dyspnea Obstruction smoking and exacerbation frequency) [26] index scores have been shown to predict mortality in COPD patients.

As expected, mortality risk which is greater as lung function deteriorates, yet comorbidities such as cardiovascular diseases, diabetes mellitus and arterial hypertension also seem to independently contribute to reduced survival [27].

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 ECLIPSE [28] and SPIROMICS [29] studies, as well as results of the 4-year UPLIFT [30] 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 [31] and other geographical settings [31-34] 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 well-being [35]. Symptom worsening and incidence of COPD exacerbations have been linked with increased risk of cardiovascular events [36-38], lung function loss[39, 40], decreased physical activity, and de-conditioning, leading to deterioration of mental health and quality of life[41, 42], as well as increased risk of further exacerbations[35, 43]. More importantly, exacerbations are associated with an increased risk of hospitalization or death[43-47]. Based on data from 99,574 patients with COPD from the UK Clinical Practice Research Datalink, with over 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) of 1.79 (95% CI, 1.65 to 1.94)] [47]. 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 [47]. Accordingly, identifying patients at risk of exacerbations might be a key to optimizing their management and increase their survival. Factors which could potentially serve as predictors of future exacerbations include a history of COPD exacerbations [28, 48],
increased dyspnea and productive cough [48, 49], as well as raised eosinophil counts when not receiving ICS [50].

**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 on the other hand, frequent exacerbators may also be at increased risk of comorbidities[51, 52].

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[51, 53]. COPD patients have an approximately 4.5 higher risk to develop cardiovascular comorbidities [54]. 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%, though not statistically significantly, on days 6-10 following such an exacerbation [36]. 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 one year following an exacerbation [37]. The risk for such events, which included cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic attack, was particularly elevated (HR, 3.8; 95% CI, 2.7 to 5.5) in the first 30 days after an exacerbation and was almost two-
fold between 31 and 90 days after the exacerbation onset [37]. The risk of cardiovascular events was even higher in COPD patients hospitalized for acute exacerbations, with the corresponding 30-day HR being 9.9 (95% CI, 6.6 to 14.9)[37]. If no new acute COPD exacerbation occurred, the risk for cardiovascular events was no longer increased one year after the exacerbation [37].

The relationship between cardiovascular events and mortality in COPD has also been examined from a different perspective, analyzing 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 [55]. Co-existence of moderate-to-very-severe COPD and CVD is associated with increased dyspnea and worse QoL, while co-existence of mild-to-very-severe COPD is associated with greater risk of hospitalization than either condition alone [27, 56]. The presence of cardiovascular comorbidities increases mortality risk in COPD patients[57]. In particular, among patients with COPD who also have ischemic heart disease, atrial fibrillation, diabetes, or heart failure, the risk of death is increased by 27–50%, 56%, 54–70%, and 30–90% versus patients having COPD alone, respectively [57].

The contribution of cardiovascular disease on mortality in COPD patients is substantial, even among those who suffer from moderate disease. The proportion of deaths attributed to cardiovascular disease ranged from 22-44% across the Lung Health Study (LHS) III [6], the TORCH [58], the IMPACT [59], and the ETHOS [15] studies. Focusing on patients with moderate COPD (GOLD stage II), the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS) indicated that approximately only 4% of deaths were related to respiratory causes while 25% were due to lung cancer, and 28% were due to cardiovascular events[17].
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[60]. The effect(s) of the aforementioned factors to COPD and cardiovascular disease could be mediated by inflammatory and accelerated-aging mechanisms[61]. 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, and peripheral artery disease, congestive heart failure, and cardiac arrhythmias (atrial fibrillation) [61, 62].

Sometimes, 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, whilst 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[63]. On the same line, β2 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 β2-agonist-induced tachycardia may further increase cardiovascular risk[64]. In contrast, some cardiovascular medications may
also have a beneficial impact on COPD, even though there have been concerns about non-selective beta-blockers that may adversely affect the respiratory system[65]. Similarly, there are treatments for COPD, such as ICS that may reduce non-respiratory (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, COPD mortality in these patients is often difficult to be attributed 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 globally ban cigarette smoking. Existing data from the US also show the effect of banning public cigarette smoking on reducing cancer incidence[66]. Undoubtedly, public smoking ban would reduce deaths among COPD patients but would not reduce the proportion 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 up to date, as no study has been conducted to address this. To date, only 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[67]. The recent RETHINC trial, in which a
LABA/LAMA combination was administered in symptomatic smokers without COPD did not show any beneficial effect [68], 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 non-pharmacological COPD management interventions that are recommended. Although COPD remains the 3rd cause of death worldwide, over the recent years, mortality in COPD has decreased from 15% to 5% probably due to medical and pharmaceutical advances combined with public smoking ban. 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[69, 70]. Interestingly, during the COVID-19 pandemic the number of hospital admissions among patients with COPD dramatically decreased [71] suggesting that measures like social distancing, protection by their relatives, self-isolation, vaccination, and the use of face mask had a very strong impact on decreasing exacerbations in COPD patients (50% reduction over the 1st and 2nd wave of the pandemic).

NON-PHARMACOLOGICAL INTERVENTIONS TO REDUCE MORTALITY IN COPD PATIENTS

Several non-pharmacological interventions have been shown effective in reducing mortality in patients with COPD. The first recognized 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. [6, 72, 73]. Long term oxygen therapy has been also recognized beneficial in increasing survival in patients with respiratory failure, especially those with a resting partial arterial oxygen pressure (PaO₂)≤55mmHg[9, 10]. This reduction in mortality has been shown to be as great as 35% in patients who received supplementary oxygen for at least 15 hours/day 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 hypoxemia [74, 75] those with hypoxemia only on exertion [76] or patients with only nocturnal hypoxemia.[77].

Non-invasive mechanical ventilation (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 [11, 12, 78]. COPD patients treated with both oxygen supplementation and NIMV had a better survival compared to those treated with long term oxygen therapy alone[70]. Several years ago, lung volume reduction surgery has been shown able to increase survival in COPD patients with emphysematous lesions with upper lobe predominance[13]. Nowadays, interventional bronchoscopic methods are used to perform lung volume reduction in patients with severe emphysema also leading to survival benefits[79-81], yet these studies are lacking a proper design for drawing conclusions. Finally pulmonary rehabilitation has been also shown to lead to improvements in survival of COPD patients[7, 8].
PHARMACOLOGICAL INTERVENTIONS TO REDUCE MORTALITY IN COPD PATIENTS

Mortality data overview on 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 randomized double blind–placebo controlled trials [58, 82, 83]. The first, TORCH study [58] was conducted in 444 centers and included more than 6000 patients. The study duration was 3 years and patients were randomized 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 endpoint 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 lead to an absolute risk reduction of 2.6% in the combination therapy group compared to the placebo group (Hazard ratio 0.825 [95% confidence interval (CI), 0.681 to 1.002]), the p value was 0.052, hardly failing to reach statistical significance. Thus, although the combination therapy had shown a 17.5% (95% CI, −0.2 to 31.9) reduction in the risk of death from any cause during the 3-year observation period compared to placebo, the study was characterized 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 on 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%) than the one 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 [58]. 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 emphasized that the statistical threshold of p ≤ 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 luck. Thus, \( p=0.052 \) means that this probability is 5.2%, whereas a p-value of 0.049 (which would had declared the finding statistical significant) would have meant that the probability that the mortality reduction is not real but is due to chance is 4.9%, a 0.3% probability difference. Furthermore, this p-value might change with slight change in the date that the study is terminated. This is clearly illustrated in the mortality analysis of the UPLIFT study, which took place two years later [82].

The UPLIFT study [82] which was conducted in 487 sites and lasted for 4 years, compared treatment with 18 μg of tiotropium once daily with placebo. The primary
objective was prebronchodilator and postbronchodilator 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 death in the tiotropium group (14.4%) compared to placebo (16.3%), corresponding to a hazard ratio of 0.87 (95% CI, 0.76 to 0.99). The main criticism on these findings was that as stated above, many of the patients randomized to the tiotropium arm were also receiving additional treatment for COPD, while many of them were receiving ICS/LABA combinations[82, 84]. However, an alternative view could be that maximizing therapy in COPD, (i.e. the addition of tiotropium to whatever therapy the patient was receiving) can lead to mortality reduction. Furthermore, mortality was not the primary endpoint 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 on particular time-points significance was lost [85] (see figure).

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 predefined timepoint should be used. This is important to keep in mind when also analyzing the mortality reduction in TORCH.

Following a pos-thoc analysis of the TORCH trial showing a significant reduction of cardiovascular mortality in the ICS/LABA combination [86] the SUMMIT[83] study was designed. The study was conducted in 1368 centers and included more than 16000 COPD patients who either suffered from cardiovascular
comorbidities or were at increased risk for cardiovascular death. Patients were randomized in 4 treatment arms to receive a fixed dose combination of fluticasone furoate and vilanterol, fluticasone furoate, vilanterol or placebo. The primary endpoint of the study was the time to death from any cause. Although SUMMIT was an event-driven trial, completed after the occurrence of 1000 deaths, it failed to show any difference on 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[83]. Although the SUMMIT probably included the largest cohort in COPD, it used a very ambitious primary endpoint. We must also state that the inclusion criterion regarding FEV1 on SUMMIT[83] was 50-70%, while in TORCH[58] it was <60%, 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 on COPD treatment

The first major studies examining the efficacy of triple combinations on COPD patients were the so-called TRILOGY, TRINITY, and TRIBUTE studies. All three studies were designed to compare the triple extra-fine combination regimen (beclomethasone dipropionate, formoterol furoate and glycopyrronium, BDP/FF/G) with dual combinations of (ICS/LABA or LABA/LAMA) and with tiotropium. In TRILOGY the triple combination was compared with ICS/LABA, in TRINITY 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/glycopyrronium). All three studies lasted for 52 weeks, and their
primary endpoint 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[87]. Comparison of the pooled
groups receiving BDP/FF/G, BDP/FF, BDP/FF+TIO (N=3745) versus patients
receiving TIO, IND/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 to 1.02; p=0.066). Similarly,
comparison of the 2.0% mortality rate in BDP/FF/G (N=2528) with the 2.7% rate
in TIO, IND/GB (N=1844) did not yield statistically significant results (HR, 0.72,
95% CI, 0.49 to 1.06; p=0.096). However, comparison of the 1.5% mortality rate
of BDP/FF/G, BDP/FF, BDP/FF+TIO (N=3745) versus the 2.2% rate in TIO,
IND/GB (N=1844), yielded a statistically significant (p=0.037), HR of 0.65 (95%
CI, 0.43 to 0.97)[87]. When examining mortality rates in triple therapy versus
LABA/LAMA, in the BDP/FF/G pool (N=2582), 51 (2%) deaths were recorded
vs 21 deaths (2.7%) recorded in the group receiving IND/GLY (N=768) in
TRIBUTE. Moreover, when including both patients receiving open (BDP/FF
+TIO in TRINITY) and patients receiving closed (BDP/FF/G in TRILOGY,
TRINITY, and TRIBUTE) triple therapy (N=3065), the number of deaths was 59
(1.9%) vs 21 deaths (2.7%) 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 two 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 non-respiratory causes could be related to the decrease in exacerbations [36, 37].

Some years later, the IMPACT [14] study was the first study on a triple combination to include all-cause mortality as a prespecified endpoint. IMPACT was a phase 3, randomized, double-blind parallel-group trial which included more than 10000 participants and compared triple therapy of the inhaled glucocorticoid fluticasone furoate (100 μg), the LAMA umeclidinium (62.5 μg), and the LABA vilanterol (25 μg) with dual combinations.

With respect to mortality, a total of 50 patients (1%) died during the study in the triple-therapy group, versus 49 patients (1%) in the FF/VI and 39 patients (2%) in the UME/VI group (which was half the size of the first 2 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 umeclidinium–
vilanterol was 0.58 (95% CI, 0.38 to 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 (ITT) population [59]. 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 an HR 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 analyzed 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 randomization, the HR for on-treatment all-cause mortality was 0.44 (95% CI, 0.27 to 0.71; $p<0.001$) for those randomized to triple therapy versus UMEC/VI, while the respective HR including off-treatment data and additional vital status follow-up was 0.63 (95% CI, 0.44 to 0.89; $p=0.009$). Upon randomization, approximately 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 randomization, 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 criticized because patients with a history of asthma were not excluded from study participation, provided they did not currently suffer from asthma[88]. In both TRIBUTE and IMPACT, prior ICS treatment was withdrawn at the time of randomization 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, Swissa and Ariel converted cumulative moderate or severe exacerbation incidence curves from the TRIBUTE and IMPACT trials into monthly rates of exacerbation [89]. Based on this analysis, they suggested that both in the IMPACT and TRIBUTE trials, the favorable 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 four 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 [15] 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- 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 to 0.87). However, this finding was interpreted cautiously, as the analysis was performed with vital status at Week 52 missing for 384 of 8,509 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 intent-to-treat population [90]. Besides the prespecified endpoint of time to death from any cause, which was assessed in the ITT 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, FEV₁ % 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 analyzed 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 significantly a 49% reduction of risk of death from any cause in the subgroup receiving 320-μg–budesonide triple therapy compared to the LABA/LAMA (HR, 0.51; 95% CI, 0.33 to 0.80; unadjusted P = 0.0035), equivalent to a number needed to treat of 80 (95% CI, 58 to 198). The respective on-treatment HR was 0.50 (95% CI, 0.30 to 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 with the 320-μg–budesonide triple therapy compared to the budesonide–formoterol was 28% (HR, 0.72; 95% CI, 0.44 to 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[90].
At baseline, approximately 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- 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 HR remained consistently below 1 throughout the 1-year observation period[90]. Thus the post-hoc analysis of IMPACT by Swissa and Ariel was not replicated in the ETHOS trial, which clearly cast doubts about the conclusions drawn by Swissa and Ariel[89].

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 than in the latter group, while the mean FEV1% predicted (40.1 versus 43.4) 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-year study observation were predominantly male, not frequent exacerbators, who used ICS at screening, had high symptom burden, and did not show reversibility to bronchodilation[90].

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[90].

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

Since the effect of triple therapy on the reduction of all-cause mortality in COPD patients resulted from studies which included patients on high risk for COPD exacerbations, the use of triple therapy in patients of low exacerbation risk remains poorly studied. A pooled analysis was recently performed by Miravitlles and colleagues using data from the randomized controlled trials TONADO 1, TORNADO 2, DYNAGITO, WISDOM, UPLIFT and TIOSPIR [91] 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 FEV₁ % predicted, exacerbation history in previous year, body mass index 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 to 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%) in the LAMA/LABA arm and 66 (2.1%) deaths in the LAMA/LABA/ICS arm], with the corresponding HR 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% (9/41) in the LAMA/LABA arm and 24% (11/45) 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 the latest years, mainly due to the wealth of available treatments and the improvements in the management of the disease. This improvement of survival is observed both in routine clinical practice and in randomized 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 increase rate of deaths make the study of COPD mortality challenging. The numbers needed to benefit and to harm for the different pharmacological and non-pharmacological interventions for COPD are shown on Table 1.

TORCH, SUMMIT and UPLIFT were all performed in years where clinical practice regarding COPD treatment was somehow different compared to nowadays. In contrast, the IMPACT and the ETHOS studies reflect the current clinical practice which mainly includes triple therapy regimens. However, it should be emphasized that TORCH was the only longitudinal study having mortality as the primary outcome (SUMMIT although had mortality as primary outcome was of pragmatic design). Thus, TORCH was a pioneer and landmark study in COPD, which set a difficult and hard 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. On the other hand, 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 three-year duration and had additional important endpoints such as loss of lung function and exacerbation reduction, allowing to demonstrate that patients often died from causes others than COPD. On the other hand, IMPACT, and ETHOS had one common element which lies in the fact that during the study, exacerbations were decreased and the occurrence of even one exacerbation probably reflected increased disease severity. All the above 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.

If someone looks on the data it is obvious that in the UPLIFT study, a large proportion of patients received tiotropium on the top of 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 hypothesize that a greater 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 Mega-Trials since they have been designed to be completed in a shorter period of time and they also lack a placebo comparator, while in contrast including potent comparator arms. Despite that, mortality
seems to be reduced with triple therapy. However, we must keep 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 luck.

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 randomized in the LABA/LAMA arm [89]. In contrast, the difference observed in ETHOS cannot be attributed to ICS withdrawal. In the subgroup analyses, the benefit of 320μg BGF/GLY/FORM versus dual regimens was observed regardless of ICS use at the time of screening[90]. On the other hand, triple therapy seemed to be superior from 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 health care system etc, the cause of death is not always clear. Accordingly, mortality rates might be affected by the performance of intubation and ICU admission in patients with severe exacerbations. Furthermore, patients experiencing severe COPD exacerbations might finally die in the ICU due to complications such as infections, septic shock and myocardial infarction. In these cases, a different cause of death will be recorded and probably the patients will be categorized as having died from other causes than COPD.
Accordingly, the effect of COPD in the mechanism leading to death might not be recognized. 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 for exacerbations. The recent pooled analysis examining this hypothesis had several limitations[91], the main being the absence of randomization, 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 was 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 [92]. 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[93-95].

**Conclusion**

When looking on data from different studies, one can observe that mortality rates decrease over the years. Based on the available evidence, even though no dramatic effect can be attributed to a single treatment, over the years, overall mortality
was 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 optimizing 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 non-pharmacological treatments to prevent exacerbations and decrease risk of mortality is of utmost importance. Lastly, regular patient follow-up to optimize pharmacological and non-pharmacological interventions and to ensure symptom monitoring is required throughout the patients' lifetime [96]. In other words, if we want to reduce the mortality rate in COPD, we must recognize 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[51]. 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, randomized controlled trials with long observation periods which will include mortality as a primary end-point is also
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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Figure Legend
Hazard ratios (tiotropium/ control) and 95% confidence intervals for mortality including data from prematurely discontinued patients from Day 1,340 to Day 1,510. Cumulative censoring represents the total number of censored patients up to each time point. (figure borrowed from [85] after permission).
Table 1

Number needed to benefit (NNTB) and number needed to harm (NNTH) for the different pharmacological and non-pharmacological interventions.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>NNTB</th>
<th>NNTH#</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
<td>21 (in 10 years)</td>
<td>N/A</td>
<td>[97]</td>
</tr>
<tr>
<td>LTOT</td>
<td>5 in 5 years</td>
<td>N/A</td>
<td>[98]</td>
</tr>
<tr>
<td></td>
<td>6 in 2 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIMV</td>
<td>7.7 in 1 year</td>
<td>N/A</td>
<td>[99]</td>
</tr>
<tr>
<td>LVRS</td>
<td>246 in 5 years (NETT)</td>
<td>N/A</td>
<td>[13] [100]</td>
</tr>
<tr>
<td></td>
<td>7 in 5 years in patients with predominantly upper lobe disease and low exercise capacity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>6 in 2 years @</td>
<td>N/A</td>
<td>[101]</td>
</tr>
<tr>
<td>Triple therapy $</td>
<td>120 (FF/UMEC/VI vs UMEC/VI)</td>
<td>33 FF/UMEC/VI vs UMEC/VI</td>
<td>[59], [90]</td>
</tr>
<tr>
<td>(ICS/LABA/LAMA)</td>
<td>80 BGF vs GFF</td>
<td>58 BGF vs GFF</td>
<td>[102]</td>
</tr>
</tbody>
</table>


@ the quality of evidence in the study was low, there was a high heterogeneity and any significant effect of rehabilitation on mortality remains controversial.

$ For pharmaceutical studies any effect on mortality was not a primary outcome.
Figure 1