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# Reducing the Risk of Mortality in Chronic Obstructive Pulmonary Disease With Pharmacotherapy: A Narrative Review



Matthew Mintz, MD; Igor Barjaktarevic, MD, PhD; Donald A. Mahler, MD; Barry Make, MD; Neil Skolnik, MD; Barbara Yawn, MD; Bree Zeyzus-Johns, MD; and Nicola A. Hanania, MD, MS

## Abstract

In 2020, chronic obstructive pulmonary disease (COPD) was the fifth leading cause of death in the United States excluding COVID-19, and its mortality burden has been rising since the 1980s. Smoking cessation, long-term oxygen therapy, noninvasive ventilation, and lung volume reduction surgery have had a beneficial effect on mortality; however, until recently, the effects of pharmacologic therapies on all-cause mortality have been unclear. Inhaled pharmacologic treatments for patients with COPD include combinations of long-acting muscarinic receptor antagonists (LAMAs), long-acting- $\beta_2$ -agonists (LABAs), and inhaled corticosteroids (ICS). The recent IMPACT and ETHOS clinical trials reported mortality benefits with ICS/LAMA/LABA triple therapy compared with LAMA/LABA dual therapy. In IMPACT, fluticasone furoate/umeclidinium/vilanterol therapy significantly reduced the risk of on-/off-treatment all-cause mortality vs umeclidinium/vilanterol (hazard ratio, 0.72; 95% CI, 0.53 to 0.99;  $P=.042$ ). The ETHOS trial found a reduction in the risk of on-/off-treatment all-cause mortality in patients treated with budesonide/glycopyrrolate/formoterol vs glycopyrrolate/formoterol (hazard ratio, 0.51 [0.33 to 0.80]; nominal  $P=.0035$ ). Both trials included populations of patients with symptomatic COPD at high risk of future exacerbations, and a post hoc analysis of the final retrieved vital status data suggested that the observed mortality benefits are conferred by the ICS component. In conclusion, triple therapy reduces the risk of mortality in patients with symptomatic COPD characterized by moderate or severe airflow obstruction and a recent history of moderate or severe exacerbations. This benefit is likely to be driven by reductions in exacerbations. Future research efforts should focus on improving the long-term prognosis of patients living with COPD.

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Chronic obstructive pulmonary disease (COPD) has a global prevalence of 11.7%<sup>1</sup> and incidence rates ranging from 90.0 to 503.1 per 100,000 people.<sup>2</sup> In 2020, excluding COVID-19, chronic lower respiratory disease was the fifth leading cause of death in the United States<sup>3,4</sup>; since 1980, its mortality and economic burden have been rising.<sup>5</sup> Significant comorbidities are associated with COPD, adding to its associated risk of mortality,<sup>6</sup> and patients also experience exacerbations, which are associated with increased risk of all-cause mortality.<sup>7-10</sup>

Despite new treatment options becoming available in recent decades, death rates attributable to COPD have not improved as much as for other chronic diseases, such as cardiovascular disease.<sup>11-14</sup>

Therapeutic interventions for COPD have largely focused on improving lung function, symptoms, and health-related quality of life as well as reducing exacerbations rather than reducing mortality risk. A limited number of interventions have been found to reduce COPD-related mortality, with smoking cessation being one of the most beneficial and cost-effective methods;



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## ARTICLE HIGHLIGHTS

- Despite new treatment options becoming available, the mortality and economic burden of chronic obstructive pulmonary disease (COPD), a disease characterized by dyspnea, chronic cough, and sputum production, have been rising since 1980, with comorbidities associated with COPD and COPD exacerbations increasing the risk of mortality.
- A limited number of therapeutic interventions for COPD, including smoking cessation, long-term oxygen therapy, noninvasive ventilation, and lung volume reduction surgery, have been found to reduce COPD-related mortality. However, the focus of most pharmacologic interventions has been on improvement of lung function, symptoms, and health-related quality of life as well as exacerbation reduction.
- The recent phase 3 IMPACT and ETHOS clinical trials found mortality benefits with inhaled corticosteroid/long-acting muscarinic receptor antagonist/long-acting  $\beta_2$  agonist (ICS/LAMA/LABA) triple therapy compared with LAMA/LABA dual therapy in populations of patients with symptomatic COPD at high risk of future exacerbations.
- The all-cause mortality benefit observed with ICS/LAMA/LABA treatment may be driven by a reduction in exacerbations, probably due to the ICS component, highlighting that patients with moderate to severe COPD at risk of future exacerbations are likely to benefit most from triple therapy.
- In COPD, when the number needed to treat is considered, taking the differing lengths of interventions into account, triple therapy has had mortality benefits similar to or greater than those of interventions that primary care physicians routinely use in their practice to reduce their patients' mortality risk, such as cardioprotective or smoking cessation strategies.

however, it is often difficult for patients to achieve.<sup>15</sup> Long-term oxygen therapy has also been reported to reduce mortality in patients with severe COPD and hypoxemia, as has pulmonary rehabilitation in patients with severe to very severe COPD.<sup>16,17</sup>

This article reviews the evidence supporting the efficacy of current inhaled therapies at reducing mortality risk in patients with COPD in clinical trials and observational studies with all-cause mortality as a prespecified end point. In addition,

characteristics of patients included in these studies, which may influence mortality benefits of treatments, are explored.

### CLINICAL PRESENTATION, DIAGNOSIS, AND PATHOGENESIS

COPD is characterized by dyspnea, chronic cough, and sputum production.<sup>6</sup> Increases in respiratory symptoms and decreases in lung function of patients with COPD are associated with worsening health-related quality of life,<sup>18,19</sup> and symptoms may reduce patients' ability to engage in physical activity.<sup>20</sup>

In patients with symptoms indicating COPD and/or with a history of exposure to risk factors such as tobacco smoke or other noxious substances, spirometry is required for a diagnosis.<sup>6</sup> The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document classifies airflow limitation severity using spirometric cutoff points, which includes GOLD stage 1 (mild; forced expiratory volume in 1 second [FEV<sub>1</sub>]  $\geq$ 80% of predicted values), GOLD stage 2 (moderate; FEV<sub>1</sub> 50% to 79% of predicted values), GOLD stage 3 (severe; 30% to 49% FEV<sub>1</sub> of predicted values), and GOLD stage 4 (very severe; FEV<sub>1</sub> <30% of predicted values).<sup>6</sup> In addition, patients are assessed for their risk of exacerbation (based on prior exacerbation history) as well as symptom burden. An exacerbation that can be managed at home with an inhaled short-acting- $\beta_2$ -agonist may be considered mild,<sup>6</sup> whereas moderate exacerbations may require further treatment with antibiotics or oral corticosteroids.<sup>6</sup> However, severe and very severe exacerbations require an emergency department visit and/or hospitalization and may also be associated with acute respiratory failure.<sup>6</sup> Symptom burden can be assessed by short comprehensive measures, such as the modified Medical Research Council questionnaire<sup>21</sup> (Table 1) and the COPD Assessment Test questionnaire.<sup>22</sup> The COPD Assessment Test is an 8-item questionnaire that assesses health status impairment in COPD. Each item is scored 0 to 5 for a total score of 0 to 40. A score below 10 indicates

TABLE 1. mMRC Dyspnea Scale

mMRC scale <sup>21</sup>	GOLD-modified mMRC scale <sup>6</sup>	Impact
mMRC grade 1	mMRC grade 0	I only get breathless with strenuous exercise
mMRC grade 2	mMRC grade 1	I get short of breath when hurrying on the level or walking up a slight hill
mMRC grade 3	mMRC grade 2	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath after a mile or so (or after 1/4 hour) when walking at my own pace on the level
mMRC grade 4	mMRC grade 3	I stop for breath after walking about 100 yards or after a few minutes on the level
mMRC grade 5	mMRC grade 4	I am too breathless to leave the house or I am breathless when undressing

GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council. Used with the permission of the Medical Research Council.

that COPD symptoms are having a low impact on a patient's life; 10 to 20, a medium impact; above 20, a high impact; and above 30, a very high impact.<sup>22</sup>

COPD is driven by a chronic inflammatory response that results in emphysema and small airway fibrosis.<sup>6</sup> This leads to progressive lung function decline, with patients frequently experiencing exacerbations and/or concomitant diseases that increase the risk of mortality.<sup>6</sup>

## OBSERVATIONS

### Current Management Strategies for COPD

Studies indicate that exacerbations, especially those requiring hospitalization (severe exacerbations), are associated with increased risk of all-cause mortality, with studies reporting that patients who experienced an exacerbation in the previous year have an increased risk of death vs patients who did not have an exacerbation.<sup>7-10</sup> Furthermore, a large-scale 15-year observational study in patients with COPD reported that the risk of death has also been found to increase with increasing exacerbation frequency, with each new severe exacerbation increasing the risk up to fivefold after the tenth hospitalization vs the risk after the first hospitalization.<sup>10</sup>

Nonpharmacologic COPD management is primary to a comprehensive strategy to

manage COPD. It includes smoking cessation, avoidance of environmental exposures, vaccinations, pulmonary rehabilitation, and long-term oxygen therapy in appropriate patients.

Pharmacologic treatment options are used to reduce symptoms, to improve health status and exercise tolerance, and to reduce COPD exacerbation risk.<sup>6,23,24</sup> Patients are assigned initial maintenance therapy based on symptom burden, exacerbation history, and treatment goals. Treatments include bronchodilator monotherapies for the least symptomatic patients and combinations of long-acting muscarinic receptor antagonists (LAMAs) and long-acting- $\beta_2$ -agonists (LABAs)—dual bronchodilator therapy, for more symptomatic patients, or LABA and inhaled corticosteroids (ICS) for patients with exacerbations.<sup>6</sup> For patients still experiencing worsening symptoms or recurring exacerbations with LAMA/LABA or LABA/ICS therapy, escalation to triple ICS/LAMA/LABA therapy is advised.<sup>6</sup> After implementation of therapy, the patient's status is routinely reviewed and treatment adjusted as necessary. Notably, in current strategic documents, such as the GOLD recommendations, although mortality reduction is mentioned as a treatment goal for stable COPD, there is no recommendation around mortality and treatment decisions.<sup>6,23,25</sup>

TABLE 2. COPD Monotherapy and Dual Therapy Clinical Studies With All-Cause Mortality as an Outcome

Study	Duration	Treatment comparison	No. of patients	Analysis period	Study population	All-cause mortality incidence		Risk reduction (95% CI)	P value
						Control	Active comparator		
Observational studies									
Retrospective database study <sup>36</sup>	3 years	FP/SAL vs reference group	4665	NR	No specific criteria	Reference group (n=3620) 36.4%	FP/SAL (n=317) 21.4%	NR	NR
OUTPUL database study <sup>37</sup>	1 year	ICS/LABA vs LABA	18,615	NR	COPD with ≥1 comorbidity	LABA and/or LAMA (n=6408) 14.3%	ICS/LABA and/or LAMA (n=12,207) 11%	17% (3 to 28)	.024
Randomized controlled trials									
TORCH study <sup>38</sup>	3 years	FP/SAL vs placebo	6112	On-treatment	FEV <sub>1</sub> <60% predicted Mean exacerbations per year: 1	Placebo (n=1524) 15.2%	FP/SAL (n=1533) 12.6%	17.5% (-0.2 to 31.9)	.052
INSPIRE <sup>39</sup>	2 years	FP/SAL vs tiotropium	1323	On-treatment	Post-bronchodilator FEV <sub>1</sub> <50%	Tiotropium (n=665) 6%	FP/SAL (n=658) 3%	52% (15 to 73)	.012
UPLIFT study <sup>40</sup>	4 years	Tiotropium vs placebo	5993	On-treatment	Post-bronchodilator FEV <sub>1</sub> <70%	Placebo + CT (n=411) 13.7%	Tiotropium + CT (n=381) 12.8%	16% (3 to 27)	.016
SUMMIT study <sup>41</sup>	Event driven (median exposure: 1.8 years)	FF/VI vs placebo	16,485	On-/off-treatment	FEV <sub>1</sub> : 50%-70% High CV risk	Placebo (n=4111) 6.7%	FF/VI (n=4121) 6.0%	12% (-4 to 26)	.137

ACM, all-cause mortality; COPD, chronic obstructive pulmonary disease; CT, current therapy; CV, cardiovascular; FEV<sub>1</sub>, forced expiratory volume in 1 second; FF, fluticasone furoate; FP, fluticasone propionate; ICS, inhaled corticosteroid; LABA, long-acting β<sub>2</sub> agonist; LAMA, long-acting muscarinic antagonist; NR, not reported; SAL, salmeterol; VI, vilanterol.

### All-Cause Mortality as an Outcome for COPD Pharmacologic Treatment in Clinical Studies

As the goals of care for COPD focus on symptoms and future exacerbation risk, clinical trial outcomes have traditionally focused on reducing exacerbation rates and improving symptoms, health status, and lung function.<sup>26</sup> Rate of risk-adjusted all-cause mortality is a prognostic indicator for any given disease as a reduction in the risk of death can be used to evaluate overall treatment efficacy. It is well established that LAMA/LABA and ICS/LAMA/LABA therapy in patients with moderate to severe COPD confers benefits in exacerbation risk, lung function, dyspnea, and health status. However, their effects on all-cause mortality are less clear.<sup>27-35</sup>

**Monotherapy and Dual Therapy Clinical Studies.** Clinical studies of monotherapy and dual therapies in patients with COPD (defined as a FEV<sub>1</sub>/forced vital capacity ratio of <0.7) including all-cause mortality as an outcome are summarized in [Table 2](#).

**Observational Studies.** Soriano and colleagues<sup>36</sup> compared all-cause mortality during a 3-year period in patients 50 years of age and older with physician-diagnosed COPD identified in the primary care setting. All-cause mortality in patients receiving treatment with dual ICS/LABA therapy (fluticasone propionate [FP]/salmeterol [SAL]) or FP or SAL monotherapy was compared with a reference group of patients regularly using other COPD treatments but who had not received ICS or LABA since their diagnosis. Treatment with FP/SAL and FP monotherapy significantly reduced all-cause mortality vs the reference group (Cox-adjusted *P* values: FP/SAL, *P*=.0008; FP alone, *P*=.0028). After adjustment for covariates (including sex, age, smoking status, comorbid conditions, mention of asthma in patients' records, and use of oral corticosteroids), patients receiving FP/SAL had the lowest mortality risk vs the reference group (hazard ratio [HR], 0.48; 95% CI, 0.31 to 0.73), followed by patients receiving FP alone (HR, 0.62; 95% CI, 0.45 to 0.85); all-cause

mortality risk was not significantly reduced in patients receiving SAL alone vs the reference group (HR, 0.79; 95% CI, 0.58 to 1.07; *P*=.123).<sup>36</sup>

The observational OUTPUT study took place during a 3-year period and included patients 45 years of age and older with physician-diagnosed COPD and 1 or more comorbidities. Concomitant respiratory diseases in the study population included asthma, chronic respiratory disease other than COPD, pulmonary infections, and acute pulmonary symptoms. All-cause mortality was a primary end point, and results indicated that addition of ICS to a long-acting bronchodilator reduced risk of all-cause mortality vs bronchodilator monotherapy (HR, 0.83; 95% CI, 0.72 to 0.97; *P*=.024).<sup>37</sup> Interestingly, in a subanalysis of patients with a recent out-of-hospital COPD exacerbation, all-cause mortality benefits observed with ICS addition to long-acting bronchodilators were even greater (HR, 0.63; 95% CI, 0.44 to 0.90; *P*=.012).<sup>37</sup> These results are interesting as not only was mortality benefit conferred with ICS/LABA therapy vs LABA monotherapy, but mortality benefits were more pronounced in patients with recent out-of-hospital exacerbations, defined as 1 prescription or more of both oral corticosteroids and antibacterials in the 6 months preceding the beginning of follow-up.<sup>37</sup>

**Randomized Controlled Trials.** The primary end point of the TORCH trial was rate of 3-year all-cause mortality in patients with severe COPD receiving FP/SAL 500/50 µg dual therapy or placebo. Patients 40 to 80 years of age with post-bronchodilator FEV<sub>1</sub> of less than 60% of predicted normal values were enrolled. After adjustment of results to account for interim safety and efficacy analyses, the primary end point was not met, with no significant reduction in all-cause mortality with FP/SAL vs placebo (HR, 0.83; 95% CI, 0.68 to 1.00; *P*=.052).<sup>38</sup>

INSPIRE was a 2-year study in patients with symptomatic COPD aged 40 to 80 years and percentage predicted post-bronchodilator FEV<sub>1</sub> of less than 50%. The

TABLE 3. COPD Triple Therapy Clinical Trials With On-/Off-Treatment All-Cause Mortality as an Outcome

Trial	Duration	Treatment comparison	No. of patients	Study population	All-cause mortality annual rate		Risk reduction (95% CI)	P value
					Control	Active comparator		
3-study pooled analysis: TRILOGY TRINITY TRIBUTE <sup>42</sup> <i>Post hoc analysis</i>	1 year	BDP/GLY/FOR, BDP/FF, or BDP/FOR + TIO vs IND/GLY	5589	Severe to very severe COPD at increased risk of exacerbations	IND/GLY (n=1844) 2.7%	BDP/GLY/FOR, BDP/FF, or BDP/FOR + TIO (n=3745) 2.0%	29% (-2 to 50)	.066
IMPACT study (on-treatment; original analysis) <sup>31</sup>	1 year	FF/UMECVI vs UMECVI	10,355	High symptom burden (CAT score $\geq 10$ )	UMECVI (n=2070) 1.88%	FF/UMECVI (n=4151) 1.2%	42% (12-62)	.01
IMPACT study (on-/off-treatment; original analysis) <sup>31</sup>				% predicted post-bronchodilator FEV <sub>1</sub> <50% and a history of $\geq 1$ moderate or severe exacerbation	UMECVI (n=2070) 2.90%	FF/UMECVI (n=4151) 2.14%	29% (1-49)	.043
IMPACT study (on-/off-treatment; including additional vital status data) <sup>43</sup> <i>Post hoc analysis</i>				% predicted post-bronchodilator FEV <sub>1</sub> of 50%-80% and a history of $\geq 2$ moderate exacerbations or $\geq 1$ severe exacerbations	UMECVI (n=2070) 3.19%	FF/UMECVI (n=4151) 2.36%	28% (1-47)	.042
ETHOS study (on-treatment; including additional vital status data) <sup>44</sup> <i>Post hoc analysis</i>	1 year	BUD/GLY/FOR 320/18/9.6 $\mu$ g vs GLY/FOR	8509	High symptom burden (CAT score $\geq 10$ )	GLY/FOR (n=2120) 2.12%	BUD/GLY/FOR 320/18/9.6 $\mu$ g (n=2137) 1.17%	50% (19-70)	.0056 <sup>a</sup>
ETHOS study (on-/off-treatment; original analysis) <sup>34,44</sup>				FEV <sub>1</sub> /FVC ratio of <0.70	GLY/FOR (n=2120) 2.31%	BUD/GLY/FOR 320/18/9.6 $\mu$ g (n=2137) 1.31%	46% (13-66)	.0111 <sup>a</sup>
ETHOS study (on-/off-treatment; including additional vital status data) <sup>44</sup> <i>Post hoc analysis</i>				% predicted post-bronchodilator FEV <sub>1</sub> of $\geq 25\%$ -<50% and $\geq 1$ moderate or severe exacerbations in the previous year	GLY/FOR (n=2120) 2.64%	BUD/GLY/FOR 320/18/9.6 $\mu$ g (n=2137) 1.40%	49% (20-67)	.0035 <sup>a</sup>
				% predicted post-bronchodilator FEV <sub>1</sub> of $\geq 50\%$ -65% and $\geq 2$ moderate exacerbations or $\geq 1$ severe exacerbations in the previous year				

BDP, beclomethasone dipropionate; BUD, budesonide; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; FF, fluticasone furoate; FOR, formoterol; FVC, forced vital capacity; GLY, glycopyrrolate; IND, indacaterol; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

<sup>a</sup>Nominal P value as the study hierarchy was not reached.



effect of FP/SAL 500/50 µg vs tiotropium 18 µg on all-cause mortality was evaluated as an additional efficacy and safety end point. Post hoc analysis found that on-treatment mortality risk was significantly lower with FP/SAL vs tiotropium (HR, 0.48; 95% CI, 0.27 to 0.85;  $P=.012$ ).<sup>39</sup>

UPLIFT was a 4-year study investigating efficacy of the LAMA tiotropium 18 µg vs placebo in patients with COPD 40 years of age and older and percentage predicted post-bronchodilator FEV<sub>1</sub> of 70% or less. All-cause mortality was evaluated as a secondary end point. Analysis of on-treatment deaths (until 30 days after last dose of treatment) found that tiotropium significantly reduced all-cause mortality vs placebo (HR, 0.84; 95% CI, 0.73 to 0.97;  $P=.016$ ). Analysis until the end of the protocol-defined treatment period (up to day 1440) also found that mortality was significantly lower in patients receiving tiotropium vs placebo (HR, 0.87; 95% CI, 0.76 to 0.99;  $P=.034$ ). However, analysis including all patients up to the end of the 30-day follow-up period (day 1470) did not find significance (HR, 0.89; 95% CI, 0.79 to 1.02;  $P=.086$ ), nor did the analysis of all known data (including vital status information received after day 1470; HR, 0.89; 95% CI, 0.78 to 1.00;  $P=.058$ ).<sup>40</sup>

SUMMIT was an event-driven study in patients with moderate COPD and increased risk of cardiovascular disease. Patients were 40 to 80 years of age with percentage predicted post-bronchodilator FEV<sub>1</sub> of 50% to 70% and modified Medical Research Council dyspnea scale score of 2 or higher, indicating a slower walking pace than people of the same age on the level due to breathlessness or a need to stop for breath when walking (Table 1). Increased risk of cardiovascular disease was defined as being 60 years or older and receiving medication for 2 or more of the following conditions: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral artery disease. Reduction in all-cause mortality with the ICS/LABA fluticasone furoate (FF)/vilanterol (VI) 100/25 µg vs placebo was the primary end point. Follow-up continued until 1000 deaths or more had occurred. The median study

period for patients was 1.8 years and was similar across treatment groups. No significant difference in all-cause mortality reduction was found between treatment groups (HR, 0.88; 95% CI, 0.74 to 1.04;  $P=.137$ ).<sup>41</sup>

In summary, clinical trials investigating all-cause mortality as primary, secondary, or additional end points with LAMA/LABA or ICS/LABA therapy and monotherapies in patients with COPD have produced conflicting results. Notably, although these trials were conducted in patients with COPD, study populations between trials differ in terms of COPD severity, symptoms, and comorbidities. Mortality benefits are likely to be affected by patients' characteristics, as evidenced by OUTPUT, in which ICS/LABA therapy was reported to have enhanced mortality benefits vs bronchodilator monotherapy in a subpopulation of recently exacerbating patients.<sup>37</sup> Overall, differences in study populations should be carefully considered when interpreting all-cause mortality as an outcome across COPD clinical trials.

**Triple Therapy Clinical Studies.** Clinical trials of triple therapies in patients with COPD including all-cause mortality as an outcome are summarized in Table 3.

A pooled analysis evaluated fatal adverse events in three 52-week studies of the ICS/LAMA/LABA beclomethasone dipropionate (BDP)/glycopyrronium (GLY)/formoterol fumarate (FOR) in patients with severe to very severe COPD at increased risk of exacerbations.<sup>42</sup> These studies included treatment comparisons between BDP/GLY/FOR and BDP/FF (ICS/LABA), tiotropium (LAMA), BDP/FOR plus tiotropium in a separate inhaler (ICS/LABA+LAMA), and indacaterol/glycopyrronium bromide (LAMA/LABA). There were no significant reductions in the risk of mortality between ICS-containing regimens and non-ICS-containing regimens (HR, 0.71; 95% CI, 0.50 to 1.02;  $P=.066$ ). Similar results were found with BDP/FOR/GLY vs non-ICS-containing treatments (HR, 0.72; 95% CI, 0.49 to 1.06;  $P=.096$ ). Interestingly, no differences between ICS-containing and non-ICS-containing treatments were found for respiratory-related deaths (HR, 1.01; 95% CI, 0.45 to 2.22;  $P=.989$ ), but deaths due to

nonrespiratory causes were significantly reduced between these regimens (HR, 0.62; 95% CI, 0.43 to 0.97;  $P=.037$ ).<sup>42</sup>

The IMPACT randomized controlled trial enrolled patients with symptomatic COPD and either percentage predicted post-bronchodilator FEV<sub>1</sub> of less than 50% and history of 1 or more moderate (requiring antibiotics or oral corticosteroid therapy) or severe (requiring hospitalization) exacerbations in the previous year or percentage predicted post-bronchodilator FEV<sub>1</sub> of 50% to 80% and history of 2 or more moderate exacerbations or 1 or more severe exacerbations in the previous year.<sup>31</sup> IMPACT evaluated 52 weeks of treatment with the ICS/LAMA/LABA FF/umeclidinium (UMEC)/VI 100/62.5/25 µg vs FF/VI (ICS/LABA) 100/25 µg and UMEC/VI (LAMA/LABA) 62.5/25 µg. All-cause mortality was assessed as a prespecified other end point. Analysis of patients on-treatment found that all-cause mortality risk was significantly reduced in patients receiving FF/UMEC/VI vs UMEC/VI (HR, 0.58; 95% CI, 0.38, 0.88;  $P=.010$ ) but not vs FF/VI (HR, 0.95; 95% CI, 0.64 to 1.40;  $P=.780$ ). Similarly, analysis of patients across both the on- and off-treatment periods found that the risk of all-cause mortality was significantly reduced in patients treated with FF/UMEC/VI vs UMEC/VI (HR, 0.71; 95% CI, 0.51 to 0.99;  $P=.043$ ) but not vs FF/VI (HR, 0.90; 95% CI, 0.67 to 1.20;  $P=.458$ ).<sup>31</sup> Results were supported by a post hoc analysis incorporating patients originally censored because of incomplete vital status data at week 52, allowing reporting of mortality data for 99.6% of the IMPACT population.<sup>43</sup> Treatment with FF/UMEC/VI significantly reduced the risk of all-cause mortality vs UMEC/VI (HR, 0.72; 95% CI, 0.53 to 0.99;  $P=.042$ ), but no significant difference was seen between FF/UMEC/VI and FF/VI groups (HR, 0.89; 95% CI, 0.67 to 1.16;  $P=.387$ ) in the analysis including patients across the on- and off-treatment periods.<sup>43</sup>

The ETHOS randomized controlled trial enrolled patients with symptomatic COPD and either percentage predicted post-bronchodilator FEV<sub>1</sub> of 25% to less than 50% and 1 or more moderate or severe

exacerbations in the previous year or percentage predicted post-bronchodilator FEV<sub>1</sub> of 50% or more to 65% and 2 or more moderate or 1 or more severe exacerbations in the previous year.<sup>34</sup> ETHOS evaluated 52 weeks of treatment with the ICS/LAMA/LABA budesonide (BUD) 320 µg or 160 µg/glycopyrrolate (GLY) 18 µg/formoterol (FOR) 9.6 µg vs GLY/FOR (LAMA/LABA) or BUD 320/FOR (ICS/LABA). All-cause mortality was a secondary end point. Results found that BUD 320/GLY/FOR resulted in reductions in all-cause mortality risk vs GLY/FOR (HR, 0.54; 95% CI, 0.34 to 0.87) and BUD 320/FOR (HR, 0.78; 95% CI, 0.47 to 1.30) in the analysis of patients across the on-/off-treatment period. However, as the secondary end point of annual rate of severe exacerbations did not show a significant difference between BUD 320/GLY/FOR and GLY/FOR, significance was only termed nominal for the reduction in all-cause mortality risk owing to the statistical hierarchy.<sup>34,44</sup> These all-cause mortality results were supported by a post hoc analysis incorporating patients originally censored because of missing vital status data at week 52, allowing reporting of mortality data for 99.6% of the ETHOS population. Treatment with BUD 320/GLY/FOR resulted in a significantly lower risk of all-cause mortality vs GLY/FOR (HR, 0.51; 95% CI, 0.33 to 0.80; nominal  $P=.0035$ ) and no difference in risk of all-cause mortality vs BUD320/FOR (HR, 0.72; 95% CI, 0.44 to 1.16;  $P=.1721$ ).<sup>44</sup> The updated analyses included an assessment of on-treatment data only, which also found a significant reduction in all-cause mortality risk in patients treated with BUD 320/GLY/FOR vs GLY/FOR (HR, 0.50; 95% CI, 0.30 to 0.81;  $P=.0056$ ) and a reduction vs BUD 320/FOR (HR, 0.82; 95% CI, 0.47 to 1.41;  $P=.4640$ ).<sup>44</sup> None of the analyses found a mortality benefit for BUD 160/GLY/FOR vs either BUD/FOR or GLY/FOR.<sup>44</sup>

In summary, clinical trials of triple therapies in patients with COPD investigating all-cause mortality as an outcome have produced consistent results. IMPACT and ETHOS both reported significant mortality benefits with

ICS/LAMA/LABA triple therapy vs LAMA/LABA dual therapy but no significant differences vs ICS/LABA dual therapy. In addition, the pooled analysis by Vestbo and colleagues<sup>42</sup> reported significant mortality benefits with ICS-containing vs non-ICS-containing treatments, although this effect was observed only for non-respiratory-related mortality. Notably, these trials included populations of patients with symptomatic COPD at high risk of exacerbations, and as such it is not known whether the same benefit applies to patients with less severe disease. In addition, the IMPACT and ETHOS trials included only patients with COPD who were either current or former smokers<sup>31,34</sup>; therefore, it may not be possible to apply these findings to patients who have never smoked. Furthermore, results from the Vestbo pooled analysis also suggest that ICS-containing therapy could be exerting mortality benefits through direct or indirect effects on comorbidities commonly associated with severe, symptomatic COPD.

All these trials investigating triple therapies were conducted during a 1-year time frame; therefore, caution should be exercised in considering outcomes during longer time periods as mortality benefits with pharmacotherapy may not demonstrate linear trends. For example, in the TORCH study, which investigated dual therapy with ICS/LABA vs ICS or LABA monotherapy and placebo, an increased COPD-related mortality rate was observed in the third year of the study compared with the first 2 years in patients who received ICS, LABA, or placebo.<sup>38</sup>

### Exacerbations as a Driver of Mortality in COPD

Observational studies in patients with COPD have reported an increased risk of death with increasing exacerbation frequency.<sup>8,10</sup> Inhaled corticosteroids are often prescribed to patients with COPD to reduce exacerbation frequency, and IMPACT and ETHOS both included study populations at high risk of experiencing exacerbations.<sup>6,31,34,43,44</sup> Results of these studies suggest that mortality benefits of triple therapy are driven by a reduction in exacerbation frequency,

although it is of interest that in ETHOS, triple therapy did not significantly reduce severe exacerbation rates vs LAMA/LABA therapy, unlike in IMPACT.

Original analyses from SUMMIT reported no significant differences in all-cause mortality in patients treated with FF/VI vs placebo.<sup>41</sup> A post hoc analysis of SUMMIT applied the IMPACT exacerbation criteria to the study population to investigate any potential all-cause mortality benefits in patients at high risk of experiencing exacerbations. In patients with 2 or more moderate or 1 or more severe exacerbations in the prior year, significant benefit in all-cause mortality was observed with the ICS-containing therapy (FF/VI) vs placebo (mortality reduction, 34.2%; HR, 0.66; 95% CI, 0.47 to 0.91).<sup>45</sup> This again suggests that exacerbation prevention could be a potential driver of all-cause mortality benefits.<sup>45</sup> Furthermore, exacerbations have been linked with increased cardiovascular risk, and the SUMMIT population was at a heightened risk of cardiovascular events.<sup>46-48</sup> Therefore, the mortality benefits conferred in the frequently exacerbating SUMMIT subpopulation may have also been driven by a reduction in exacerbations, which in turn reduced cardiovascular-related mortality.

While ICS therapy has shown treatment benefits for exacerbation reduction in patients with COPD, it is important to balance these benefits against the associated risks of long-term ICS therapy. A systematic review observed that ICS use significantly increased the risk of local adverse effects, such as dysphonia, as well as increased the risk of respiratory infections (eg, pneumonia). In addition, a significantly increased risk of diabetes-related outcomes and bone fractures was seen in patients who received high ICS doses or prolonged exposures.<sup>49</sup> As patients with COPD are often elderly with comorbidities, receiving ICSs for a prolonged time may make these patients more susceptible to adverse effects related to ICS therapy.<sup>49</sup>

In summary, data suggest that the all-cause mortality benefit observed with ICS/LAMA/LABA treatment is driven by a reduction in exacerbations, probably due to the

ICS component. This highlights that patients with moderate to severe COPD at risk of future exacerbations are likely to benefit most from triple therapy.

### Placing the Mortality Benefits of Triple Therapy for COPD in Context

Although triple therapy has been found to provide mortality benefits vs dual LAMA/LABA therapy, long-term ICS use has been associated with increased pneumonia risk in patients with COPD and increased risk of osteoporosis and fractures.<sup>43,50-53</sup> A Cochrane review concluded that ICS delivered alone or in combination with a LABA can increase serious pneumonias in patients with COPD,<sup>54</sup> and results from the IMPACT and ETHOS trials indicated that the risk of first on-treatment pneumonia was significantly higher in patients receiving ICS/LAMA/LABA vs LAMA/LABA therapy.<sup>31,34,43</sup> However, while increased risk of pneumonia with ICS treatment is an important concern for patients, the exacerbation and all-cause mortality benefits of using triple therapy to treat COPD have been found to outweigh this risk, and pneumonia was not associated with mortality in the IMPACT and ETHOS trials.<sup>31,34,43</sup> A post hoc analysis of IMPACT found that FF/UMEC/VI reduced the risk of combined time to first moderate/severe exacerbation or investigator-reported pneumonia vs FF/VI (HR, 0.87; 95% CI, 0.82 to 0.92;  $P < .001$ ) and UMEC/VI (HR, 0.86; 95% CI, 0.81 to 0.94;  $P < .001$ ), finding an overall benefit with FF/UMEC/VI in this population of patients (Figure).<sup>31,43,55</sup>

Although COPD is currently the fifth leading cause of death in the United States, excluding COVID-19, treatment strategies continue to focus on symptom reduction rather than on reducing the risk of mortality.<sup>5,6,56,57</sup> To help compare the all-cause mortality benefits of ICS/LAMA/LABA for COPD with those of treatments for other leading causes of death, a number needed to treat (NNT) for each intervention can be applied and compared. The NNT helps conceptualize the value of certain interventions, demonstrating the number of patients who need to receive an intervention to achieve

1 specific outcome. However, NNTs are dependent on the length of follow-up, with differences typically increasing during longer periods of observation, and need to be considered against the treatments being compared and the population being considered.<sup>58</sup>

The NNT for ICS/LAMA/LABA vs LAMA/LABA to prevent 1 death is 147 in IMPACT for FF/UMEC/VI vs UMEC/VI and 105 in ETHOS for BUD 320/GLY/FOR vs GLY/FOR (based on on-treatment events during 1 year of treatment in each trial). For reference, both statins, a routine intervention for heart disease, and smoking cessation demonstrate NNTs (based on events during 5 to 14.5 years) ranging from 164 to 625 (Table 4).<sup>15,59,60</sup> A review of all-cause mortality results with ICS/LAMA/LABA triple therapies highlighted that absolute risk reductions in all-cause mortality with triple therapies are similar to or greater than those seen with cardioprotective treatments or smoking cessation strategies.<sup>61</sup> When considering mammography, data from the Cancer Intervention and Surveillance Modeling Network have demonstrated a number needed to screen to prevent 1 death of 84 for annual screening in women 40 to 84 years of age, increasing to 144 if screening is performed biennially in women 50 to 74 years of age.<sup>62</sup> Thus, when looking at NNT, taking the differing lengths of interventions into account, the mortality benefit associated with ICS/LAMA/LABA therapy in patients with COPD at high risk of exacerbations is similar to or better than that of interventions that primary care physicians commonly use in practice to reduce mortality risk in their patients.

Causes of mortality in patients with COPD are not limited to COPD but include other causes, such as cardiovascular disease and cancer.<sup>65</sup> Therefore, the mortality benefit with ICS/LAMA/LABA triple therapy may not be solely driven by exacerbation reduction, but may also contribute to the mortality benefit seen in other conditions. For example, the onset of an exacerbation leading to hospitalization is associated with an increase in the risk of cardiovascular events and death. As triple therapy reduces

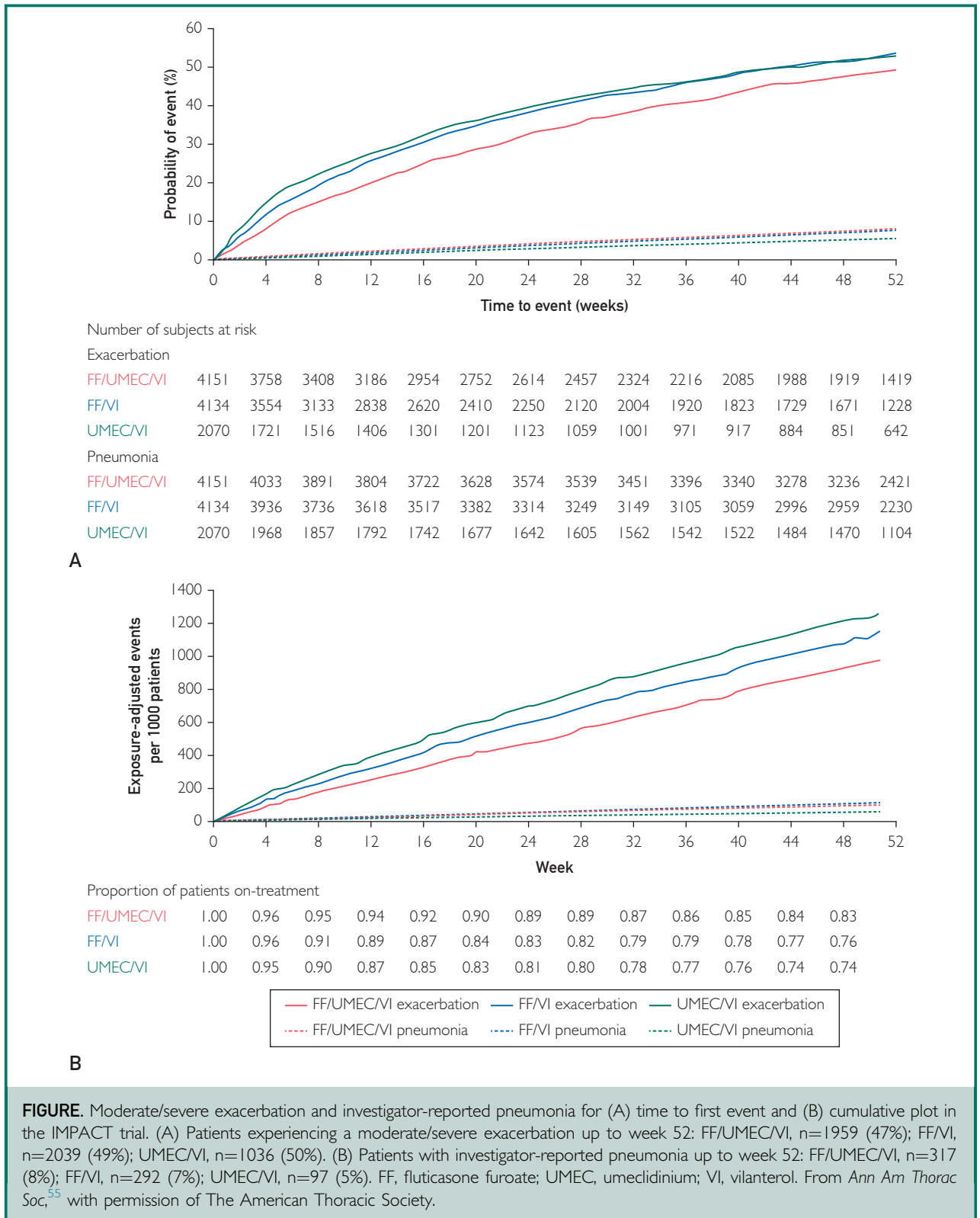


TABLE 4. Number Needed to Treat for All-Cause Mortality Reduction in Common Interventions

Disease state	Intervention vs comparator	No. <sup>a</sup>	Duration	All-cause mortality rate		Estimated ARR	NNT <sup>b</sup>	Reference
				Intervention	Comparator			
COPD	FF/UMEC/VI 100/62.5/25 µg vs UMEC/VI 62.5/25 µg	6221	1 year	FF/UMEC/VI 1.20% <sup>c</sup>	UMEC/VI 1.88% <sup>c</sup>	0.68%	147	43
COPD	BUD/GLY/FOR 320/18/9.6 µg vs GLY/FOR 18/9.6 µg	4257	1 year	BUD/GLY/FOR 1.17% <sup>c</sup>	GLY/FOR 2.12% <sup>c</sup>	0.95%	105	44
Hyperlipidemia	Simvastatin 20 mg vs placebo	4444	5.4 years	Simvastatin 8.2%	Placebo 11.5%	0.61%	164	59
Hyperlipidemia	Simvastatin 40 mg vs placebo	20,536	5 years	Simvastatin 12.9%	Placebo 14.7%	0.36%	278	60
Hypertension	Ramipril 10 mg vs placebo	9297	5 years	Ramipril 10.4%	Placebo 12.2%	0.36%	278	63
Type 2 diabetes	Metformin vs diet	753	10 years	Metformin 13.5 per 1000 patient-years	Diet/placebo 20.6 per 1000 patient-years	0.71%	141	64
Smoking	Smoking cessation intervention with ipratropium or placebo vs usual care	5887	14.5 years	Smoking cessation 8.83 per 1000 patient-years	Usual care 10.38 per 1000 patient-years	0.16%	625	15
Smoking	Sustained quitters vs continuous smokers <sup>d</sup>	5887	14.5 years	Sustained quitter 6.04 per 1000 patient-years	Continuous smoker 11.09 per 1000 patient-years	0.51%	196	15

<sup>a</sup>Population sizes provided are for the comparator groups, not the total study population.

<sup>b</sup>NNT = 1/ARR.

<sup>c</sup>On-/off-treatment all-cause mortality.

<sup>d</sup>Comparator groups were not randomized but determined 1 year after randomization.

Note: it has been assumed that the risk reduction is constant over time for studies >1 year in duration and that all patients have been followed up for the full duration of the study.

ARR, absolute risk reduction; BUD, budesonide; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; FOR, formoterol; GLY, glycopyrronium; ICS, inhaled corticosteroid; LABA, long-acting β<sub>2</sub> agonist; LAMA, long-acting muscarinic antagonist; NNT, number needed to treat; UMEC, umecidinium; VI, vilanterol.



the risk of exacerbations in patients with COPD, it may also reduce mortality due to cardiovascular events. A key limitation of current COPD clinical studies is the lack of information on specific causes of mortality.

## CONCLUSION

Triple therapy with ICS/LAMA/LABA has been found to reduce the risk of all-cause mortality in patients with symptomatic COPD characterized by moderate or severe airflow obstruction and a recent history of moderate or severe exacerbations. This mortality benefit appears to be driven primarily by a reduction in moderate/severe exacerbations. Future research efforts should focus on improving the long-term prognosis of patients with COPD.

## POTENTIAL COMPETING INTERESTS

M. Mintz has received consulting fees from AstraZeneca and GSK and speaking fees from AstraZeneca, Boehringer Ingelheim, and GSK. I. Barjaktarevic has received grants from AMGEN, GE Healthcare, Theravance, and Mylan and has consulted for Grifols, Theravance, Mylan, Boehringer Ingelheim, Verona Pharma, Aerogen, Inhibrx, GSK, and AstraZeneca, outside the work related to this manuscript. D. Mahler has been on advisory boards for AstraZeneca, Boehringer Ingelheim, GSK, Mylan, Teva, Theravance, and Verona and speaks bureaus for AstraZeneca, Boehringer Ingelheim, and Teva and is on the Board of Trustees of CHEST Foundation; he receives royalties from the Salem Media Group for COPD: Answers to Your Questions (2015) and from pharmaceutical companies for use of BDI/TDI; he also runs an educational website for those with COPD and their families (<https://www.donaldmahler.com>). B. Make has received research support and consultancy fees from AstraZeneca. N. Skolnik has received research support from Sanofi, AstraZeneca, Boehringer Ingelheim, GSK, Bayer, and Novo Nordisk and speaker fees from AstraZeneca, Boehringer Ingelheim, Lilly, GSK, and Bayer and served as a consultant or on an advisory board for AstraZeneca, Teva, Lilly, Boehringer Ingelheim, Sanofi, Sanofi Pasteur, GSK, Bayer,

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**Abbreviations and Acronyms:** **BDP**, beclomethasone dipropionate; **BUD**, budesonide; **COPD**, chronic obstructive pulmonary disease; **FEV<sub>1</sub>**, forced expiratory volume in 1 second; **FF**, fluticasone furoate; **FOR**, formoterol fumarate; **FP**, fluticasone propionate; **GLY**, glycopyrronium; **GOLD**, Global Initiative for Chronic Obstructive Lung Disease; **HR**, hazard ratio; **ICS**, inhaled corticosteroid; **LABA**, long-acting- $\beta_2$ -agonist; **LAMA**, long-acting muscarinic receptor antagonist; **NNT**, number needed to treat; **SAL**, salmeterol; **UMEC**, umecidinium; **VI**, vilanterol

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