Impact of triple therapy on mortality in COPD

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To date, there are no conclusive data that triple therapy limits mortality in COPD. Future, well-designed and -powered trials are needed to validate the findings around mortality. https://bit.ly/3ZtzmT1

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Abstract

Only a few therapies have been shown to prolong survival in specific patients with COPD. In recent years, the IMPACT and the ETHOS trials suggested that triple therapy (a combination of inhaled corticosteroid (ICS), long-acting muscarinic antagonist (LAMA) and long-acting β_2-agonist (LABA) given in a single inhaler) may reduce mortality compared with dual bronchodilation.

These results need however to be interpreted with caution. These trials were not powered by design to evaluate the impact of triple therapy on mortality as mortality was a secondary outcome. In addition, mortality reduction has to be put in perspective with the low mortality rate in both studies (<2%). Furthermore, a key methodological issue is that up to 70–80% of patients had ICS withdrawal at the enrolment in the LABA/LAMA arms, but none in the ICS-containing treatment arms. It is possible that ICS withdrawal may have contributed to some early death events. Finally, the inclusion and exclusion criteria of both trials were designed to select patients likely to respond to ICS.

There are no conclusive data yet that triple therapy reduces mortality in COPD. Future, well-designed and -powered trials are needed to validate the findings on mortality.

Commentary on

- Lipson DA, *et al*. Once-daily single-inhaler triple *versus* dual therapy in patients with COPD. *N Engl J Med* 2018; 378: 1671–1680.
- Rabe KF, *et al*. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med* 2020; 383: 35–48.

Context

COPD is an airway disease with persistent respiratory symptoms that causes globally ~3 million deaths every year [1]. Tobacco exposure has been proven to be the main risk factor for the development of COPD [2]. With the increasing prevalence of smoking in developing countries, and ageing populations in high-income countries, prevalence of COPD is expected to rise over the next 40 years. By 2030, there may be over 4.5 million deaths annually from COPD and related conditions [1]. Only smoking cessation in mild and moderate COPD patients [3], vaccination, long-term oxygen therapy in severely hypoxaemic COPD patients, and lung volume reduction surgery in selected COPD patients with emphysema were found to have a consistent benefit on mortality [4–6]. Pharmacological treatment choices such as inhaled bronchodilators are central to symptom management and are commonly given on a regular basis to prevent

or reduce symptoms. However, none of the individual studies that were powered to evaluate the effects of pharmacological treatments on COPD mortality have detected a significant survival benefit [7–10].

In recent years, two large randomised controlled trials provided new evidence on reduction of exacerbations with combination therapy including an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA) and a long-acting β_2-agonist (LABA) given in a single inhaler (triple therapy). These trials are called the IMPACT ("Informing the Pathway of COPD Treatment") and ETHOS ("Efficacy and Safety of Triple Therapy in Obstructive Lung Disease") trials [11, 12]. These trials also suggested a reduction in mortality with triple therapy compared with dual bronchodilation [11–14].

Here we describe the methods and results of the IMPACT and ETHOS trials with a specific focus on the impact of triple therapy on COPD mortality and discuss the strengths and limitations of these trials and how their design could have affected their findings.

Methods

Impact

The IMPACT trial [11] was a phase 3, multicentre, randomised, double-blind, placebo-controlled trial. Patients of 40 years of age or older, with physician-diagnosed symptomatic COPD, assessed with a COPD Assessment Test (CAT) score ⩾10, and forced expiratory volume in 1 s (FEV_1) <50% and a history of one moderate or severe exacerbation in the previous year, or an FEV_1 of 50–80% of the predicted normal value and at least two moderate exacerbations or one severe exacerbation in the previous year, were included. Participants were randomised in a 2:2:1 ratio to receive either a triple therapy including fluticasone furoate (FF) at a dose of 100 µg, umeclidinium (UMEC) at a dose of 62.5 µg, and vilanterol (VI) at a dose of 25 µg, or with FF/VI (at doses of 100 µg and 25 µg, respectively) or UMEC/VI (at doses of 62.5 µg and 25 µg, respectively) for 52 weeks (table 1). The primary endpoint was the annual rate of moderate or severe COPD exacerbations. The two co-primary treatment comparisons were triple therapy *versus* UMEC/VI, and triple therapy *versus* FF/VI with a superiority hypothesis with triple therapy on reducing exacerbations. The predefined key secondary endpoints were the FEV_1 and change of the St. George's Respiratory Questionnaire (SGRQ).

Ethos

The ETHOS trial [12] was a phase 3, multicentre, randomised, double-blind, placebo-controlled trial. Patients of 40 years of age or older, with physician-diagnosed symptomatic COPD, assessed with CAT score ⩾10, and FEV_1 <50% and a history of one moderate or severe exacerbation in the previous year, or an FEV_1 of 50–65% of the predicted normal value and at least two moderate exacerbations or one severe exacerbation in the previous year, were included. Patients were randomised to 320 µg of budesonide (BUD), glycopyrrolate and formoterol (320 µg BUD/GLY/FOR), 160 µg BUD/GLY/FOR, GLY/FOR or 160 µg BUD/FOR administered in a single inhaler (randomised 1:1:1:1) for 52 weeks (table 1) [12, 14]. The primary endpoint was the annual rate of moderate or severe COPD exacerbations with a superiority hypothesis with triple therapy over dual therapy. The predefined key secondary endpoints were time to death (all-cause), SGRQ response and changes in pre-bronchodilator FEV_1.

Results

In the phase 3, 52-week IMPACT study, 10 355 patients with symptomatic COPD and a history of exacerbations were randomised 2:2:1 to treatment with FF/UMEC/VI, FF/VI or UMEC/VI, administered in a single inhaler [11]. Triple *versus* dual therapy significantly reduced the annual moderate/severe exacerbations. The rate of moderate or severe exacerbations in the triple-therapy group was 0.91 per year, as compared with 1.07 per year in the FF/VI (rate ratio with triple therapy 0.85 (95% CI 0.80–0.90); 15% difference; p<0.001) (table 2). Improvements from baseline with FF/UMEC/VI compared with UMEC/VI were also maintained throughout the study for both trough FEV_1 and SGRQ. In addition, the data from the IMPACT trial showed that FF/UMEC/VI reduced risk of all-cause mortality compared with LAMA/LABA (UMEC/VI). The hazard ratio for triple therapy *versus* UMEC/VI was 0.58 (95% CI 0.38–0.88; 42% difference; unadjusted p=0.01), and the hazard ratio for FF/VI *versus* UMEC/VI was 0.61 (95% CI 0.40–0.93; 39% difference; unadjusted p=0.02) [11, 13].

In the ETHOS trial, 16 033 patients were screened of which 8588 were randomised to either 320 µg BUD/GLY/FOR (n=2157), 160 µg BUD/GLY/FOR (n=2137), GLY/FOR (n=2143) or 160 µg BUD/FOR (n=2151). Population characteristics were similar to those of the IMPACT trial (table 2). In the overall population, the ETHOS trial showed similar results to the IMPACT trial. Triple therapy (either 320 and 160 µg BUD/GLY/FOR) significantly reduced annual exacerbations compared with GLY/FOR (rate ratio 0.76 (95% CI 0.69–0.83); p<0.001) or 160 µg BUD/FOR (rate ratio 0.87 (95% CI 0.79–0.95); p=0.003)

TABLE 1 Main characteristics of the IMPACT and ETHOS trials

Study (study period)	Inclusion/exclusion criteria			Treatment		Included patients	Characteristics of patients at inclusion			
	Age and symptoms	FEV_1 and exacerbation history[#]	History of asthma/ eosinophils	ICS use before inclusion	Treatment arms		Mean age, years	Men (%)	Mean blood Eosinophils	Bronchodilator reversibility
IMPACT (2014–2017)	Age ⩾40 years CAT ⩾10	FEV_1 <50% and ⩾1 moderate-to-severe exacerbation OR 50%<FEV_1<80% and ⩾1 severe exacerbation or ⩾2 moderate exacerbations	Prior (but not current) history of asthma allowed No restriction regarding blood eosinophils	70%	Randomisation 2:2:1 ratio: 1) ICS (FF)+LAMA (UMEC) +LABA (VI) (triple therapy); 2) ICS (FF)+LABA (VI); 3) LAMA (UMEC)+LABA (VI)	10 355	65	66%	170 cells per mm^3	18%
ETHOS (2015–2019)	Age 40–80 years CAT ⩾10	FEV_1 <50% and ⩾1 moderate-to-severe exacerbation OR 50%<FEV_1<65% and ⩾1 severe exacerbation or ⩾2 moderate exacerbation	Prior (but not current) history of asthma allowed No restriction regarding blood eosinophils	80%	Randomisation 1:1:1:1 ratio: 1) ICS (BUD 320 µg)+LABA (FOR)+LAMA (GLY) (triple therapy, high-dose ICS) 2) ICS (BUD 160 µg)+LABA (FOR)+LAMA (GLY) (triple therapy, low-dose ICS) 3) ICS (BUD 320 µg)+LABA (FOR) 4) LAMA (GLY)+LABA (FOR)	8588	65	60%	167 cells per mm^3	31%

FEV_1: forced expiratory volume in 1 s; CAT: COPD Assessment Test; ICS: inhaled corticosteroid; FF: fluticasone furoate; LAMA: long-acting muscarinic antagonist; UMEC: umeclidinium; LABA: long-acting β_2-agonist; VI: vilanterol; BUD: budesonide; GLY: glycopyrrolate; FOR: formoterol. [#]: exacerbation history in the past 12 months.

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TABLE 2 Main outcomes of the IMPACT and ETHOS trials

Study	Primary outcome: rate of moderate/severe exacerbations per year	Secondary/exploratory outcomes		
		Mean SGRQ	Lung function	Mortality
IMPACT	• 0.91 with triple therapy	Mean change from baseline in SGRQ:	Mean change from baseline in FEV_1:	• 50 (1.2%) deaths in the FF/UMEC/VI arm
	• 1.07 with FF/VI (RR with triple therapy of 0.85 (95% CI 0.80–0.90); p<0.001)	• −1.8 (−2.4 to −1.1; p <0.001) with triple therapy compared with FF/VI	• +97 mL (85–109); p<0.001 with triple therapy compared with FF/VI	• 49 (1.2%) in the FF/VI arm (no difference with FF/UMEC/VI)
	• 1.21 with UMEC/VI (RR with triple therapy of 0.75 (95% CI 0.70–0.81); p<0.001)	• −1.8 (−2.6 to −1.0; p <0.001) with triple therapy compared with UMEC/VI	• +54 mL (39–69); p<0.001 with triple therapy compared with UMEC/VI	• 39 (1.9%) in the UMEC/VI arm (HR of 0.58 (95% CI 0.38–0.88), p=0.011, between FF/UMEC/VI and UMEC/VI)
ETHOS	• 1.08 with high-dose triple-therapy	Mean change from baseline in SGRQ:	Least square means change from baseline in FEV_1:	• 28 (1.3%) deaths in the high-dose triple therapy arm
	• 1.07 with low-dose triple-therapy	• −1.88 (−2.84 to −0.91) with high-dose triple therapy compared with GLY/FOR	• +35 mL (12–57); p=0.003 with triple therapy compared with GLY/FOR	• 39 (1.8%) in the low-dose triple therapy arm (no difference with high-dose triple therapy arm)
	• 1.42 with GLY/FOR (RR with high-dose triple therapy of 0.76 (95% CI 0.69–0.83); p<0.001)	• −1.47 (−2.43 to −0.51) with high-dose triple therapy compared with BUD/FOR	• +76 mL (54–99); p<0.0001 with triple therapy compared with GLY/FOR	• 49 (2.3%) in the GLY/FOR arm (HR of 0.51 (95% CI 0.33–0.80), p=0.004, between triple therapy and GLY/FOR)
	• 1.24 with BUD/FOR (RR with high-dose triple therapy of 0.87 (95% CI 0.79–0.95); p=0.003)			• 34 (1.6%) in the BUD/FOR arm (HR of 0.72 (95% CI 0.44–1.16), p=0.17, between triple therapy and BUD/FOR)

SGRQ: St George's Respiratory Questionnaire; FEV_1: forced expiratory volume in 1 s; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; RR: rate ratio; HR: hazard ratio; BUD: budesonide; GLY: glycopyrrolate; FOR: formoterol.

[12, 14] (table 2). In addition, triple therapy showed significant improvement in both FEV_1 and SGRQ compared with dual therapy but without reaching minimal clinically important differences (MCID). Finally, the ETHOS trial reported a hazard ratio of all-cause mortality over 1 year of 0.51 (95% CI 0.33–0.80) comparing triple therapy (BUD/GLY/FOR) with dual bronchodilator therapy (GLY/FOR) [12, 14].

Commentary

COPD is a leading cause of mortality worldwide and several large trials have evaluated whether COPD-related treatments reduce mortality. Although rarely powered by design to investigate mortality, various previous randomised controlled trials have assessed the effect of different bronchodilators on mortality in COPD as well. No statistically significant difference in mortality was observed with LABA/ICS, LABA alone or ICS alone compared with placebo in previous trials [7, 10]. Even the SUMMIT trial (Study to Understand Mortality and Morbidity in COPD) involving patients with moderate COPD with heightened cardiovascular risk which was powered to study all-cause mortality, did not show a significant effect for FF/VI compared with FF (hazard ratio 0.91 (95% CI 0.77–1.08); p=0.284) or VI alone (hazard ratio 0.96 (95% CI 0.81–1.14); p=0.655) [7].

Besides smoking cessation, only few therapies have been shown to prolong survival in specific patients with COPD including long-term oxygen therapy, vaccination and lung volume reduction surgery in selected patients [1, 4, 5]. The IMPACT and ETHOS trials suggested for the first time that bronchodilators could also improve mortality [11–14]. Both trials reported a markedly large (40–50%) reduction of mortality with LAMA/LABA/ICS over LAMA/LABA combinations in patients with COPD [11–14]. These results need, however, to be interpreted with caution.

First, in both trials, mortality was a secondary or an exploratory outcome. Therefore, these trials were not powered by design to evaluate the impact of triple therapy on mortality. Furthermore, mortality reduction has to be put in perspective with the low mortality rate in both studies. Indeed, mortality findings were based on 164 deaths out of 8588 participants (mortality rate of 1.9%) in ETHOS and 138 deaths out of 10 355 participants (mortality rate of 1.3%) in IMPACT [11–14].

Second, both the ETHOS and IMPACT trials have shown a significant reduction in mortality with triple therapy in the first year of treatment. However, by stratification over follow-up time, some discrepancies have to be pointed out [13–15]. Indeed, during the first 90 days after treatment initiation, there was a significantly lower proportion of deaths in the triple therapy group than in the dual therapy group in both the IMPACT and ETHOS studies (rate ratio of mortality of 0.24 (95% CI 0.12–0.48) and 0.37 (0.15–0.95), respectively). By contrast, during the subsequent 91–365 days of follow-up, the death rate was more similar or no longer statistically significant for triple and dual therapy (rate ratio 1.03 (0.71–1.50) and 0.86 (0.57–1.31) for the IMPACT and ETHOS trials, respectively) [13–15]. This would suggest that triple therapy only has a protective effect during the first 3 months of use, with no sustained benefit thereafter when the large majority of deaths occurred, or that withdrawal of ICS has an acute harmful effect compared to maintenance of ICS. Therefore, several methodological issues have been raised to explain this controversial benefit of triple therapy [16]. A key methodological issue is the management of treatment of patients at enrolment. Treatment had to be discontinued at randomisation for all patients. However, up to 70–80% of patients had ICS withdrawal at the enrolment of both the ETHOS and IMPACT studies (table 1) in the LABA/LAMA arms but none of the patients in the ICS containing treatment arms. By comparison, only 33% of patients had ICS before inclusion in SUMMIT [7]. It is possible that ICS discontinuation may have contributed to some early death events. This effect of ICS discontinuation is especially prominent in IMPACT where, in the first month, the incidence rate of first exacerbation under LAMA/LABA was higher than under LAMA/LABA/ICS. This may be due to the fact that in both the IMPACT and ETHOS trials, patients had raised eosinophil counts at baseline (table 1). In these patients, especially those with blood eosinophils over 300 cells·μL^{-1}, ICS discontinuation increases exacerbations and might therefore contribute to a higher mortality [17].

Third, the inclusion and exclusion criteria of both ETHOS and IMPACT were designed to select patients likely to respond to ICS. Patients with a previous history of asthma or atopy were not excluded. In addition, up to one-fifth of patients in the IMPACT study and almost one-third in ETHOS had significant bronchodilator reversibility (table 1). This is in contrast to other trials, such as FLAME [18], that included patients that were less likely to respond to ICS, as they excluded patients with a current or previous diagnosis of asthma or atopy or allergic rhinitis, or patients with respiratory symptoms before the age of 40 years, or patients with eosinophils $\geqslant$600 cells per mm^3. Furthermore, the patients included in IMPACT and ETHOS were more symptomatic with more frequent moderate or severe exacerbations compared with previous trials [11, 12]. In both trials, more than half of patients had two or more moderate or severe exacerbations during the year before inclusion. By contrast, a recent pooled analysis from six randomised controlled trials including COPD patients with a lower exacerbation risk (*e.g.* <20% of patients reported $\geqslant$2 exacerbations in the prior year) showed contrasting results [19]. No statistically significant difference in time to death was observed between LAMA/LABA (3133 patients) and LAMA/LABA/ICS (3133 patients) after propensity score matching including exacerbation history in the previous year (hazard ratio for LAMA/LABA 1.06 (95% CI 0.68–1.64); p=0.806). This suggests triple therapy may predominantly benefit selected patients with a high risk of exacerbation (>2 exacerbations per year).

Therefore, the difference of inclusion criteria and baseline characteristics of patients in the ETHOS and IMPACT trials may have affected all outcomes and also mortality compared with previous trials.

Implications for research and practice

The management of COPD should be based on a systematic approach to identify the phenotype and comorbidities that can influence the prognosis. The current COPD treatment guidelines recommend a stepwise approach and personalisation of treatments [1]. In patients with symptomatic severe COPD (FEV_1 <50%) and a history of exacerbations, triple therapy has shown a reduction of exacerbations over a LAMA–LABA association. However, as discussed above, there are no conclusive data yet that triple therapy reduces mortality. Even if there is mortality benefit, this may be driven by maintaining corticosteroid therapy in ICS responsive groups. Therefore, future studies need to consider ICS responsiveness to evaluate the effect of ICS withdrawal on mortality. Furthermore, following an adaptive selection method that aims at avoiding the previous medications' withdrawal effect will be important for future studies to evaluate the effect of triple therapies [20].

Conclusion

There are no conclusive data yet that triple therapy causally reduces mortality in COPD. In both the ETHOS and IMPACT trials, even if a potential reduction in mortality was observed (secondary outcome), there are several methodological issues that prompt to interpret these results with caution. Therefore, reduction of exacerbations in symptomatic patients with severe COPD and a history of exacerbations

should remain the main objective of triple therapy. Future, well designed and powered trials are needed to validate the findings on mortality.

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