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REVIEW

# Triple Therapy for COPD: Historical Perspective and Current Controversies

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## ABSTRACT

The use of a combination of three inhaled drugs has recently been established as the first choice for some patients in the algorithm for the treatment of chronic obstructive pulmonary disease. In this review, we aim to give an overview of the development that has led to the establishment of this treatment strategy, as well as to summarize the current challenges that its use presents in real life. Due to the benefits of open triple therapies, various combinations have been developed with a triple therapy effect in one single inhaler. The clinician should bear in mind the potential benefits of prescribing triple combinations, either escalating from double therapies or unifying open therapies into a triple therapy. Specifically, the role of single-inhaler triple therapy in the reduction of mortality risk deserves a thorough evaluation. Consequently, triple therapy should be used as part of the escalation of treatment as the disease progresses.

**Keywords:** COPD. Inhaled medications. Mortality. Triple therapy.

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## INTRODUCTION

The use of a combination of three inhaled drugs, consisting of a long-acting $\beta_2$-agonist (LABA), a long-acting muscarinic antagonist (LAMA) and an inhaled corticosteroid (ICS), has been recently established as the first choice for some patients in the algorithm for the treatment of chronic obstructive pulmonary disease (COPD)[1,2]. In this scenario, it is important to take into account the development of this triple therapy, its challenges and its results in order to fully understand its role in the treatment of the disease. In this review, we aim to present an overview of the development that has led to the establishment of this treatment strategy, as well as to summarize the current challenges that its use presents in real life.

## TRIPLE THERAPY IN COPD: THE BACKGROUND

The study of the efficacy and safety of combining three inhaled drugs for the treatment of COPD began to be explored for the first time in 2004 when Aaron et al.[3] published the method in their study *Canadian Optimal Therapy of COPD Trial* (OPTIMAL in short), the results of which were made public in 2007[4]. In this multicenter clinical trial, which was not sponsored by any pharmaceutical company, the authors explored the efficacy of the combination of salmeterol with fluticasone propionate and tiotropium in 449 patients with COPD with a one-year follow-up. The comparison groups were tiotropium, tiotropium + salmeterol and tiotropium + salmeterol/fluticasone propionate, and the primary endpoint was the proportion of patients who experienced an exacerbation of COPD that required treatment with systemic steroids or antibiotics. Although the results were inconclusive and the authors could not demonstrate that the addition of fluticasone–salmeterol to tiotropium therapy influenced rates of COPD exacerbation, they observed that this triple combination did improve lung function, quality of life, and hospitalization rates in patients with moderate to severe COPD.

This study began a path that was followed by subsequent studies with the aim of trying to clarify the clinical impact of combining three inhaled drugs in the treatment of COPD. At that time, the role of this triple combination in patients with severe COPD could only be understood by exploring the role of various molecules in various inhalation devices. Consequently, this led to the development of numerous studies (Table 1) in different types of patients, settings and endpoints that allowed us to form a clearer understanding of the potential role of this triple combination. The most frequently explored combination was the coadministration of salmeterol/fluticasone propionate at a dose of 50/250 µg every 12 hours in an accuhaler device, together with tiotropium 18 µg once daily in a handihaler device. The results showed the added effect of triple therapy using different devices that would pave the way to a new therapeutic step in patients with advanced COPD. As a result, the therapy began to be included in the recommendation documents at the time, and was mentioned as a second option in the document of the Global Initiative for Obstructive Lung Disease (GOLD) 2011[5].

Interestingly, shortly thereafter and during the development of the studies that would

**Table 1.** Combination of multiple inhalers triple therapy explored in the literature

| LABA/ICS | | | | LAMA | | | | References |
|---|---|---|---|---|---|---|---|---|
| Molecules | Dose* | Inhaler | Posology | Molecule | Dose* | Inhaler | Posology | |
| Beclomethasone/formoterol | 200/12 | pMDI | 1 puff/24 h | Glycopyrronium | 12.5, 25, 50 | pMDI | 1 puff/24 h | (74) |
| Fluticasone furoate/vilanterol | 100/25 | Ellipta | 1 puff/24 h | Umeclidinium | 62.5, 125 | Ellipta | 1 puff/24 h | (75) |
| Fluticasone propionate/ salmeterol | 250/25 | pMDI | 2 puffs/12 h | Tiotropium | 18 | Handihaler | 1 puff/24 h | (4) |
| Fluticasone propionate/ salmeterol | 500/50 | Accuhaler | 1 puff/12 h | Tiotropium | 18 | Handihaler | 1 puff/24 h | (76-78) |
| Fluticasone propionate/ salmeterol | 250/50 | Accuhaler | 1 puff/12 h | Tiotropium | 18 | Handihaler | 1 puff/24 h | (78-85) |
| Fluticasone propionate-salmeterol | 250/50 | Accuhaler | 1 puff/12 h | Umeclidinium | 62.5, 125 | Ellipta | Once daily | (86) |
| Budesonide/formoterol | 400/12 | Turbuhaler | 1 puff/12 h | Tiotropium | 18 | Handihaler | 1 puff/24 h | (87, 88) |
| Budesonide/formoterol | 200/6 | Turbuhaler | 2 puffs/12 h | Tiotropium | 18 | Handihaler | 1 puff/24 h | (89-91) |
| Budesonide/formoterol | 200/6 | Turbuhaler | 1 puff/12 h | Tiotropium | 18 | Handihaler | 1 puff/24 h | (92) |

*Metered dose expressed in µg per actuation.
ICS: inhaled corticosteroids; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; pMDI: pressurized metered dose inhaler.

lead to knowledge about the efficacy of triple therapy in separate devices, another new form of treatment began to be developed by combining two long-acting bronchodilators from different families in a single inhalation device[6,7]. The development of the LABA/LAMA combinations led to certain debate over the best option for carrying out triple inhaled therapy, since, at that time, this triple therapy could be achieved in three ways: giving the three drugs separately, adding a LAMA to a LABA/ICS combination, or adding an ICS to a LABA/LAMA combination. Unfortunately, neither at that time nor since have there been any clinical trials that have directly evaluated the prospective efficacy and safety of these different ways of constructing a triple therapy and, at that time, there was speculation about the different options, depending on the type of disease COPD or asthma[8]. In any case, the open triple combinations explored in these studies have always been a combination of LABA/ICS + LAMA (Table 1), and none have investigated the efficacy of a LABA/LAMA + ICS combination.

Similarly, there are few studies that have compared two triple combinations in different devices. The two main studies are the *Gruppo Lavoro Italiano Sarcopenia-Trattamento e Nutrizione* (GLISTEN) study[9], which compared combining salmeterol/fluticasone propionate either with tiotropium or with glycopyrronium, and the study by Manoharan et al.[10] comparing tiotropium with aclidinium when added to an unspecified LABA/ICS combination. Both studies found similar efficacy for each of the clinical outcomes explored.

**Table 2.** Summary of single-inhaler triple therapy combinations

| LABA | LAMA | ICS | Inhaler | Dose | Stage |
|---|---|---|---|---|---|
| Formoterol | Glycopyrronium | Beclomethasone | pMDI NEXThaler | 2 puffs/12 h | Approved for COPD |
| Formoterol | Glycopyrronium | Budesonide | pMDI | 2 puffs/12 h | Approved for COPD |
| Formoterol | Glycopyrronium | Fluticasone propionate | pMDI | 1 puff/12 h | Stage III |
| Indacaterol | Glycopyrronium | Mometasone | Breezhaler | Once daily | Approved for asthma |
| Vilanterol | Umeclidinium | Fluticasone furoate | Ellipta | Once daily | Approved for COPD |
| Batefenterol | | Fluticasone furoate | Ellipta | Once daily | Stage II |

COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; pMDI: pressurized metered dose inhaler.

## SINGLE-INHALER TRIPLE THERAPIES FOR COPD

Due to the expected results of triple therapy in severely affected COPD patients, various combinations with a triple therapy effect in one single inhaler have been developed (Table 2). First, the combination of beclomethasone, formoterol and glycopyrronium using its extrafine pressurized metered dose inhaler formulation (pMDI) has been explored by three major clinical trials[11-13]. Additionally, it also became available in an extrafine multi-dose dry powder presentation in the NEXThaler device, while a higher dose formulation of the ICS for the treatment of bronchial asthma became available too[14]. Overall, this combination has the advantage of providing an extrafine particulate formulation with good lung deposition and of being available in both pMDI and dry powder for the treatment of COPD.

The second combination is formed by vilanterol, umeclidinium and fluticasone furoate[15,16]. This combination is available in the Ellipta multi-dose dry powder device. Its advantages include its single-dose, once-daily dosing and the availability of various drug combinations in the same device, which favors the escalation of therapies as the disease progresses[17] and allows adaptation of the same device to various types of patients with different needs, with excellent pulmonary deposition being shown in both mild and severe patients[18,19].

The third combination available for the treatment of COPD is the combination of formoterol, budesonide and glycopyrronium[20,21] in a pMDI. In addition to the robustness and safety of the molecules, the combination employs one of the most striking technical advantages, its formulation through micro pearls. These micro pearls are engineered porous phospholipid microparticles with aerodynamic diameters in the respirable range of 1-2 µm[22]. When compared to suspensions of simple drug microcrystals, the co-suspensions produced by their irreversible association with the porous particles had significantly better suspension stability.

These three single-inhaler triple combinations are currently approved for COPD. Additionally, a fourth triple combination of mometasone,

glycopyrronium and indacaterol in a single-dose dry powder inhaler has been approved for asthma[23,24]. Although the use of this fourth triple combination is not currently contemplated for COPD, it should be kept in mind for its possible future developments. It consists of a fixed combination with molecules of proven efficacy and allows once-daily dosing. In addition, the Breezhaler device has the lowest internal resistance of all powder devices and ensures adequate lung deposition[25,26]. Of note, the availability of inhaled drugs and their combinations in Breezhaler is the widest of all inhalation devices, with all families of inhaled drugs and all their combinations, double and triple, being available, and allowing easy and convenient treatment escalation without changing the inhalation device[17].

Finally, in addition to these triple combinations already on the market, there are at least two more in process of development. On the one hand, the combination of Fluticasone propionate with formoterol and glycopyrronium has recently been published after its first phase 3 trial in India[27]. It is administered in a pMDI every 12 hours and shows similar efficacy to open-label triple therapy. On the other hand, the combination of batefenterol with fluticasone furoate is also under development. Batefenterol is a first-in-class bronchodilator molecule that has a truly dual mechanism, with a muscarinic antagonist and beta agonist (MABA) included within the same molecule. Therefore, although, strictly speaking, the result is a combination of two drugs, a MABA plus an ICS, the therapeutic effect is actually that of triple therapy. This combination with triple therapy effect has been explored in Phase I and II trials with once-daily administration using the Ellipta multi-dose dry powder device[28,29].

## WHAT DOES TRIPLE THERAPY IN COPD PROVIDE VERSUS SINGLE OR DUAL THERAPIES?

The results of clinical trials of triple therapy in a single inhalation device versus dual or single therapies have been extensively reported in numerous studies, not only in the original clinical trials, but also in pooled analyses of clinical trials, post-hoc analyses, systematic reviews and narrative reviews[30-34]. Advantages in lung function and patient-reported outcomes have been reported in trials comparing single-inhaler triple therapies to multiple treatments in symptomatic patients with moderate to very severe airflow limitation and increased risk of exacerbations. To cut a long story short, the impact of triple therapy on lung function is different if the benefit is assessed against dual therapy of ICS/LABA or LABA/LAMA therapy. In the first case, the gains through forced expiratory volume in one second ($FEV_1$) can easily exceed 100 mL. In the second case, however, the functional benefits of adding an ICS to dual bronchodilator therapy are smaller, around 50 mL, or in some cases, not significant[31]. This suggests that adding a second bronchodilator to improve lung function is preferable to an ICS, which is to be expected. However, despite this different behavior, when we evaluate the differences in improvement by looking at the reduction in the risk of exacerbations, the perception of dyspnea or the improvement of quality of life, the differences between adding a second bronchodilator or adding an ICS are not so striking. On average, clinical improvements are reported in most cases, but they usually do not reach the traditional threshold level for clinical significance. These results open up the debate on the impact in real life of this triple therapy compared

to previous double therapies. One argument in this context is that the definition of a clinically relevant difference should be reconsidered in patients with severe COPD who require complex and advanced treatments. In any case, these papers show us the average improvement we should expect in patients with COPD with a high disease impact despite treatment, and whose treatment has been intensified.

In this context, the role of the eosinophil and the therapeutic response to ICS is a factor that needs to be kept in mind in light of current knowledge. Although analyzing the role of the eosinophil as a marker of response to ICS is controversial and beyond the scope of this review[35], it is currently accepted that patients with a higher blood eosinophil count may have a greater response to ICS[36]. Consequently, the most recent versions of the two main documents of recommendations on the management of COPD in Spain –GOLD and the Spanish COPD guide (GesEPOC)– place the indication of this triple therapy in patients with a previous history of exacerbations with a high blood eosinophil count[1,37].

## WHAT IS THE BENEFIT OF SINGLE INHALER VERSUS OPEN TRIPLE THERAPIES?

Although improvements in various clinical outcomes are evident, it could probably be argued that the observed effects are, to some extent, predictable[38]. It is logical to expect that if we increase the intensity of treatments in symptomatic patients or patients with a high impact of the disease, improvements will occur. However, the interesting question is whether triple therapy in a single inhalation device offers any advantage over triple therapy in different devices.

Although direct comparisons can be made (as discussed below), all these comparisons are influenced by two relevant factors. Firstly, the change of inhalation device. It is common for triple therapy in separate devices to use different devices to achieve delivery of the three drugs (Table 1), and any possible differences found could have been influenced by the change of device. Secondly, the change in molecule may also be relevant. It has been described that inhaled drugs often have an individualized response at the patient level, which may lead to a certain degree of unpredictability which qualifies their effectiveness[39,40]. Consequently, a change in molecule could lead to a change in effectiveness, despite the molecule belonging to the same pharmacological group[41]. Therefore, any comparison between open versus closed triple therapies will be affected by whether the comparator groups share the same inhaler and molecules or not.

The clinical trials evaluating these comparisons are limited in number but consistent in their findings. For the beclomethasone-based combination, the *Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic-obstructive pulmonary disease* (TRINITY) study found that treatment with a fixed-dose triple combination achieved clinical benefits comparable to open therapy[13]. The only statistical differences found were in quality of life at weeks 26 and 52, favoring the open triple therapy, and in the rate of moderate to severe exacerbations in the subgroup of patients with two or more exacerbations in the previous 12 months, favoring the fixed-dose combination[42]. Subsequently, a meta-analysis

comparing single-inhaler triple therapies with open triple therapies found no differences in the risk of moderate-severe exacerbations, nor in hospitalizations, lung function or quality of life[43]. In addition, in the triple therapy containing fluticasone furoate, the authors concluded that the fixed-dose combination was no less effective than separate triple therapy in two inhalers in terms of lung function, symptoms, exacerbations or safety[44].

Therefore, with the overall data from the trials, we can say that switching from an open triple therapy to a fixed-dose combination results in similar clinical efficacy in the type of patient explored in these trials. In this context, the question therefore arises of the possible clinical benefits of unifying an open triple therapy. After reviewing the literature, three potential benefits can be identified. First, the fewer inhalers a patient has to handle has been associated with a decrease in inhaler handling errors[45], which could lead to greater effectiveness. This is especially relevant considering that this is a treatment which consists of all three families of inhaled drugs available for the treatment of COPD. Consequently, if critical errors were made due to poor technique, all the three drugs would not be adequately received. Secondly, by reducing the number of devices, greater adherence to treatment is to be expected[46]. At this point, however, it is important to remember that therapeutic adherence is a complex concept involving numerous factors, of which the number of devices is only one[47]. In any case, it is important to emphasize that therapeutic adherence should be a central element in the clinical interview and that, in every contact with the health care system, the professionals who care for these patients should take the opportunity to emphasize health education concepts such as therapeutic adherence. Third, another potential benefit of using triple therapy is the price. A quick analysis of the prices of the different inhaled drug combinations reveals an interesting situation[32]. First, triple therapies inhaled in a single device are cheaper than some dual therapies. Second, almost all the open combinations are more expensive than the closed ones with, in many cases, considerable price differences. Third, not all open combinations are more expensive than fixed-dose combinations, so cost-effectiveness studies are needed to assess the budgetary impact of this change at the level of the health system, taking into account the impact on the reduction of exacerbations and, therefore, the use of health resources. Currently, an initial evaluation of the cost-effectiveness of single versus multiple inhalers triple therapy indicates that a single-inhaler triple dose would improve health outcomes and reduce costs compared with open triple therapies for the treatment of patients with symptomatic COPD[48].

These potential benefits of triple therapy in a single inhalation device have been reinforced by the emergence of new observational studies in real life. A recent real-world, observational, retrospective cohort study analyzed electronic health records in the Spanish National Healthcare System database to identify COPD patients initiating single-inhaler or multiple-inhaler triple therapies from 4,625 eligible cases between June 2018 and December 2019[49]. At the 12-month follow-up, single-inhaler triple therapy patients had a reduced risk of exacerbations and a lower all-cause mortality risk, all of which was accompanied by greater adherence to therapy throughout the follow-up. Accordingly, this effect was also associated

with significantly reduced use of health care resources and a subsequent reduction in the cost of care, with substantial adjusted mean annual cost savings. In addition, the 24-week *INvestigation of TRelegy Effectiveness: usual PractIce Design* (INTREPID) pragmatic trial demonstrated the clinical benefits of once-daily single-inhaler triple therapy versus multiple-inhaler triple therapy in patients with symptomatic COPD[48]. Although the impact on prolongation of survival was not very striking, a reduction in the cost of treatment with triple therapy in a single inhalation device versus separate devices was observed, as mentioned above.

Consequently, if a COPD patient needs to receive three inhaled drugs for the treatment of their clinical condition, for the reasons outlined above, it makes more sense to administer them in a single inhalation device than in separate devices, due to improvements in therapeutic compliance, with the consequent impact on therapeutic effectiveness and the potential influence on costs.

## THE MORTALITY EFFECT

### COPD therapies and mortality before triple therapy studies

Currently, one of the most controversial aspects of the impact of triple therapy is related to its potential impact on reducing the risk of mortality[50,51]. Despite a considerable amount of research into the relationship between triple therapy and mortality, the existing evidence should be viewed with caution. The history of inhaled drugs in COPD mortality goes back to the end of the last century with trials of single and dual therapies and has been marked by controversy.

Before the advent of triple therapy in a single device there had been four large published clinical trials evaluating mortality. The first study was the *Towards a Revolution in COPD Health* (TORCH) clinical trial evaluating the relationship between a salmeterol-fluticasone combination versus placebo on mortality risk as the primary endpoint[52]. After evaluating more than 6000 patients over three years, the differences in mortality were significant in the crude analysis. However, when adjusted for the intermediate analyses performed, the statistical significance was lost, with a p-value of 0.052.

The second mortality analysis was the *Understanding Potential Long-Term Impacts on Function with Tiotropium* (UPLIFT) study, which evaluated almost 6000 patients followed for four years on treatment with tiotropium or placebo and where the assessment of mortality was a secondary endpoint[53]. When comparing the two study arms during follow-up, patients with tiotropium had a statistically significant lower risk of mortality compared to the control group. However, at the 30-day follow-up after the end of the trial, these differences were no longer significant with a final overall p-value of 0.058.

Until that time, these data provided indications that a long-acting bronchodilator with or without ICS could have an impact on survival, albeit with borderline p-values influenced by various methodological considerations. In this context, a work that contributed to establishing the possible relationship of inhaled drugs with mortality was the *Investigating New Standards for Prophylaxis in Reducing Exacerbations*

(INSPIRE) study, which comparatively evaluated a tiotropium versus a salmeterol-fluticasone propionate arm in more than 1300 COPD patients followed for two years[54]. Although the results of the study were officially negative, since no difference in the rate of exacerbations was found between the study arms, a small, unexpected, statistically significant beneficial effect on the risk of death was found, favoring the combination with ICS. Furthermore, analysis of these previous studies led to the idea that patients with a history of cardiovascular disease would be far more prone to the risk of mortality[55].

Consequently, at that time it seemed to make sense to conduct a clinical trial with mortality as the primary endpoint and focused on patients with a history of cardiovascular risk factors. This study was the *Study to Understand Mortality and MorbidITy* (SUMMIT), a clinical trial to evaluate the impact on mortality of a LABA/ICS combination in patients with a history of cardiovascular risk factors[56]. Unfortunately, the trial results clearly showed that treatment with fluticasone furoate and vilanterol did not affect mortality or cardiovascular outcomes in patients with moderate COPD and elevated cardiovascular risk. These results seemed to put an end to the relationship between inhaled treatments and survival in COPD.

## Triple therapies studies and mortality: the effect

With the secondary analyses of triple therapy trials, the story seems to have taken a new turn. These new results were mainly based on two trials evaluating triple therapy combinations vs double therapies. The *Informing the Pathway of COPD Treatment* (IMPACT) trial evaluated the relative benefits and risks of fluticasone furoate-vilanterol-umeclidinium in patients with symptomatic COPD and a history of exacerbations[16]. Mortality was evaluated as an exploratory endpoint, and the authors found that all-cause mortality was significantly lower with the regimens that included the inhaled glucocorticoid fluticasone furoate (triple therapy with fluticasone furoate, vilanterol and umeclidinium and double therapy with fluticasone furoate and vilanterol) than with umeclidinium–vilanterol. The mortality analysis was preliminary and therefore had to be subsequently updated once all the information regarding mortality was finalized[57]. The results of this final analysis confirmed that triple therapy reduced the risk of all-cause mortality compared to dual bronchodilator therapy.

The *Efficacy and Safety of Triple Therapy in Obstructive Lung Disease* (ETHOS) trial evaluated the reduction in mortality risk as a secondary endpoint between a triple combination of budesonide, formoterol and glycopyrronium and double bronchodilation with formoterol-glycopyrronium[21]. In this trial, the authors found that the risk of death from any cause in the 320 µg triple therapy group was 46% lower than that in the double bronchodilation group. Again, this analysis had to be re-evaluated once all the information on clinical outcomes was collected at the end of the follow-up. The reanalysis consistently found a decreased risk of mortality for triple therapy versus dual bronchodilator therapy[58].

Additionally, although studies with the combination of beclomethasone, formoterol, and

glycopyrronium did not directly assess mortality risk, a pooled analysis of clinical trials of the development of this triple therapy showed a reduction in mortality risk that was significant only for non-respiratory events[59].

## Triple therapies studies and mortality: the precautions

These trials consistently showed a reduction in mortality risk with the use of triple therapy in a single inhalation device. However, among other issues, these papers left open the question as to why studies not designed to assess mortality found this effect, while the studies specially designed to measure this outcome such as TORCH[52] or SUMMIT[56] failed to find this association. Various arguments could be put forward in this debate, such as the different molecules, the different inhalation devices, the greater efficacy of a combination of three drugs, or the characteristics of the patients included, among others. However, in order to make a balanced critical interpretation of the data, it is essential to bear in mind some methodological limitations of these mortality analyses.

The first consideration is related to the population analyzed. It is important to keep in mind that the patients chosen had a high disease impact profile, with active symptoms and previous exacerbations. Consequently, these results lack external validity for the complete population of patients with COPD as they are limited to a specific type of patient.

In the same vein, a second nuance should be considered regarding the type of analysis carried out. Superiority trial analysis should be carried out in the intention-to-treat population. However, the data indicate that these results were provided in two different population sets, namely on-treatment (which corresponds to a per-protocol analysis) and on/off treatment (corresponding to a truly intention-to-treat analysis). Interestingly, the most strikingly significant data between the two arms were obtained in the on-treatment population, i.e., per protocol. When the intention-to-treat population is analyzed, the differences still exist, but are very close to non-significance. This could imply that if some of the other factors presented above were to be corrected, the differences might easily become not significant.

Another aspect to keep in mind concerns the confounding variables by which the analysis is adjusted. We currently know that there are a certain number of variables associated with mortality in COPD, such as exacerbations[60], hyperinflation[61], comorbidities[62], or dyspnea[63], among others. Consequently, these variables should have been considered in the analyses, since their irregular distribution among the study groups could confound the results. However, as can be seen in Table 3, very few of the variables were used to adjust these analyses, and they were generally decided by the researchers. This prevents us from accepting the results as evidence-based truth, and they must rather be taken as suggestive exploratory data with which to formulate a hypothesis.

In addition to the considerations outlined above, the patients were unevenly distributed between groups. In the IMPACT study, the number of patients in the dual bronchodilator therapy comparator group was half that in the groups with ICSs and, in addition, the

**Table 3.** Relation of confounders in major clinical trials analysing mortality as an endpoint

| Study | N | Comparators | Objective | Confounders |
|---|---|---|---|---|
| UPLIFT | 5,992 | Tiotropium<br>Placebo | Secondary | None |
| TORCH | 6,112 | Salmeterol-fluticasone<br>Placebo | Primary | Interim analysis<br>Smoking status |
| INSPIRE | 1,323 | Salmeterol-fluticasone<br>Tiotropium | Secondary | None declared |
| SUMMIT | 16,485 | Vilanterol-fluticasone<br>Placebo | Primary | Age<br>Gender |
| IMPACT | 10,355 | Vilanterol-fluticasone furoate-umeclidinium<br>Vilanterol- umeclidinium<br>Vilanterol-fluticasone furoate | Exploratory | Treatment group<br>Age<br>Gender |
| ETHOS | 8,509 | Budesonide-formoterol-glycopyrronium<br>Formoterol-glycopyrronium<br>Budesonide- formoterol | Secondary | Baseline post-bronchodilator $FEV_1$% predicted<br>Age |

FEV: forced expiratory volume.

number of patients who completed the trial was also lower, producing an imbalance in the number of cases analyzed in each group. Most strikingly, in the ETHOS study, not all deaths were counted equally in all groups in the mortality analysis, since in the triple therapy group there were fewer deaths included out of the total deaths that occurred[58,64].

One statistical detail which must be added is the fact that the mortality analyses were not adjusted for multiplicity, increasing the possibility of finding a significant result by chance. Finally, a considerable number of patients were receiving ICSs at baseline before starting the trials: about 80% and 67% in ETHOS and IMPACT, respectively. These patients with previous use of ICSs were distributed proportionately among the study groups, so the cases assigned to double bronchodilator therapy suffered a de-escalation of treatment when the ICS was withdrawn. Interestingly, when the analysis was repeated limiting it to patients without this de-escalation, there were no differences between the groups[57], which suggests that we may be witnessing an effect influenced, at least partially, by the de-escalation of the treatment, as already outlined by others[65,66].

Another relevant aspect is the presence of cases of bronchial asthma. The protocol of these trials indicates that cases with a current diagnosis of asthma were excluded, but not those that were diagnosed with asthma in the past. Notably, we have known for some time that asthma is a chronic disease and that patients who are well controlled with medication or considered to be in remission from their asthma continue to have airway inflammation and bronchial hyperresponsiveness[67,68]. Interestingly, a high number of cases were receiving ICSs at baseline. Because the researchers did not show any analyses in cases without prior asthma, it is possible that prior history of asthma is a confounding variable in the results. In this same context, it would be expected that an ICS dose escalation would have an effect on therapeutic efficacy, in this case, on

the risk of mortality. Interestingly, the only trial exploring two doses of ICS, the ETHOS study[58], clearly indicates that it is the higher dose of those explored that achieves this effect. This effect could be attributed to a dose-response relationship or that the study was underpowered for this dose of ICS. In any case, there have been no reports of this dose-response analysis in patients without a previous history of asthma.

Finally, it is necessary to reflect on the clinical relevance of the association. Although reducing the risk of mortality is always a relevant objective, a different vision can be obtained if, instead of focusing on the risk of mortality, we estimate the expected prolongation of survival. The INTREPID pragmatic trial investigated the clinical benefits of triple therapy versus continuing therapy with multiple-inhaler triple therapy for patients with symptomatic COPD in usual clinical practice[69]. The authors observed that using triple therapy in a single device was associated with an additional time of 0.174 life years, which corresponded to approximately two months[48].

In summary, the results of the studies of triple therapy in reducing the risk of mortality provide highly significant data on this clinical outcome in a clear way for the first time in the history of inhaled treatments for COPD. Furthermore, the results are consistent between different clinical trials with different combinations, suggesting that there is a clear underlying principle. However, the limitations and methodological considerations discussed above and summarized in table 4 indicate that these results should be taken with caution considering that these resaults are close to non-significance. Accordingly, these data should be considered more as hypothesis-generating information rather than as a result that could be used to support clinical decisions based on an evidence-based approach. In this context, a new clinical trial with triple therapy and mortality as the primary endpoint is therefore needed.

**Table 4.** Limitations and methodological concerns on triple therapy trials evaluating mortality

| |
|---|
| Highly selected population |
| It may include some asthmatics |
| It may involve a descaling effect |
| Secondary or exploratory objectives |
| Not corrected for multiplicity |
| Non-balanced groups |
| Not adjusted for covariates |
| Intention to treat analysis |

FEV: forced expiratory volume.

## COMPARATIVE STUDIES

In the context of the current and future development of combinations with a triple therapy effect for COPD, it would be desirable to have a direct head-to-head comparison study that would enable us to compile a profile of the patient who benefits most from each of the different options available. Although, unfortunately, up to now there have been no such clinical trials, we do have some studies that allow us to obtain some comparative data.

First, a comparative study funded by Chiesi evaluated the pulmonary deposition of the triple combination of beclomethasone-formoterol-glycopyrronium in an extrafine formulation administered by a pMDI, versus the combination of fluticasone furoate-vilanterol-umeclidinium in an Ellipta device in 20 patients with COPD[70]. As expected, the authors found that the small airways deposition of all

three components was higher in the extrafine beclomethasone combination.

That same year, a systematic literature review and network metanalysis were published on randomized controlled trials using triple therapies[71]. This metanalysis was funded by AstraZeneca and the authors' conclusion was that budesonide-based triple therapy had a comparable efficacy to other triple fixed-dose and open triple combination therapies in reducing exacerbations and improving lung function and symptoms in patients with moderate to very severe COPD.

More recently, another network metanalysis was released, on this occasion funded and led by GlaxoSmithKline[72]. The authors reported a favorable efficacy effect with fluticasone furoate triple therapy at 24 weeks in terms of lung function, annualized rate of moderate-severe exacerbations, health status and rescue medication use.

Finally, an independent group from Canada using an observational study approach evaluated budesonide-based and fluticasone-based triple therapies administered in two inhalers on the incidence of exacerbation, mortality and severe pneumonia[73]. The authors concluded that budesonide-based triple therapy with two inhalers was generally just as successful at reducing exacerbations in a real-world clinical environment for COPD treatment as fluticasone-based triple therapy. However, the budesonide-based triple therapy was linked to a lower incidence of severe pneumonia and perhaps all-cause mortality, although this was found particularly in individuals without a history of exacerbations, who may not need triple therapy.

## CONCLUSIONS

The evaluation of triple therapies, either in fixed doses in a single device or in separate devices, provides us with information on the average efficacy that we can expect when applied to patients with COPD who require an escalation of medication due to suffering a symptomatic or high-impact form of the disease. In addition, the unification of triple therapies in a single inhalation device maintains efficacy, with improvements in treatment adherence, real-life effectiveness, and cost. Consequently, triple therapy is a treatment that should be used as part of the escalation of treatment as the disease progresses. Issues currently being debated, such as the formulation of new combinations, the adaptation of other existing combinations for COPD or their clinical impact on relevant outcomes such as mortality, will have to be satisfactorily addressed in the near future to enable us to continue advancing towards the goal of providing personalized medicine in COPD.

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## DISCLOSURES

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