



Triple Therapy Versus Dual Bronchodilation and Inhaled Corticosteroids/Long-Acting β -Agonists in COPD: Accumulating Evidence from Network Meta-Analyses

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ABSTRACT

Guidelines are mainly based on evidence of well-designed randomized controlled trials (RCTs), but there are limitations to the transferability of conclusions of RCTs to usual care mainly because the patients enrolled in RCTs are selected and not representative of the population encountered in daily practice; moreover, the research environment is substantially different from that of the real world. Because of the scarcity of data generated in large unselected populations in everyday clinical practice, the possibility of using meta-analyses can be considered. Recently, several meta-analyses have attempted to clarify the role of triple therapy containing a long-acting β -agonist (LABA), a long-acting muscarinic antagonist

(LAMA) and an inhaled corticosteroid (ICS) delivered from a single inhaler in chronic obstructive pulmonary disease (COPD), also considering that there is a big difference in the use of triple therapy between what is recommended by COPD guidelines or strategies and the prescriptive behaviour of clinicians. Taking into account the results of the most recent meta-analyses, we believe that triple therapy provides modest clinical benefit in the general COPD population, but in patients on LABA/LAMA combination therapy, who still experience acute exacerbations of COPD (AECOPDs) and have blood eosinophil counts ≥ 300 cells· μl^{-1} , it is of clinical relevance. On the contrary, adding a LAMA to an ICS/LABA combination elicits relevant clinical benefit in the general COPD population, supporting the role of dual bronchodilation therapy for the treatment of COPD. The quantitative synthesis of the currently available clinical evidence seems to suggest that, in patients with COPD already on ICS/LABA combination, the therapy can be improved without an increase of cardiovascular severe adverse events (SAEs) when a LAMA is added to the combination.

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Key Summary Points

Large efficacy RCTs, which are essential to show that novel treatments are effective and safe during research and development programmes, have clear limitations in relation to the transferability of their conclusions to usual care mainly because the enrolled patients are selected and not representative of the population encountered in daily practice; moreover, the research environment is substantially different from that of the real world

Alternatively, the possibility of using meta-analyses can be taken into account. Meta-analysis can be considered as a systematic evaluation of all studies that have been conducted to answer a specific question or hypothesis

Recently, several meta-analyses have attempted to clarify the role of triple therapy delivered in a single inhaler in COPD

The results of meta-analyses described in this article suggest that triple combination therapy offers only a further modest clinical benefit in the general COPD population, but it is clinically relevant when a patient is on LABA/LAMA therapy and still suffers from AECOPD and has blood eosinophil counts ≥ 300 cells· μl^{-1} , but adding a LAMA to an ICS/LABA combination induces a relevant clinical benefit in the general COPD population without increasing the risk of cardiovascular SAEs

Unfortunately, the step-up approach from dual bronchodilation to triple therapy proposed by the GOLD strategy does not reflect the important differences in AECOPDs (they differ in aetiology, severity and biological substrate), and thus it is not tailored to the patient's specific needs to be treated

TRIPLE THERAPY IN COPD MANAGEMENT

The use of triple therapy containing a long-acting β -agonist (LABA), a long-acting muscarinic antagonist (LAMA) and an inhaled corticosteroid (ICS) is common in patients with chronic obstructive pulmonary disease (COPD) [1, 2], and this despite the restrictive recommendations of COPD guidelines or strategies [3–5]. In particular, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy [5] states that the threshold of > 100 eosinophils· μl^{-1} in blood of patients already taking LAMA/LABA who are still having acute exacerbations of COPD (AECOPDs) identifies individuals with a greater likelihood of achieving clinical benefit when escalating to triple therapy, whereas the magnitude of effect on AECOPDs will be greater at higher eosinophil counts, particularly ≥ 300 eosinophils· μl^{-1} . For patients with < 100 eosinophils· μl^{-1} , the escalation to triple therapy is unlikely to have a major influence on AECOPDs.

However, several studies have reported that even patients with mild or moderate COPD severity are treated with triple therapy, regardless of the risk of AECOPDs, and this not only by general practitioners [1], but also by specialists [2]. At least in Italy, the prescription of triple therapy was associated in a statistically significant manner with older age, current and former smoking habit, higher GOLD stage, the number of moderate and severe AECOPDs and heart failure [6]. In another study, being an older male and having been prescribed an ICS/LABA fixed-dose combination (FDC) at diagnosis were strong predictors of triple therapy use within 1 year from the diagnosis [7].

These findings indicate that there is a large difference between what is recommended by the COPD guidelines or strategies and the prescriptive behaviour of clinicians. The guidelines and especially the GOLD strategy are mainly based on evidence of well-designed randomized controlled trials (RCTs) that involve a substantial number of patients without any bias [8]. However, it has been highlighted that large efficacy RCTs, which are essential to show that novel treatments are effective and safe during

research and development programmes, have clear limitations related to the transferability of their conclusions to usual care mainly because the enrolled patients are selected and not representative of the population encountered in daily practice; moreover, the research environment is substantially different from that of the real world [9].

To support this concept, there are data from the Salford Lung Study, a 12-month open-label effectiveness RCT conducted in UK primary care that evaluated the effectiveness and safety of initiating fluticasone furoate/vilanterol 100/25 µg once daily compared with continuing COPD maintenance therapy (usual care) [10]. This study documented that the mean annual rates of moderate or severe AECOPDs, but not severe AECOPDs, and the incidence of overall severe adverse events (SAEs), including fatal SAEs and pneumonia SAEs, were substantially higher in both arms compared with the efficacy RCTs [9]. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

THE VALUE OF META-ANALYSES

The limitations in transferability of conclusions of RCTs to usual care indicate that these conclusions should not be included into routine care guidelines without careful consideration [11]. In effect, a full evaluation of any new treatment also needs effectiveness data generated in large unselected populations in everyday clinical practice [11].

Alternatively, even considering the scarcity of such data, the possibility of using meta-analyses can be taken into account. Meta-analysis can be considered as a systematic evaluation of all studies that have been conducted to answer a specific question or hypothesis [12]. A quantitative synthesis of the currently available data via meta-analysis allows providing consistent and homogeneous estimates after having evaluated the consistency/variability of the results between the primary studies included in the review (i.e., the between-study heterogeneity), investigated the causes of any observed

heterogeneity (i.e., through subgroup or meta-regression analyses) to improve scientific understanding, calculated a summary effect size along with a confidence interval and assessed the robustness of the cumulative effect size through sensitivity analyses and formal evaluations of the potential sources of study bias, including publication bias, that stem from the primary studies and might have an impact on the calculated summary effect [13, 14].

However, many consider the research synthesists in medicine as 'research parasites' of primary studies, although it could be argued that primary studies without context, comparison or summary are ultimately of limited value [12]. Nevertheless, it has recently been authoritatively stated that 'Research parasites can serve to increase scientific diversity by adding another "trophic level", thus improving the functioning of the scientific "ecosystem"' [15].

Obviously, meta-analyses must be transparent, reproducible and updatable, and focused on well-defined questions. They must satisfy all the recommended items reported by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-P 2015 checklist, which means the use of a formal methodological approach for the literature search, study screening (including critical appraisal of eligible studies according to pre-defined criteria), data extraction, coding and often statistical analysis, along with detailed, transparent documentation of each step [16].

META-ANALYSES EVALUATING TRIPLE THERAPY IN COPD

Meta-analyses and real-life retrospective analyses seem to support the use of triple therapy using multiple inhalers in patients with COPD [17]. Recently, several meta-analyses have attempted to clarify the role of triple therapy delivered from a single inhaler in COPD also because they have been able to include the results of the RCTs with triple therapy that have gradually been released to the scientific community.

The meta-analysis of Zheng and colleagues, which searched for the data to be included in the analysis up to 13 April 2018, was the first to

be published [18]. It included 21 trials (19 papers). Compared with dual bronchodilation with LABA and LAMA, triple therapy significantly reduced the rates of moderate or severe AECOPDs and improved the trough FEV₁ and mean St. George's Respiratory Questionnaire (SGRQ) total score; it was associated with significantly increased risk of pneumonia but not with all-cause mortality, and increased risk of AEs, SAEs and cardiovascular events. Compared with dual therapy with ICS and LABA, triple therapy significantly reduced the rates of moderate or severe AECOPDs and the number of patients with at least one moderate or severe AECOPD, prolonged the time to the first moderate or severe AECOPD and was associated with significant improvements in trough FEV₁ and mean SGRQ total score. No statistically significant associations were found for all-cause mortality, increased risk of AEs, SAEs, cardiovascular events or pneumonia events.

Soon after, we published a meta-analysis, which included relevant studies available up to 30 May 2018, and compared triple therapy delivered from a single inhaler or using multiple inhalers with dual bronchodilator therapy [19]. Triple therapy was significantly better than LABA/LAMA combination in reducing the risk of moderate or severe AECOPD and improving trough FEV₁ from baseline and mean SGRQ score, whereas there were no significant differences in the risk of pneumonia. The person-based number needed to treat (NNT) per year of ICS/LABA/LAMA combination versus LABA/LAMA combination was ≈ 38 , but it was significantly lower in patients with ≥ 300 eosinophils· μl^{-1} than in those with < 300 eosinophils· μl^{-1} . The protective effect of ICS/LABA/LAMA therapy versus LABA/LAMA therapy for the risk of moderate or severe AECOPD was greater in patients with higher blood eosinophil counts, ranging from a relative risk of 0.57 (95% CI 0.48–0.68) for counts of ≥ 400 cells· μl^{-1} to a relative risk of 0.70 (95% CI 0.62–0.80) for counts of ≥ 150 cells· μl^{-1} . The overall meta-regression analysis indicated that the blood eosinophil count was a significant effect modifier of ICS/LABA/LAMA therapy in preventing the risk of moderate or severe AECOPD.

In this meta-analysis, we also considered the risk of pneumonia and calculated the person-based number needed to harm (NNH) of ICS/LABA/LAMA therapy versus LABA/LAMA therapy [19]. The value was rather high, 195.34 (95% CI 85.06– ∞). However, in the subset analysis performed by examining the only RCT that included fluticasone furoate in the triple combination, the person-based NNH for ICS/LABA/LAMA therapy diminished to 33.89 (95% CI 30.69–37.84) versus LABA/LAMA therapy.

In another meta-analysis, we investigated the value of adding a LAMA to already consolidated ICS/LABA therapy [20]. The meta-analysis included 13 RCTs from 11 studies published between 2007 and 2018 with data obtained from 15,519 patients with COPD. Compared with ICS/LABA combination, ICS/LABA/LAMA combination improved trough FEV₁, protected against AECOPD, an effect that was not associated with the eosinophil level, and did not increase the risk of cardiovascular SAEs. The overall person-based NNT of ICS/LABA/LAMA combination versus ICS/LABA combination was 3.97 to have a patient with a ≥ 100 ml increase from baseline in trough FEV₁ and 26.07 concerning the protection against the risk of AECOPD.

The fourth meta-analysis that compared triple inhaler therapy (ICS/LABA/LAMA) with dual inhaler therapy (ICS/LABA or LABA/LAMA), excluded studies that had compared the effect of ICS de-escalation or withdrawal as both treatment arms had received a triple inhaler before de-escalation to dual therapy and this could affect the result [21]. It included 12 RCTs totalling 19,322 patients. Pooled analysis demonstrated a significant reduction in moderate-to-severe AECOPDs with triple therapy. Additionally, triple therapy caused a significant increase in trough FEV₁ and significant reduction in the mean SGRQ score. Triple therapy was associated with a significant increase in pneumonia risk compared with LABA/LAMA, but there was no significant difference in the risk of pneumonia between triple therapy and ICS/LABA. Furthermore, there were no significant differences in other AEs between triple and dual combinations.

Since in all these meta-analyses the triple therapies included both single-inhaler triple therapy and separate triple therapies, the effects

of single-inhaler triple therapy in COPD were analysed in a further meta-analysis [22]. Seven studies with a total of 8757 COPD patients were included in the analysis. Single-inhaler triple therapy was associated with a significantly lower risk of AECOPD compared mainly with LABA/LAMA (rate ratio, 0.69), but also with ICS/LABA (rate ratio, 0.81) therapy, and it also induced a more significant improvement in lung function and quality of life compared with LABA/LAMA and ICS/LABA, although it was associated with a higher risk of pneumonia compared with LABA/LAMA (risk ratio, 1.38) therapy. In any case, single-inhaler triple therapy did not improve the overall mortality compared with the other treatment options.

In a more recent meta-analysis that excluded pilot or cohort studies, studies that evaluated de-escalation from triple to dual therapy, case-control studies, retrospective studies and subgroup analyses, 12 RCTs with 19,322 patients were included in the final evaluation [23]. Also this study showed a significant reduction in moderate-to-severe AECOPDs with triple therapy (rate ratio, 0.75), an increase in trough FEV₁ (0.09 l), significant reduction in the mean SGRQ score (−1.67) with more patients experiencing ≥ 4-point reduction of the SGRQ score and an increased risk of pneumonia compared with LABA/LAMA (odds ratio, 1.25).

WHAT DO THESE META-ANALYSES SUGGEST?

It is important to point out that much of our first meta-analysis was generated by data coming from the InforMing the PATHway of COPD Treatment (IMPACT) study, a large trial that enrolled 10,355 patients with COPD who were treated in a randomized manner for 52 weeks with a once-daily FDC of fluticasone furoate, vilanterol and umeclidinium, or fluticasone furoate and vilanterol or vilanterol and umeclidinium [24]. An analysis of the IMPACT trial explored the relationship of blood eosinophil counts with ICS therapy across different clinical outcomes including AECOPDs, lung function and health status [25]. There was an increase in AECOPD rates in the vilanterol/umeclidinium

group when the blood eosinophil count was increased, whereas this increase did not influence the rate of moderate and severe AECOPDs in ICS-containing treatment groups, though their reduction was larger when ICS was present. When ICS-containing treatments were compared with dual bronchodilation, there was an increasing effect size at higher baseline blood eosinophil counts for the transition dyspnea index (TDI) and SGRQ total score at week 52, but not for FEV₁, although the correlation was evocative of a similar effect. A greater effect of ICS at higher blood eosinophil counts for preventing AECOPDs requiring oral corticosteroids was noted, but with a substantial overlap in the treatment of AECOPDs with both antibiotics and oral corticosteroids. This finding supports the view that ICS treatment in patients with higher blood eosinophil counts is more effective for AECOPDs that are not associated with bacterial infections.

Since blood eosinophil counts ≥ 300 cells· μl^{-1} could allow recognizing patients with a higher probability of taking advantage of ICS treatment, great importance is given to the use of ICS/LABA combinations when blood eosinophils are ≥ 300 cells· μl^{-1} , but also when patients are at high risk of AECOPDs (history of two or more moderate AECOPDs or one severe AECOPD in the previous year at > 100 eosinophils· μl^{-1}) [8]. When the blood eosinophil count is < 100 cells· μl^{-1} , ICSs should not be administered unless patients are also asthmatic because at this value these drugs will probably not be able to prevent AECOPDs [26]. The real question is whether patients with 100–300 eosinophils· μl^{-1} in the blood should be treated with ICSs because there is no solid documentation supporting such an approach. It has been suggested that the decision to add an ICS should be based on considerations of probable benefits and possible risks in any single individual [26].

Suissa and Ariel [27] have pointed out that the lower rate of a first AECOPD with triple therapy observed in the IMPACT study [24] and also in the Extrafine Inhaled Triple Therapy versus Dual Bronchodilator Therapy in Chronic Obstructive Pulmonary Disease (TRIBUTE) study [28], which compared a single-inhaler

triple combination of beclomethasone dipropionate, formoterol and glycopyrronium versus indacaterol plus glycopyrronium FDC in terms of the rate of moderate-to-severe AECOPDs over 52 weeks of treatment and enrolled 1532 patients who were symptomatic with severe or very severe airflow limitation and had at least one moderate or severe AECOPD in the previous year, was entirely due to a lower rate in the 1st month of follow-up, while the rate was comparable to LABA/LAMA in the subsequent 11 months. They defined this trend as a 'depletion of susceptibles'. In their opinion, this pattern implies that there is a subgroup of patients who could benefit from triple therapy, while all other patients derive the same benefit from LABA/LAMA. Especially the history of asthma and the prior use of ICS that is withdrawn at randomization should be considered critical factors in identifying such subgroups of responders.

Furthermore, they highlighted that the difference in the rate of death per month over time for the IMPACT trial was restricted in the first 4 months of follow-up. It is their opinion that this early mortality pattern corresponds to the one from a Canadian cohort of > 30,000 asthmatic patients in which suspending ICS treatment increased asthma mortality as a function of time since ICS discontinuation, mostly observed in the first 3 months after suspension, in which the risk of death increased over four-fold [29].

However, Papi and colleagues [30] performed a post hoc analysis of TRIBUTE and observed that triple therapy not only prolonged the combined estimate of time to exacerbation versus LAMA/LABA but the effect size increased for multiple events, with the effect on the third exacerbation reaching statistical significance. Furthermore, the subgroup that gained most benefit from triple therapy over the duration of the study was the group in which patients were not receiving ICS prior to study entry. The authors therefore stressed, correctly in our opinion, that according to the suggestions of Suissa and Ariel [27], ICS withdrawal might be considered in the first month of treatment with triple therapy, but we do not know whether withdrawing ICS could trigger subsequent exacerbations at a later time.

The higher risk of pneumonia with fluticasone furoate that appeared in our first meta-analysis [19] should indicate that this is the only ICS that really induces the occurrence of pneumonia. However, it must be considered that the IMPACT study enrolled high-risk 2011 GOLD D COPD patients, all having had at least two AECOPDs or at least one AECOPD with a $FEV_1 < 50\%$ in the previous year [24]. Correctly, it has been pointed out that differences in the rate of pneumonia observed in studies with fluticasone, beclomethasone or budesonide may vary for reasons other than the ICS used [26]. Actually, differences in study design or AE reporting and characteristics of the population studied (oldness, lower body mass index, more severe airflow limitation, recurrent AECOPDs, low blood eosinophil counts and higher ICS doses) are all factors that have the potential to influence the risk of pneumonia and, in any case, while the risk appears lower for budesonide, it is critical to consider that the budesonide trials were shorter, and so they must be considered less precise [26]. In particular, the Randomized, Double-Blind, Parallel-Group, 24-Week, Chronic-Dosing, Multi-Center Study to Assess the Efficacy and Safety of PT010, PT003, and PT009 Compared With Symbicort® Turbuhaler (KRONOS) study [31], which demonstrated that single-inhaler triple therapy with budesonide/formoterol/glycopyrronium improved lung function with a very low rate of pneumonia compared with budesonide/formoterol therapy, lasted 24 weeks, enrolled 2011 GOLD B patients, with about 75% of them without any moderate or severe AECOPD in the previous year also because no AECOPD in the previous year was required.

Considering the results of the meta-analyses described in this article, we believe that triple combination therapy offers only a further modest clinical benefit in the general COPD population, but it is clinically important when a patient is on LABA/LAMA therapy and still suffers from AECOPD and has blood eosinophil counts ≥ 300 cells· μl^{-1} [32]. On the contrary, adding a LAMA to an ICS/LABA combination induces relevant clinical benefit in the general COPD population without increasing the risk of cardiovascular SAEs that should always be possible when a LAMA is added to the combination [32].

Obviously, our opinion may have to change when the data from the Study to Assess the Efficacy and Safety of PT010 Relative to PT003 and PT009 in Subjects With Moderate to Very Severe COPD (ETHOS) study are fully available and included in a new meta-analysis. The ETHOS study has compared two doses of single-inhaler triple therapy with budesonide/formoterol/glycopyrrolate 320/9.6/18 µg and 160/9.6/18 µg formoterol/glycopyrrolate 18/9.6 µg and budesonide/formoterol 320/9.6 µg, all formulated using a new co-suspension delivery technology. It has included 8572 symptomatic patients with moderate-to-very severe COPD and a history of AECOPD(s) [33]. Baseline demographics showed that 55.9% of patients had experienced ≥ 2 moderate/severe AECOPDs in the previous year, 79.1% were receiving an ICS-containing treatment at study entry, and 59.9% had blood eosinophil counts ≥ 150 cells/ μl^{-1} . According to a preliminary report, this triple therapy showed statistically significant improvements in moderate-to-very severe COPD even at half the budesonide dose [34].

It is likely, however, that the addition of the ETHOS study data will not greatly change our conclusions based on the already published meta-analyses. In any case, we believe that these meta-analyses allow us to better allocate triple therapy in the context of COPD management. Also, we must point out that while meta-analyses have progressed as a technique to be helpful for summarizing a large number of RCTs and for overcoming the incongruities raised by those trials, they deal with populations and not with single individuals. Thus, we strongly believe that clinicians must use clinical judgement when applying the conclusions of this and other studies to the individual patient.

In any case, the step-up approach from dual bronchodilation to triple therapy proposed by the GOLD strategy [5] does not reflect the important differences in AECOPDs (they differ in aetiology, severity and biological substrate), and thus it is not tailored on the patient's specific needs to be treated [35, 36]. Furthermore, we must ascertain the COPD phenotype so that addition of an ICS to the LABA/LAMA therapy offers real additional clinical value,

regardless of a preventive effect on AECOPDs, and verify what kind of benefit it is, or whether dual bronchodilation must be preferred also because it should be a less expensive treatment in real life [36]. In effect, Fabbri and colleagues [37] have pointed out that the single-inhaler triple therapy versus inhaled corticosteroid plus long-acting β 2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY) [38] and single-inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY) [39] studies have shown that triple therapy is effective in patients currently defined as GOLD severity B (i.e., highly symptomatic but at low risk of exacerbations, for whom long-acting bronchodilators alone or in combination, but no combination that includes ICS, are still recommended [5]).

Finally, it seems fair to point out that, although we believe that the term asthma-COPD overlap (ACO) should be abandoned because it does not identify a clearly independent disease entity and rather indicates asthmatic patients who have smoked or still smoke [39], the view of many specialists is that it is correct to treat patients with ACO who remain symptomatic or suffer from frequent exacerbations with triple therapy despite initial inhaler therapy [40]. A recent pilot study, which compared the efficacy of LAMA/ICS/LABA triple therapy with ICS/LABA dual therapy, showed that 4-week once-daily treatment of ACO patients with umeclidinium 62.5 µg added to fluticasone furoate/vilanterol 200/25 µg produced significant improvements from baseline in lung function compared with once-daily treatment with fluticasone furoate/vilanterol µg alone [41]. It is obvious that more and larger studies are needed to validate such an approach, also possibly using a meta-analytical approach.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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