Triple therapy in the management of chronic obstructive pulmonary disease: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE
To compare the rate of moderate to severe exacerbations between triple therapy and dual therapy or monotherapy in patients with chronic obstructive pulmonary disease (COPD).

DESIGN
Systematic review and meta-analysis of randomised controlled trials.

DATA SOURCES
PubMed, Embase, Cochrane databases, and clinical trial registries searched from inception to April 2018.

ELIGIBILITY CRITERIA
Randomised controlled trials comparing triple therapy with dual therapy or monotherapy in patients with COPD were eligible. Efficacy and safety outcomes of interest were also available.

DATA EXTRACTION AND SYNTHESIS
Data were collected independently. Meta-analyses were conducted to calculate rate ratios, hazard ratios, risk ratios, and mean differences with 95% confidence intervals. Quality of evidence was summarised in accordance with GRADE methodology (grading of recommendations assessment, development, and evaluation).

RESULTS
21 trials (19 publications) were included. Triple therapy consisted of a long acting muscarinic antagonist (LAMA), long acting β2 agonist (LABA), and inhaled corticosteroid (ICS). Triple therapy was associated with a significantly reduced rate of moderate or severe exacerbations compared with LAMA monotherapy (rate ratio 0.71, 95% confidence interval 0.60 to 0.85), LAMA and LABA (0.78, 0.70 to 0.88), and ICS and LABA (0.77, 0.66 to 0.91). Trough forced expiratory volume in 1 second (FEV1) and quality of life were favourable with triple therapy. The overall safety profile of triple therapy is reassuring, but pneumonia was significantly higher with triple therapy than with dual therapy of LAMA and LABA (relative risk 1.53, 95% confidence interval 1.25 to 1.87).

CONCLUSIONS
Use of triple therapy resulted in a lower rate of moderate or severe exacerbations of COPD, better lung function, and better health related quality of life than dual therapy or monotherapy in patients with advanced COPD.

Study Registration
Prospero CRD42018077033.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Triple therapy with long acting muscarinic antagonists (LAMA), long acting β2 agonists (LABA), and inhaled corticosteroids (ICS) are commonly used in patients with chronic obstructive pulmonary disease (COPD).

Meta-analyses have previously shown that triple therapy using multiple inhalers can improve forced expiratory volume in 1 second (FEV1) and health status, but evidence of triple therapy versus dual therapy for preventing exacerbations is not well documented.

WHAT THIS STUDY ADDS

In a meta-analysis of 21 trials, moderate to high quality evidence indicated that use of triple therapy significantly decreased the risk of moderate or severe COPD exacerbations compared with dual therapy (of ICS and LABA, or LAMA and LABA) or LAMA monotherapy, together with improvements in lung function, and in a range of other clinically relevant measures.

Triple therapy should be limited to patients with more severe COPD symptoms that cannot be adequately managed by dual therapy.

Results suggested that triple therapy delivered in a single inhaler is non-inferior to the use of multiple inhaler in terms of clinical efficacy, but this needs further examination.
matter. Therefore, in the present study, we performed a meta-analysis to examine eligible randomised controlled trials assessing the effect of triple inhaled therapy on the risk of exacerbation, and to obtain more comprehensive, accurate, and precise results about this effect.

Methods
The present study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. This study was prospectively registered in Prospero (https://www.crd.york.ac.uk/PROSPERO/; CRD42018077033).

Search strategy and selection criteria
An independent review of the PubMed, Embase, Cochrane Library website, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov databases was performed from inception to 18 February 2018 (updated on 13 April 2018). The search was conducted with the following keywords: long acting β2 agonists (salmeterol, indacaterol, vilanterol, formoterol, olodaterol), long acting antimuscarinics (glycopyrronium, umeclidinium, aclidinium, tiotropium), inhaled corticosteroids (budesonide, fluticasone, beclomethasone, mometasone, ciclesonide), QVA149, Ultibro, Anoro, Duaklir, Spiolto, and chronic obstructive pulmonary disease (COPD). We reviewed reference lists of all primary studies and review articles for additional references. When a duplicate publication of the same trial was found, the study with the most complete, recent, and updated report was included.

Studies that met the following criteria were included in the analysis:
- Patients: stable, moderate to very severe COPD (FEV1 <80% of predicted value)
- Intervention: triple therapy (of LABA, LAMA, and inhaled corticosteroids)
- Control: dual therapy (of LABA and LAMA, LABA and inhaled corticosteroids, or LAMA and inhaled corticosteroids) or monotherapy (LAMA, LABA, or inhaled corticosteroids)
- Primary outcome: moderate or severe exacerbation
- Other efficacy outcomes: severe exacerbations, death, FEV1, safety (adverse events, serious adverse events, pneumonia and cardiovascular events), and quality of life (St George’s respiratory questionnaire [SGRQ] score)
- Study: prospective randomised trials with a duration of at least four weeks.

Data extraction
Data were independently extracted by two reviewers, and the results were compared to avoid bias from the data extraction process. We extracted the following characteristic information from each study: participants (sample size, mean age, sex, baseline lung function), interventions (intervention treatment and inhaler type, control treatment and inhaler type), outcomes (exacerbations, severe exacerbations, death, adverse events, serious adverse events, pneumonia and cardiovascular events, mean change of FEV1, and SGRQ score), and design (study design, withdrawals, and duration of follow-up). If the data were not reported in the original article, we extrapolated them from the accompanying graphs or ClinicalTrials.gov.

Assessment of risk of bias in included studies
We assessed the study quality of each included study with the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions. We took into account the following items: allocation sequence generation, concealment of allocation, blinding of participants and investigators, incomplete outcome data, selective outcome reporting, and other sources of bias. The risk of bias was examined by two reviewers concurrently, and discrepancies were resolved by consensus.

Data analysis
We performed all statistical analyses using the Stata software (version 12.0). We clarified the metric of analysis for primary outcome (moderate or severe exacerbation) as the following: exacerbation rates per patients per year or during follow-up (effect measure: rate ratio), number of patients with at least one exacerbation (effect measure: risk ratio), and time to first exacerbation (effect measure: hazard ratio). Risk ratios and their associated 95% confidence intervals were used as the effect measures for the outcomes of death and safety, mean differences with corresponding 95% confidence intervals were used as the effect measures for continuous outcomes (FEV1 and SGRQ score).

Statistical heterogeneity was assessed with the Q test and I^2 statistic. I^2 values of more than 50% were considered to represent significant heterogeneity, whereby the random effects model was used; in all other cases, the fixed effects model was used. We intended to explore potential causes of heterogeneity for effectiveness and safety data on the basis of duration of follow-up (<6 vs ≥6 months) and eosinophil level. We did a sensitivity analysis by excluding trials at high risk of bias. Potential publication bias was evaluated by funnel plots when 10 or more trials were pooled. All statistical analyses were two sided, and a P value of less than 0.05 was regarded as statistically significant. We also used the GRADE approach (grading of recommendations assessment, development, and evaluation) to rate the quality of evidence and generate absolute estimates of effect for the outcomes.

Patient involvement
No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the
research to study participants or the relevant patient community.

**Results**

**Eligible studies and characteristics**

Of 931 articles obtained from the initial search of the databases, 21 randomised controlled trials (19 publications) were included in the final analysis. Excluded studies are summarised in the appendix. Detailed baseline characteristics of the included randomised controlled trials are summarised in table 1, and patient inclusion criteria of included trials were summarised in eTable 1. Six trials used fixed triple therapy (LAMA, LABA, and inhaled corticosteroids contained in one inhaler), and 15 trials used separate triple therapy (three treatments used with different inhalers). Two studies reported twin trials as a pooled result. The duration of the studies ranged from eight to 52 weeks. Two studies directly compared fixed triple therapy with open triple therapy. Most of the studies were judged to have a low risk of bias according to the Cochrane instrument (fig 2 and fig 3). COPD exacerbation was defined as a sustained worsening of respiratory symptoms that were mild (self managed by the patient), moderate (requiring oral or systemic corticosteroids or antibiotics (or both)), or severe (requiring hospital admission or resulting in death).

**Triple therapy versus LAMA**

Ten trials compared triple therapy with LAMA monotherapy in patients with COPD, and the main outcomes and quality of evidence are summarised in table 2. Compared with LAMA monotherapy, triple therapy significantly reduced the rates of moderate or severe exacerbation (rate ratio 0.71, 95% confidence interval 0.60 to 0.85; eFigure 1A), reduced the number of patients with one or more moderate to severe exacerbations (risk ratio 0.74, 95% confidence interval 0.56 to 0.97; eFigure 1B), and prolonged time to first moderate or severe exacerbations (hazard ratio 0.69, 95% confidence interval 0.54 to 0.88; eFigure 1C). Triple therapy significantly decreased the rate of severe exacerbation (rate ratio 0.58, 0.47 to 0.72; eFigure 2A). We found no statistically significant associations for all cause mortality (eFigure 2B). Use of triple therapy was associated with significant improvements in trough FEV1 (mean difference 0.07, 0.06 to 0.08; eFigure 2C) and mean SGRQ total score (−2.78, −3.87 to −1.70; eFigure 2D).

Compared with LAMA monotherapy, triple therapy was not associated with increased risk of adverse events, cardiovascular events, and pneumonia events, but was associated with a decreased risk of serious adverse events (eFigures 3-6).

**Triple therapy versus LAMA and LABA**

Three trials compared triple therapy with LAMA/LABA dual therapy in patients with COPD, with the main outcomes and quality of evidence summarised in table 2. Compared with dual therapy of LAMA and LABA, triple therapy significantly reduced the rates of moderate or severe exacerbations (rate ratio 0.78, 95% confidence interval 0.70 to 0.88; eFigure 1A), and prolonged time to first moderate or severe exacerbations (hazard ratio 0.85, 95% confidence interval 0.79 to 0.91; eFigure 1C). Triple therapy significantly decreased the rate of severe exacerbation (risk ratio 0.68, 95% confidence interval 0.59 to 0.78; eFigure 2A). No statistically significant associations were found for all cause mortality (eFigure 2B). Triple therapy was associated with significant improvements in trough FEV1 (mean difference 0.04, 95% confidence interval 0.02 to 0.07; eFigure 2C) and mean SGRQ total score (−1.81, −2.57 to −1.04; eFigure 2D). Compared with dual therapy of LAMA and LABA, triple therapy was not associated with increased risk of adverse events, serious adverse events, or cardiovascular events, but was associated with significantly increased risk of pneumonia events (eFigures 3-6).

**Triple therapy versus inhaled corticosteroids and LABA**

Eleven trials compared triple therapy with dual therapy of inhaled corticosteroids and LABA in patients with COPD, with the main outcomes and quality of evidence summarised in table 2. Compared with the dual therapy of inhaled corticosteroids and LABA, triple therapy significantly reduced the rates of moderate or severe exacerbations (rate ratio 0.77, 95% confidence interval 0.66 to 0.91; eFigure 1A), reduced the number of patients with at least one moderate or severe exacerbation (risk ratio 0.76, 95% confidence interval, 0.62 to 0.93; eFigure 1B), and prolonged time...
Table 1 | Characteristics of studies evaluating triple inhaled therapy

<table>
<thead>
<tr>
<th>Study (first author, year)</th>
<th>Intervention (dose/day)</th>
<th>Triple therapy</th>
<th>No of patients</th>
<th>Mean Age (years)</th>
<th>Male (%)</th>
<th>FEV1 Trough (L) Proportion (%) of predicted value</th>
<th>Follow-up (weeks)</th>
<th>Industry funded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aaron, 2007</td>
<td>FP 1000 µg, SAL 100 µg, TIO 18 µg Separate inhalers</td>
<td>145</td>
<td>67.5</td>
<td>57.9</td>
<td>1.05</td>
<td>39.4</td>
<td>52</td>
<td>No</td>
</tr>
<tr>
<td>Cazzola, 2007\textsuperscript{21}</td>
<td>FP 1000 µg, SAL 100 µg, TIO 18 µg Separate inhalers</td>
<td>26</td>
<td>68.1</td>
<td>53.8</td>
<td>1.01</td>
<td>38.7</td>
<td>12</td>
<td>NA</td>
</tr>
<tr>
<td>Hanania, 2012\textsuperscript{22}</td>
<td>FP 500 µg, SAL 100 µg, TIO 18 µg Separate inhalers</td>
<td>173</td>
<td>61.3</td>
<td>50</td>
<td>1.70</td>
<td>NA</td>
<td>24</td>
<td>Yes</td>
</tr>
<tr>
<td>Hoshino, 2011\textsuperscript{23}</td>
<td>FP 500 µg, SAL 100 µg, TIO 18 µg Separate inhalers</td>
<td>14</td>
<td>73.0</td>
<td>87.5</td>
<td>1.36</td>
<td>64.6</td>
<td>12</td>
<td>NA</td>
</tr>
<tr>
<td>Hoshino, 2013\textsuperscript{24}</td>
<td>FP 500 µg, SAL 100 µg, TIO 18 µg Separate inhalers</td>
<td>16</td>
<td>73.0</td>
<td>88.7</td>
<td>1.75</td>
<td>39.4</td>
<td>12</td>
<td>NA</td>
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<tr>
<td>Jung, 2012\textsuperscript{25}</td>
<td>FP 500 µg, SAL 100 µg, TIO 18 µg Separate inhalers</td>
<td>223</td>
<td>67.0</td>
<td>97.3</td>
<td>1.22</td>
<td>47.4</td>
<td>24</td>
<td>Yes</td>
</tr>
<tr>
<td>Lee, 2016\textsuperscript{26}</td>
<td>BUD 640 µg, FOR 18 µg, TIO 18 µg Separate inhalers</td>
<td>287</td>
<td>66.6</td>
<td>97.2</td>
<td>1.35</td>
<td>64.6</td>
<td>12</td>
<td>Yes</td>
</tr>
<tr>
<td>Maltais, 2013\textsuperscript{27}</td>
<td>FP 500 µg, SAL 100 µg, TIO 18 µg Separate inhalers</td>
<td>14</td>
<td>73</td>
<td>86.7</td>
<td>1.38</td>
<td>NA</td>
<td>16</td>
<td>Yes</td>
</tr>
<tr>
<td>Vestbo, 2017\textsuperscript{8}</td>
<td>BDP 400 µg, FOR 24 µg, GLY 50 µg Fixed inhaler</td>
<td>1077</td>
<td>63.4</td>
<td>77</td>
<td>1.1</td>
<td>36.6</td>
<td>52</td>
<td>Yes</td>
</tr>
<tr>
<td>Welte, 2009\textsuperscript{28}</td>
<td>FP 1000 µg, SAL 100 µg, TIO 18 µg Separate inhalers</td>
<td>148</td>
<td>67.6</td>
<td>57.4</td>
<td>1.00</td>
<td>38.0</td>
<td>24</td>
<td>Yes</td>
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<tr>
<td>Cazzola, 2007\textsuperscript{21}</td>
<td>FP 1000 µg, SAL 100 µg, TIO 18 µg Separate inhalers</td>
<td>26</td>
<td>68.1</td>
<td>53.8</td>
<td>1.01</td>
<td>38.7</td>
<td>12</td>
<td>NA</td>
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<tr>
<td>Frith, 2015\textsuperscript{29}</td>
<td>FP 1000 µg, SAL 100 µg, GLY 50 µg Separate inhalers</td>
<td>257</td>
<td>68.2</td>
<td>63.4</td>
<td>1.52</td>
<td>57.3</td>
<td>12</td>
<td>Yes</td>
</tr>
<tr>
<td>Hoshino, 2013\textsuperscript{24}</td>
<td>FP 500 µg, SAL 100 µg, TIO 18 µg Separate inhalers</td>
<td>16</td>
<td>67</td>
<td>81.3</td>
<td>1.25</td>
<td>NA</td>
<td>16</td>
<td>Yes</td>
</tr>
<tr>
<td>Lipson, 2017\textsuperscript{30}</td>
<td>FF 100 µg, UMEC 625 µg, VI 25 µg Separate inhalers</td>
<td>2070</td>
<td>65.2</td>
<td>66</td>
<td>NA</td>
<td>45.4</td>
<td>52</td>
<td>Yes</td>
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<td>Lipson 2018\textsuperscript{9}</td>
<td>FF 100 µg, UMEC 625 µg, VI 25 µg Separate inhalers</td>
<td>911</td>
<td>64.2</td>
<td>74</td>
<td>1.35</td>
<td>45.5</td>
<td>52</td>
<td>Yes</td>
</tr>
<tr>
<td>Lipson 2018\textsuperscript{9}</td>
<td>FF 100 µg, UMEC 625 µg, VI 25 µg Separate inhalers</td>
<td>4151</td>
<td>65.3</td>
<td>67</td>
<td>NA</td>
<td>45.5</td>
<td>52</td>
<td>Yes</td>
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<tr>
<td>Siler, 2015A\textsuperscript{30}</td>
<td>FP 500 µg, SAL 100 µg, UMEC 125 µg Separate inhalers</td>
<td>205</td>
<td>63.2</td>
<td>69</td>
<td>1.35</td>
<td>46.7</td>
<td>12</td>
<td>Yes</td>
</tr>
<tr>
<td>Siler, 2015B\textsuperscript{30}</td>
<td>FP 500 µg, SAL 100 µg, UMEC 62.5 µg Separate inhalers</td>
<td>205</td>
<td>63.4</td>
<td>64</td>
<td>1.31</td>
<td>47.4</td>
<td>12</td>
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<tr>
<td>Siler, 2015C\textsuperscript{31}</td>
<td>FP 500 µg, SAL 100 µg, UMEC 125 µg Separate inhalers</td>
<td>207</td>
<td>63.8</td>
<td>61</td>
<td>1.16</td>
<td>44.8</td>
<td>12</td>
<td>Yes</td>
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<tr>
<td>Singh, 2016\textsuperscript{32}</td>
<td>BDP 400 µg, FF 24 µg, GLY 50 µg Fixed inhaler</td>
<td>687</td>
<td>63.3</td>
<td>74</td>
<td>1.11</td>
<td>36.9</td>
<td>52</td>
<td>Yes</td>
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<tr>
<td>Sousa, 2016\textsuperscript{33}</td>
<td>ICS, LABA, UMEC 62.5 µg Separate inhalers</td>
<td>119</td>
<td>65.2</td>
<td>83</td>
<td>1.33</td>
<td>47.6</td>
<td>12</td>
<td>Yes</td>
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<tr>
<td>Brenner, 2018\textsuperscript{34}</td>
<td>FF 100 µg, UMEC 62.5 µg, VI 25 µg Separate inhalers</td>
<td>527</td>
<td>66.7</td>
<td>74</td>
<td>1.25</td>
<td>44.5</td>
<td>24</td>
<td>Yes</td>
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<tr>
<td>Vestbo, 2018\textsuperscript{35}</td>
<td>BDP 400 µg, FOR 24 µg, GLY 50 µg Fixed inhaler</td>
<td>1077</td>
<td>63.4</td>
<td>77</td>
<td>1.1</td>
<td>36.6</td>
<td>52</td>
<td>Yes</td>
</tr>
</tbody>
</table>

LAMA=long acting muscarinic receptor antagonist; LABA=long acting β2 adrenoreceptor agonist; ICS=inhaled corticosteroids; FP=fluticasone; SAL=salmeterol; TIO=tiotropium; BDP=beclometasone dipropionate; FF=formoterol fumarate; GLY=glycopyrronium; UMEC=umeclidinium; VI=vilanterol; BUD=budesonide; FOR=formoterol; IND=indacaterol; NA=not available; FEV1=forced expiratory volume in one second.
to the first moderate or severe exacerbation (hazard ratio 0.84, 95% confidence interval 0.79 to 0.90; eFigure 1C). Triple therapy significantly decreased the rate of severe exacerbation (risk ratio 0.87, 95% confidence interval 0.75 to 1.00; eFigure 2A). No statistically significant associations were found for all-cause mortality (eFigure 2B). Triple therapy was associated with significant improvements in trough FEV1 (mean difference 0.11, 95% confidence interval 0.10 to 0.13; eFigure 2C) and mean SGRQ total score (−1.81, −2.28 to −1.35; eFigure 2D). Compared with the dual therapy, triple therapy was not associated with increased risk of adverse events, serious adverse events, cardiovascular events, or pneumonia events (eFigures 3-6).

Fixed triple therapy versus separate triple therapy
Two trials compared fixed triple therapy with separate triple therapy directly. We found no statistically significant associations for all the outcomes (table 2, eFigures 1-6).

Subgroup and sensitivity analysis
Subgroup analysis based on duration of follow-up did not suggest any substantial associations with either triple therapy versus dual therapy of inhaled corticosteroids and LABA, or triple therapy versus LAMA only (eTable 3). Descriptive analysis by subgroup of eosinophil counts suggested that blood eosinophil counts were a useful biomarker for predicting which patients were most likely to respond to the triple inhaled therapy (eTable 4). After exclusion of trials with a high risk of bias, the overall findings remained consistent (eTable 5).

Publication bias
We used funnel plots to access the publication bias, and these results did not show any evidence of obvious bias for the outcome of the number of patients with at least one moderate to severe exacerbation (triple therapy vs dual therapy of LABA and inhaled corticosteroids). However, the possibility of obvious publication bias cannot be excluded for the death outcomes (triple therapy vs dual therapy of LABA and inhaled corticosteroids; eFigure 7).
Despite the current widespread use of triple therapy in patients with COPD who have the highest symptom burden, there are few trials showing a sustained benefit on this treatment combination preventing exacerbations. In this meta-analysis of 21 trials, we found that triple therapy (of LABA, LAMA, and inhaled corticosteroids combined) was associated with a significantly larger reduction in the rate of moderate or severe COPD exacerbations than dual therapy (of LAMA and LABA).
LAMA and LABA, or inhaled corticosteroids and LABA) or monotherapy (LAMA only). Surrogate outcomes such as spirometry (FEV1) and quality of life (SGRQ score) were favourable, and the overall safety profile of triple therapy is reassuring, but pneumonia was significantly higher with triple therapy than with dual therapy of LAMA and LABA.

Comparison with other studies
Three meta-analyses have compared the efficacy and safety of tiotropium, LABA, and inhaled corticosteroid treatment compared with that of tiotropium only.5-7 All three studies revealed benefits for lung function and quality of life.5-7 However, the effect on exacerbation risk is not well documented, which was the focus of the present study. We also compared triple therapy with dual therapy (of LAMA and LABA or of inhaled corticosteroids and LABA), which had not been previously considered. The present review also describes the clinical efficacy of a triple therapy delivered in one inhaler, which had not been previously considered, and our results indicated that single inhalers were not inferior to separate inhalers.

Main findings and interpretation in light of evidence
Reductions in exacerbation and mortality risk are the most important outcomes in the management of COPD.1 Our results showed that triple therapy significantly reduced the risk of moderate or severe exacerbations compared with LAMA monotherapy and the dual therapies of inhaled corticosteroid and LABA and of LAMA and LABA. All cause mortality was not obviously decreased for triple therapy compared with other treatments. However, most trials did not exceed six months of duration, and thus were limited in the reporting of such final health outcomes. Spirometry is considered a core outcome to measure COPD severity, control, and response to treatment,3 and significant improvements in FEV1 were found to be associated with triple therapy. We did not access forced vital capacity because this outcome was seldom reported in the included trials. Moreover, the mean difference in SGRQ score, which is a preferred measurement of COPD control,34 showed a consistently positive association with triple therapy. Thus, triple therapy is favourable in the management of COPD in terms of the efficacy outcomes.

Safety results showed a higher incidence of pneumonia in the triple therapy group than in the group receiving dual therapy of LAMA and LABA, with a significant trend to increase pneumonia incidence when compared with LAMA monotherapy (which did not increase incidence significantly). It would be expected, as previous studies have been reported, that treatment including inhaled corticosteroids increases the risk of pneumonia compared with placebo.35 36 Triple therapy did not increase the risk of cardiovascular adverse events, which was consistent with previous meta-analyses suggesting that dual therapy of LAMA and LABA do not increase the risk of fatal cardiovascular events in patients with COPD compared with LAMA monotherapy or with dual therapy of inhaled corticosteroids and LABA.37 38 Some of the included trials could have excluded patients at cardiovascular risk. The observed decreased risk of serious adverse events with triple therapy compared with LAMA monotherapy could have been by chance.

Recently, single inhalers containing an inhaled glucocorticoid, LABA, and LAMA have been developed. Two trials compared the fixed triple therapy with separate triple therapy directly. Results from the TRINITY study found that the twice daily, single inhaler use of beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide combined was not inferior to twice daily use of beclometasone dipropionate, formoterol fumarate, and tiotropium with multiple inhalers.8 Similarly, another trial by Bremner and colleagues showed that single inhaler use of 100 μg fluticasone furoate, 62.5 μg umeclidinium, and 25 μg vilanterol was non-inferior to multiple inhaler use of 100 μg fluticasone furoate, 25 μg vilanterol, and 62.5 μg umeclidinium in patients with advanced COPD.13

In view of the high level of incorrect inhaler techniques seen in clinical practice,39 the availability of a single inhaler product could reduce the likelihood of inhaler use errors. Healthcare resource use data from the FULFIL trial suggest that, in a clinical trial setting over a 52 week timeframe, non-drug costs associated with the management of a single inhaler (containing LAMA, LABA, and inhaled corticosteroids) are lower than twice daily use of LABA and inhaled corticosteroids.40 Therefore, a single inhaler regimen of triple therapy offers a simplified dosing option that could improve patient adherence and outcomes, and reduce associated healthcare costs.

Where triple therapy sits in the stepwise approach to managing COPD is not yet known, but triple therapy is widely prescribed in clinical practice. Real life prescription data in the United Kingdom show that 32% of patients with COPD received triple therapy, of whom 19%, 28%, 37%, and 46% were classified as GOLD groups A, B, C, and D, respectively.41 The trials in the present meta-analysis included carefully selected patients, of whom many had severe or very severe airflow limitation, were symptomatic at screening despite treatment, and had had at least one documented exacerbation in the past year. In addition, the incidence of COPD exacerbations was low in both the triple therapy groups and control groups of the included trials (eFigure 1), which might imply that both treatments were effective in reducing the rate of COPD exacerbations. Considering that no survival benefit was associated with triple therapy, and increased risk of pneumonia was observed, our results might only apply to patients with symptomatic COPD, severe airflow limitation, and an exacerbation history, and any potential benefit could be lost if triple therapy is expanded to patients with mild COPD.

Therefore, careful identification of patients who might benefit most from triple therapy is required. The TRINITY trial suggested that the effect of triple therapy...
on exacerbation rate was greater in the subgroups with raised eosinophil concentrations. Similarly, the TRIBUTE trial indicated that triple therapy significantly reduced the exacerbation rate compared with dual therapy in patients with eosinophils of at least 2%, but not in those with eosinophils less than 2%. In addition, a post hoc analysis of IMPACT trial showed that the benefits of exacerbation reduction were observed regardless of the patients’ blood eosinophil levels at randomisation, with greater reduction in the subset of patients with eosinophil levels of at least 150 cells/µL. These findings indicated that blood eosinophil counts might be a useful biomarker for predicting patients most likely to respond to the triple inhaled therapy. Future research could more closely examine the association between eosinophil levels, patient characteristics, exacerbation history, and clinical outcomes of triple therapy.

Limitations
This study had several limitations. Firstly, patients used dual or triple therapies at baseline, so it is unknown whether the abrupt discontinuation of certain drugs could have contributed to our finding of a lower rate of exacerbations in the triple therapy group than in the monotherapy or dual therapy group. Although analysis was adjusted in some of the included trials, no subgroup analysis was done according to previous treatment. Secondly, because different LAMA, LABA, and inhaled corticosteroids from different devices and in different dosing regimens were used among the included trials, some of the improvements observed could therefore be due to differences in molecules, devices, or dosing regimens. Thirdly, all the included trials were efficacy trials, and there are no effectiveness trials on triple therapy. Future trials are needed to clarify the effectiveness or cost effectiveness of triple therapy in COPD. Finally, we saw a high level of heterogeneity between study results, especially for the primary outcomes, but the directions of effect sizes were consistent among included trials.

Conclusion
In this meta-analysis of patients with COPD, use of triple therapy resulted in a lower rate of moderate or severe COPD exacerbations and better lung function and health related quality of life than dual therapy (of inhaled corticosteroids and LABA or of LAMA and LABA) or LAMA monotherapy. However, triple therapy did not improve patients’ survival, and could increase the risk of pneumonia. Therefore, triple therapy should be limited to patients with more severe COPD symptoms that cannot be adequately managed by dual therapy. Attempts should be made to identify patients with COPD phenotypes (eg, eosinophil levels, patient characteristics, and exacerbation history) most likely to respond to the triple therapy.

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The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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5 Rojas-Reyes MX, Garcia Morales OM, Dennis RJ, Karner C. Combination inhaled steroid and long-acting beta,-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2016;6:CD008532.


Web appendix: Supplementary appendix