Triple versus LAMA/LABA combination therapy for patients with COPD: a systematic review and meta-analysis

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Abstract

Background: Recently, the addition of inhaled corticosteroid (ICS) to long-acting muscarinic antagonist (LAMA) and long-acting beta-agonist (LABA) combination therapy has been recommended for patients with COPD who have severe symptoms and a history of exacerbations because it reduces the exacerbations. In addition, a reducing effect on mortality has been shown by this treatment. However, the evidence is mainly based on one large randomized controlled trial IMPACT study, and it remains unclear whether the ICS add-on treatment is beneficial or not. Recently, a large new ETHOS trial has been performed to clarify the ICS add-on effects. Therefore, we conducted a systematic review and meta-analysis to evaluate the efficacy and safety including ETHOS trial.

Methods: We searched relevant randomized control trials (RCTs) and analyzed the exacerbations, quality of life (QOL), dyspnea symptom, lung function and adverse events including pneumonia and mortality, as the outcomes of interest.

Results: We identified a total of 6 RCTs in ICS add-on protocol (N = 13,579). ICS/LAMA/LABA treatment (triple therapy) significantly decreased the incidence of exacerbations (rate ratio 0.73, 95% CI 0.64–0.83) and improved the QOL score and trough FEV1 compared to LAMA/LABA. In addition, triple therapy significantly improved the dyspnea score (mean difference 0.33, 95% CI 0.18–0.48) and mortality (odds ratio 0.66, 95% CI 0.50–0.87). However, triple therapy showed a significantly higher incidence of pneumonia (odds ratio 1.52, 95% CI 1.16–2.00). In the ICS-withdrawal protocol including 2 RCTs, triple therapy also showed a significantly better QOL score and higher trough FEV1 than LAMA/LABA. Concerning the trough FEV1, QOL score and dyspnea score in both protocols, the differences were less than the minimal clinically important difference.

Conclusion: Triple therapy causes a higher incidence of pneumonia but is a more preferable treatment than LAMA/LABA due to the lower incidence of exacerbations, higher trough FEV1 and better QOL score. In addition, triple therapy is also superior to LABA/LAMA due to the lower mortality and better dyspnea score. However, these results should be only applied to patients with symptomatic moderate to severe COPD and a history of exacerbations.

Clinical Trial Registration: PROSPERO; CRD42020191978.

Keywords: Chronic obstructive pulmonary disease, Exacerbations, Inhaled corticosteroid, Mortality, Pneumonia
and worsen during exacerbations of COPD, which are associated with accelerated mortality [2]. To reduce the symptoms and the exacerbation, single or dual inhaled bronchodilators are recommended for the treatment depending on the severity. If the patients have severe symptoms and a history of exacerbations, the addition of inhaled corticosteroid (ICS) to long-acting muscarinic antagonist (LAMA) and long-acting beta-agonist (LABA) combination therapy has been recommended because it lowers the incidence of exacerbations [3]. Recently, a reduction of the mortality has also been shown by this treatment [4]. However, in severe COPD patients, the additional treatment of ICS could increase the incidence of pneumonia [3, 5, 6]. Therefore, a decision for the long-term use of ICS should be based on the total benefit for such patients.

Until now, five systematic reviews have been performed to evaluate the efficacy and safety of ICS add-on to LAMA/LABA treatment [7–11]. However, the included trials contain several biases, such as not using a single inhalation device [12], using different LABA between the comparison groups [13] or a short evaluation duration of only 24 weeks [14]. Therefore, the evidence from these systematic reviews is mainly from one large randomized controlled trial (RCT), the IMPACT study which was performed for 52 weeks using a single inhaler device [4], and it remains unclear whether the ICS add-on treatment is beneficial or not. Recently, a large new ETHOS trial has been performed to clarify the ICS add-on effects [15]. Therefore, we conducted a systematic review and meta-analysis to evaluate the efficacy and safety including ETHOS trial.

We searched relevant randomized control clinical trials and evaluated the efficacy and safety of ICS/LAMA/LABA (triple) versus LAMA/LABA therapy by measuring exacerbations, quality of life (QOL), dyspnea score, lung function and adverse events including pneumonia and mortality. We also compared the results of a meta-analysis of ICS add-on to LAMA/LABA (ICS add-on) with those in ICS withdrawal from triple therapy (ICS withdrawal).

Methods
Search strategy and eligibility criteria
This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance [16]. The study protocol was registered in the PROSPERO database (www.crd.york.ac.uk/prospero; registration number: CRD42020191978). We first set outcomes based on the clinical importance and then performed a systematic literature review. We searched and identified RCTs in MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) including PubMed, EMBASE databases and ClinicalTrials.gov in June 2020, using the search strategy provided in the on-line supplement [17]. Only publications in English were considered. As the inclusion criteria, participants had a diagnosis of COPD according to the GOLD report’s diagnostic criteria. Randomized controlled trials comparing triple with LAMA/LABA therapy were included if they evaluated any of our outcomes of interest for a treatment duration at least 12 weeks. Unblinded or cross-over studies were excluded from the analysis because of the unblinded bias or the short treatment duration.

Data collection and risk of bias assessment
At least two review authors (AK, MY, TI and NF) screened the titles and abstracts of all studies identified by the search strategy to check their eligibility. Next, full text assessments were performed to identify the studies for inclusion, and the data were retrieved from among the eligible studies. At least two review authors (AK, MY, TI and NF) assessed the risk of bias in the eligible studies according to the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0. If there were discrepancies in the data collection or assessment of the risk of bias, the review authors resolved the disagreements through a discussion.

Outcomes of interest
The included outcomes of interest in the current study were as follow: (i) exacerbations (number of patients experiencing one or more exacerbations per year or person-year), (ii) St George’s Respiratory Questionnaire (SGRQ) score change from the baseline, (iii) transitional dyspnea index (TDI) score change from the baseline, (iv) trough forced expiratory volume in one second (FEV1) change from the baseline, and (v) adverse events (total adverse events, serious adverse events, and pneumonia and mortality).

Statistical analysis
We analyzed the data for the exacerbations as the rate ratio, dichotomous data as Mantel–Haenszel odds ratios (ORs) and continuous data as mean difference with 95% confidence intervals (CIs) using the inverse variance (IV) test. Data were analyzed using Review Manager Software version 5.3 (Cochrane Library Software, Oxford, UK). We carefully checked whether the data were shown with standard deviation in each study and analyzed the data after conversion from standard error to standard deviation if the data were shown as standard error. Inconsistencies among the studies were assessed by the I² statistic test. Publication bias was examined using funnel plots and assessed visually when applicable. Subgroup analyses
were performed in the cause of mortality, the background of participants who had a history of exacerbations in previous year and ≥10 COPD Assessment Test (CAT) score and the blood eosinophil level. The quality of evidence was measured according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, and absolute estimates of the effect for the outcomes were also evaluated [18].

Results
Characteristics of selected studies
The search strategy yielded 632 candidate studies, excluding duplicates. After full-text assessment, we excluded 19 trials and finally identified a total of 6 RCTs eligible for the meta-analysis in the ICS add-on protocol (N = 13,579) and a total of 2 RCTs (N = 3538) in the ICS withdrawal protocol (Fig. 1 and Additional file 1:}

![Flow diagram of study selection](image-url)
Table S1). These studies were published from 2002 to 2020 and their characteristics are summarized in Table 1 and in the Additional file 1: Table S2, S3. The participants were at least 35 years of age, current or ex-smokers with a smoking history of 10 pack-years or more, and the severity of the disease was moderate to severe. The treatment period was 24 to 52 weeks. Concerning the history of exacerbations, six studies [4, 12, 13, 15, 19, 20] required a history of exacerbations in previous years, but two studies did not [14, 21]. Patients with current asthma were excluded in all eight studies, but a previous history of asthma was not excluded except in one study [20]. In the ICS add-on protocol, 65 – 80% of those in the trial’s population were taking ICS at screening (Additional file 1: Table S2).

Risk of bias
The risks of selection bias and performance bias were low. Unclear risk in the blinding of outcome assessment was found in four studies. Three trials had an unclear risk in the incomplete outcome data. In other biases, seven studies were contained unclear risk because the sponsors were all pharmaceutical companies (Additional file 1: Tables S4, S5). Concerning publication bias, funnel plots were not suitable for the assessment because they cannot be interpreted accurately if the number of studies is less than 10 [22]. Therefore, publication bias was assessed with our comprehensive on-line database searches and considered not to be seen.

Outcome assessments

Exacerbations
Four studies with 13,267 participants were included for the evaluation of exacerbations in the ICS add-on protocol. There was a significant decrease in the incidence of exacerbations with ICS/LAMA/LABA when compared with LAMA/LABA (rate ratio 0.73, 95% CI 0.64 to 0.83; P < 0.00001; I^2 = 78%; Fig. 2 and Additional file 1: Figure S1).

SGRQ score
Four studies with 10,779 participants were included for the evaluation of the SGRQ score in the ICS add-on protocol. There was a significant improvement in the SGRQ score change from the baseline with ICS/LAMA/LABA (mean difference 0.33, 95% CI 0.18 to 0.48; P < 0.00001; I^2 = 6%; Fig. 4). However, this difference was less than the MCID of 1.0 [23, 24].

TDI score
Three studies with 5521 participants were included for the evaluation of the TDI score in the ICS add-on protocol. There was a significant improvement in the TDI score change from the baseline with ICS/LAMA/LABA (mean difference 0.33, 95% CI 0.18 to 0.48; P < 0.00001; I^2 = 6%; Fig. 4). However, this difference was less than the MCID of 1.0 [23, 24].

Trough FEV_1
Two studies with 6079 participants were included for the evaluation of the trough FEV_1 in the ICS add-on protocol. Compared to LAMA/LABA, there was a significant increase in the trough FEV_1 with ICS/LAMA/LABA (mean difference 0.04, 95% CI 0.01 to 0.07; P = 0.02, I^2 = 86%; Fig. 5). However, this difference was less than the MCID of 0.05 to 0.10 L [23–25].

Adverse events
Five studies with 12,683 participants were included for the evaluation of adverse events in the ICS add-on protocol. There was no difference in the total adverse events between ICS/LAMA/LABA and LAMA/LABA (OR 1.03, 95% CI 0.93 to 1.15; P = 0.58; I^2 = 34%; Additional file 1: Figure S2). In the serious adverse events, there was also no difference between them (OR 0.95, 95% CI 0.87 to 1.04; P = 0.28; I^2 = 0%; Additional file 1: Figure S3).

Pneumonia events
Five studies with 12,683 participants were included for the evaluation of pneumonia events in the ICS add-on protocol. The treatment periods in the five studies were all 52 weeks. Compared to LAMA/LABA, there was a significant increase in the pneumonia events with ICS/LAMA/LABA (OR 1.52, 95% CI 1.16 to 2.00; P = 0.003; I^2 = 32%; Fig. 6).

Mortality
Five studies with 12,683 participants were included for the evaluation of mortality events in the ICS add-on protocol. The treatment periods in the five studies were all 52 weeks. The median incidence was 1.6% in ICS/LAMA/LABA and 2.3% in LAMA/LABA. The incidence was small, but the frequency with ICS/LAMA/LABA was significantly lower (OR 0.66, 95% CI 0.50 to 0.87; P = 0.003; I^2 = 0%; Fig. 7). In the sub-analysis of cause of mortality, fatal cardiovascular events with ICS/LAMA/LABA were significantly lower than those with LAMA/LABA (OR 0.50, 95% CI 0.31 to 0.80; P = 0.004; I^2 = 0%; Additional file 1: Figure S4).

Sub-analysis with history of exacerbations and CAT score
Sub-analysis was performed in the participants who had a history of exacerbations in the previous year and ≥ 10 CAT score, which is mainly included in the GOLD group D [3] (Additional file 1: Figure S5 – S10). When compared
### Table 1: Characteristics of included studies

| Study          | Treatment (µg)                                                                 | Number of subjects | Duration (weeks) | Key inclusion criteria                                                                 | Male (%) | Mean age (years) | Baseline FEV1 (%predicted) |
|----------------|-------------------------------------------------------------------------------|--------------------|------------------|--------------------------------------------------------------------------------------|----------|------------------|----------------------------|
| **ICS add-on protocol**                                                                                                                                  |
| Aaron 2007 O2MAL | Fluticasone 1000 Tiotropium 18 Salmeterol 100 (Separate inhalers) vs Tiotropium 18 Salmeterol 100 (Separate inhalers) | 145                | 52               | %FEV1 < 60%, ≥ 1 moderate or severe exacerbation in the previous year                  | 57.6     | 67.6             | 38.7                       |
| Ferguson 2018 KRONOS NCT02497001 | Budesonide 640 Glycopyrronium 36 Formoterol 19.2 (Fixed inhaler) vs Glycopyrronium 36 Formoterol 19.2 (Fixed inhaler) | 639                | 24               | %FEV1 ≥ 25%, < 80%, CAT ≥ 10, 40-80 yrs, ≥ 10PY Not required to have had an exacerbation within the preceding year | 70.4     | 65.0             | 50.2                       |
| Lipson 2018 IMPACT NCT02164513 | Fluticasone furoate 100 Umeclidinium 62.5 Vilanterol 25 (Fixed inhaler) vs Umeclidinium 62.5 Vilanterol 25 (Fixed inhaler) | 4151               | 52               | CAT ≥ 10, ≥ 40yrs a) %FEV1 <50%, ≥1 moderate or severe exacerbation b) %FEV1 ≥50%, <80%, ≥2 moderate or ≥1 severe exacerbation | 66       | 65.3             | 45.5                       |
| Papi 2018 TRIBUTE NCT02579850 | Beclometasone 174 Glycopyrronium 18 Formoterol 10 (Fixed inhaler) vs Glycopyrronium 43 Indacaterol 85 (Fixed inhaler) | 764                | 52               | %FEV1 < 50%, CAT ≥ 10, ≥ 40yrs, ≥ 10PY, At least 1 moderate or severe exacerbation in the previous year | 72       | 64.5             | 36.4                       |
| Kerwin 2019 Extension study NCT02538508 | Same as KRONOS                                                              | 194                | 52               | %FEV1 > 30%, ≥ 50% ≥ 40 yrs, ≥ 10PY, Not required to have had an exacerbation within the preceding year | 51.4     | 62.5             | ND                         |
| Rabe 2020 ETHOS NCT02465567 | Budesonide 640 Glycopyrronium 36 Formoterol 19.2 (Fixed inhaler) vs Glycopyrronium 36 Formoterol 19.2 (Fixed inhaler) | 2144               | 52               | %FEV1 > 25%, ≥ 65% CAT ≥ 10, 40-80 yrs, ≥ 10PY a) %FEV1 <50%, ≥1 moderate or severe exacerbation b) %FEV1 ≥50%, ≥2 moderate or ≥1 severe exacerbation | 58.8     | 64.7             | 43.6                       |
| **ICS withdrawal protocol**                                                                                                                                |
| Magnussen 2014 WISDOM NCT00975195 | Fluticasone 1000 Tiotropium 18 Salmeterol 100 (Separate inhalers) vs Tiotropium 18 Salmeterol 100 (Separate inhalers) | 1243               | 52               | %FEV1 < 50%, ≥ 40yrs, ≥ 10PY, A history of at least one documented exacerbation in the 12 months before screening | 82.5     | 63.8             | 34.2                       |
| Chapman 2018 SUNSET NCT02603393 | Fluticasone 1000 Tiotropium 18 Salmeterol 100 (Separate inhalers) vs Glycopyrronium 50 Indacaterol 110 (Fixed inhaler) | 526                | 26               | %FEV1 ≥ 40%, < 80%, ≥ 40yrs, ≥ 10PY, exacerbation; no more than one moderate or severe exacerbation in the previous year | 70.6     | 65.3             | 56.6                       |
Table 1 (continued)

| Study or Subgroup | log[Rate Ratio] | SE | Total | Total Weight | Rate Ratio IV, Random, 95% CI | Rate Ratio IV, Random, 95% CI |
|-------------------|----------------|----|-------|--------------|-------------------------------|-------------------------------|
| Ferguson 2018     | -0.734         | 0.1326 | 639   | 625          | 14.8% 0.48 [0.37, 0.62]       |                                |
| Lipson 2018       | -0.2877        | 0.0352 | 4145  | 2069         | 32.2% 0.75 [0.70, 0.80]       |                                |
| Papi 2018         | -0.1649        | 0.0814 | 764   | 768          | 23.3% 0.85 [0.72, 0.99]       |                                |
| Rabe 2020         | -0.2744        | 0.0493 | 2137  | 2120         | 29.7% 0.78 [0.69, 0.84]       |                                |
| Total (95% CI)    | 7685           | 5582  | 100.0%| 0.73 [0.64, 0.83] |                                |                                |

Heterogeneity: Tau² = 0.01; Chi² = 13.64, df = 3 (P = 0.003); I² = 78%
Test for overall effect: Z = 4.78 (P < 0.00001)

Fig. 2 Efficacy of ICS add-on to LAMA/LABA on exacerbations

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Fig. 3 Efficacy of ICS add-on to LAMA/LABA on quality of life: change from baseline in SGRQ

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Fig. 4 Efficacy of ICS add-on to LAMA/LABA on symptoms: change from baseline in TDI score

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Fig. 5 Efficacy of ICS add-on to LAMA/LABA on trough FEV₁ change from baseline
with LAMA/LABA, the sub-analysis showed a significantly lower incidence of exacerbations (rate ratio 0.76, 95% CI 0.72 to 0.80; P < 0.00001; I² = 0%; Additional file 1: Figure S5) and mortality (rate ratio 0.63, 95% CI 0.47 to 0.83; P = 0.001; I² = 0%; Additional file 1: Figure S10), and better SGRQ score with ICS/LAMA/LABA (mean difference −1.83, 95% CI −2.45 to −1.20; P < 0.00001; I² = 0%; Additional file 1: Figure S6). However, there was a significantly higher incidence of pneumonia with ICS/LAMA/ LABA treatment (rate ratio 1.60, 95% CI 1.23 to 2.09; P = 0.0005; I² = 41%; Additional file 1: Figure S9). Concerning the TDL score and trough FEV₁, data from one trial showed a significant improvement in the TDL score (mean difference 0.40, 95% CI 0.23 to 0.57; P < 0.00001; I²: not applicable; Additional file 1: Figure S7) and trough FEV₁ with ICS/LAMA/LABA (mean difference 0.05, 95% CI 0.04 to 0.07, P < 0.00001, I²: not applicable; Additional file 1: Figure S8).

Comparison between ICS add-on and ICS withdrawal protocol

There were two trials (N = 3538) evaluating the effects of ICS withdrawal from ICS/LAMA/LABA. Compared to the ICS add-on protocol, there were no differences between ICS/LAMA/LABA and LAMA/LABA in the rate of exacerbations, TDI score, and total and serious adverse events including pneumonia and mortality (Additional file 1: Figures S1 and S11–S18). However, triple therapy showed a significant better SGRQ score (mean difference −1.33 95% CI −2.26 to −0.40; P = 0.005; I² = 0%) and higher trough FEV₁ (mean difference 0.04, 95% CI 0.02 to 0.05, P = 0.0005, I² = 0%) same as in ICS add-on protocol (Additional file 1: Figures S12 and S14).

### Sub-analysis with baseline blood eosinophil count (descriptive analysis)

There were four trials that evaluated the ICS add-on effect and one trial that assessed the ICS withdrawal effect based on the baseline blood eosinophil count during exacerbations (Additional file 1: Table S6). All the studies have shown that the patients with higher level of eosinophils, such as ≥ 150 or 300, experienced markedly greater reductions in moderate or severe COPD exacerbations. Also, each trial evaluated the ICS add-on or ICS withdrawal effect based on the eosinophils in the trough FEV₁ and showed a higher level of trough FEV₁ if the...
level of eosinophils was greater than $\geq 150$ or $300$ (Additional file 1: Table S7).

**Evaluation with GRADE**
The overall quality of evidence was high for outcomes including exacerbations, SGRQ score, total adverse events, serious adverse events and pneumonia, and was moderate for the TDI score, trough FEV$_1$ and mortality (Additional file 1: Table S8). When ICS were added to LAMA/LABA for the 1,000 patients and the rate of exacerbation with LAMA/LABA was assumed to be 1.0 exacerbation event per person-year, 270 (95%CI 360 to 170) fewer exacerbations, 7 (95% CI 3 to 11) fewer mortalities and 17 (95%CI 5 to 32) more pneumonia events would have been experienced.

**Discussion**
In the current meta-analysis, we first evaluated the efficacy and safety in the comparison between ICS/LAMA/LABA and LAMA/LABA for the patients with COPD including those in the ETHOS trial. In the patients with symptomatic moderate and severe COPD and a history of exacerbations, we demonstrated that the addition of ICS to LABA/LAMA caused a higher incidence of pneumonia than LAMA/LABA but was a more preferable treatment due to the lower incidence of exacerbations, higher trough FEV$_1$ and better QOL score. We also revealed that triple therapy was superior to LAMA/LABA due to the lower mortality and better dyspnea score in these patients.

Until now, five systematic reviews have compared the effect of triple therapy with LAMA/LABA in patients with COPD [7–11]. These reviews showed that triple therapy has a risk of pneumonia but is superior to LAMA/LABA therapy due to the lower incidence of exacerbations, higher trough FEV$_1$ and better QOL score. However, these reviews also showed that there were no differences in the total and serious adverse events between triple and LAMA/LABA therapy. However, these results were mainly based on the data from one large IMPACT study [4]. In the current meta-analysis, we confirmed these results by using additional data from the ETHOS trial [15]. In addition, we demonstrated for the first time that triple therapy was superior to LAMA/LABA therapy as reflected by the lower mortality and better dyspnea score. This difference could be mainly due to the increase of participants together with the inclusion of one large ETHOS study [15]. Also, we evaluated the effect of ICS add-on to LAMA/LABA on the mortality and pneumonia events in COPD patients with a 52 week treatment duration. However, around 80% of the participants for most variables were composed of those from the IMPACT and ETHOS trials [4, 15], which aimed at evaluating exacerbations in the patients with $\geq 10$ CAT score and a history of exacerbations. Therefore, attention should be given when the results applied.

Concerning exacerbations, the four trials evaluated all demonstrated the significant superiority of triple therapy to LAMA/LABA in reducing the risk of exacerbations. However, there was a high grade of inconsistency in the meta-analysis. This might be due to differences in the inclusion criteria for the participants with a history of exacerbations in the previous year. Three trials included a history of $\geq 1$ moderate or severe exacerbations for the inclusion criteria, but one KRONOS trial excluded. When the KRONOS trial was excluded in the sub-analysis, the inconsistency disappeared. The KRONOS trial that mainly included patients with a history of less than one moderate or severe exacerbation in the previous year, also showed the superiority of triple therapy to LAMA/LABA in reducing the risk of exacerbations. However, there have been insufficient trials that examined patients with a history of less than one exacerbation to confirm this result.

In the trough FEV$_1$, we confirmed the superiority of triple therapy to LAMA/LABA. The difference of 40 mL is below the MCID of 50–100 mL, for which the index is usually used for comparison with a placebo [23–25]. However, in our present analysis, the difference in the trough FEV$_1$ might have caused a significant change in the patient’s QOL and dyspnea symptoms evaluated by the SGRQ and TDI score and a decrease of exacerbations because relationships between improvement in FEV$_1$ and QOL or exacerbations in COPD have been reported [26, 27]. In addition, a stronger relationship between the improvement in FEV$_1$ and QOL has been shown in more severe COPD [26]. Therefore, the degree of change in trough FEV$_1$ in the current analysis may affect the clinical course in the patients with more severe COPD.

Concerning the mortality, our meta-analysis demonstrated that triple therapy was associated with a significantly lower mortality in patients with COPD compared with LAMA/LABA. This result is consistent with previous studies that suggested ICS/LABA or ICS/LAMA/LABA causes a reduction in mortality in patients with COPD [28–32]. The effect of ICS on the mortality might be dose-dependent because a half dose of ICS treatment with LAMA/LABA did not reduce the mortality in the ETHOS trial [15]. In the sub-analysis of cause of the mortality, we showed that the reduction of mortality with triple therapy might be mainly due to a lower rate of fatal cardiovascular events. However, the results of a recent SUMMIT trial which aimed at evaluating the impact of ICS or ICS/LABA on the reduction of cardiovascular events and mortality, were negative. This discrepancy
may be mainly due to differences in the severity and the history of exacerbations because the participants in the SUMMIT study suffered less severe COPD with a lower rate of exacerbations in the previous year [30]. Previous studies have shown that exacerbations of COPD could increase the risk of coronary and stroke events [33, 34]. Therefore, the protective effect of triple therapy on exacerbations could lead to a lower incidence of fatal cardiac events. However, there was an imprecision in our current results because the sample size was statistically still not sufficient and the estimated duration of less than 52 weeks also not long enough for evaluating mortality. Further trials are awaited to confirm these results.

In the sub-analysis that evaluated the patients with ≥ 10 CAT score and a history of ≥ 1 moderate or severe exacerbations in the previous year, the criteria of that covers GOLD group D, triple therapy showed a significantly lower incidence of exacerbations and mortality, and improvement in the SGRQ score, but a higher incidence of pneumonia. Concerning the TDL score and trough FEV₁, the superiority of triple therapy was also shown in the sub-analysis evaluated in one study. Therefore, the patients in GOLD group D could be the main targets for ICS add-on to LAMA/LABA.

In the ICS withdrawal protocol, there was no significant difference between triple and LAMA/LABA therapy in the incidence of exacerbations and pneumonia. These results are inconsistent with those from the ICS add-on protocol. This inconsistency might be mainly explained by differences in the protocol and the basal control level of the COPD status, such as the exacerbation rate, which has been shown to be a risk for future exacerbations and pneumonia [35, 36]. In fact, in the ICS withdrawal protocol, the participants in the SUNSET trial experienced no more than one moderate or severe exacerbation in the previous year. Also, in the WISDOM trial, the participants could also have been less frequent exacerbators because the exacerbation rate in the LAMA/LABA group was lower than those in the two large IMPACT and ETHOS trials in the ICS add-on protocol (Additional file 1: Figure S1). On the other hand, our analysis demonstrated that triple therapy showed a significantly better SGRQ score and higher trough FEV₁ than LAMA/LABA in both protocols. This result suggests that, although the degree of improvement in the SGRQ score and trough FEV₁ with triple therapy was less than MCID, the certainty of this evidence is quite high.

In our current analysis, we did not address what factors determined the effectiveness of triple therapy because detailed data were not reported in the included trials except blood eosinophil count. A higher number of blood eosinophils has been shown to reflect the eosinophilic airway inflammation, which is a steroid sensitive element in asthmatic patients [37, 38]. Our current analysis and the post hoc analyses have shown a correlation between blood eosinophil counts and the efficacy [39, 40]. However, since various cut-off values, such as ≥ 150 or 300 of blood eosinophils were used in each trial, the most useful value remains unclear. In our current meta-analysis, all studies excluded current asthma but not the patients with a previous history of asthma except one, the SUNSET trial [20]. Also, around 15 to 20% of patients were included with ≥ 300 blood eosinophil counts at the baseline (Additional file 1: Table S3) [40], suggesting that these trials could have contained a selection bias that includes asthma patients potentially responsive to ICS. The previous FLAME trial, which excluded patients with current or previous asthma history, reported that the LAMA/LABA treatment showed a lower incidence of exacerbations of COPD than ICS/LABA [41]. Therefore, "pure COPD" patients might be less responsive to ICS, but further studies are needed to clarify this point.

There remains a possibility that prior ICS usage might also have affected the ICS add-on effect. In our current analysis, 65 – 80% of the trial’s population were taking ICS at screening and without any washing period except the TRIBUTE study before starting the trial in the ICS add-on protocol. Therefore, these trials cannot be strictly defined as an ICS add-on. In a post-hoc analysis of the IMPACT trial, the ICS add-on effect on the moderate or severe exacerbations was reduced among prior ICS non-users, but not in that of the ETHOS trial [15, 42]. On the other hand, both trials have shown no apparent difference in the mortality in the ICS non-users with a limited sample size [43, 44]. Therefore, the results in the ICS non-users remain unclear but the impact of ICS withdrawal could have been anticipated to be small because these trials demonstrated that both therapeutic and adverse effects could last after three months when excluding the influence of ICS withdrawal [42–44].

There are several limitations to our meta-analysis. First, the included patients had less than 80% of %FEV₁; therefore, current results are not applicable to mild COPD patients. Secondly, the participants included in our meta-analysis in the ICS add-on protocol were mainly limited to those with history of smoking, CAT score of ≥ 10 and a history of exacerbations in the previous year and without current asthma. Thirdly, the inconsistency of some meta-analyses might be due to differences in drugs that compose ICS/LAMA/LABA. However, we did not evaluate the difference of drugs in the sub-group analysis because of the lack of trials.
Conclusions
In the patients with symptomatic moderate and severe COPD and a history of exacerbations, triple therapy causes a higher incidence of pneumonia than LAMA/LABA, but is still a more preferable treatment due to the lower incidence of exacerbations, higher trough FEV1 and better QOL score. In these patients, triple therapy was also superior to LAMA/LABA due to the lower mortality and better dyspnea score.

Abbreviations
CAT: COPD Assessment Test; CENTRAL: Cochrane Central Register of Controlled Trials; CI: Confidence intervals; COPD: Chronic obstructive pulmonary disease; FEV1: Forced expiratory volume in one second; GOLD: Global initiative for chronic obstructive lung disease; LABA: Long-acting beta-agonists; LAMA: Long-acting muscarinic antagonist; MCI: Minimal clinically important difference; OR: Odds ratios; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SD: Standard deviation; SGRQ: St George’s Respiratory Questionnaire; TDI: Transitional dyspnea index.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12931-021-01777-x.

Acknowledgements
We appreciated the staffs of the Japan Council for Quality Health Care for supporting the systematic review and meta-analysis. We also thank Mr. Brent Bell for reading this manuscript.

Authors’ contributions
AK, MY, TI and NF searched the studies and analyzed the data. AK and HS drafted the manuscript. AK, TK and HS contributed to the conception and design of the study and contributed substantially to the manuscript. All authors read and approved the final manuscript.

Funding
There is no support funding for this manuscript.

Availability of data and materials
Source data and material will be made available upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
AK reports grants from Novartis, personal fees for lectures from Astellas, AstraZeneca, Kyorin, Novartis, Sanofi and Taiho, and personal fees for lectures and consulting from Boehringer Ingelheim and GlaxoSmithKline, outside the submitted work. MY reports grants from Japan Society for the Promotion of Science and Novartis, and personal fees for lectures from AstraZeneca, Meiji Seika Pharma, Novartis, Daichi Sankyo, Sanofi and Boehringer Ingelheim, outside the submitted work. TI has nothing to disclose. NF reports personal fees for lectures from AstraZeneca, outside the submitted work. TK reports grants from Novartis, and personal fees for lectures from AstraZeneca, Boehringer Ingelheim, Meiji Seika Pharma and GlaxoSmithKline, outside the submitted work. HS reports grants from MSD and Novartis, personal fees for lectures from Astellas, Kyorin, Novartis and Sanofi, and personal fees for lectures and consulting from AstraZeneca, Boehringer Ingelheim and GlaxoSmithKline, outside the submitted work.

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Received: 12 February 2021 Accepted: 10 June 2021 Published online: 22 June 2021

References
1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095–128.
2. Soler-Cataluña JJ, Martinez-Garcia MA, Román Sánchez-P, Salcedo E, Navarro M, Ochoando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60:925–31.
3. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. Eur Respir J. 2019;53:1900164.
4. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med. 2018;378:1671–80.
5. Crim C, Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, et al. Pneumonia risk with inhaled fluticasone furoate and vilanterol compared with vilanterol alone in patients with COPD. Ann Am Thorac Soc. 2015;12:27–34.
6. Crim C, Calverley PMA, Anderson JA, Holmes AP, Kilbride S, Martinez FJ, et al. Pneumonia risk with inhaled fluticasone furoate and vilanterol in COPD patients with moderate airflow limitation: the SUMMIT trial. Respir Med. 2017;131:27–34.
