Inhaled corticosteroids and FEV\textsubscript{1} decline in chronic obstructive pulmonary disease: a systematic review

Hannah R. Whittaker\textsuperscript{1*}, Debbie Jarvis\textsuperscript{1}, Mohamed R. Sheikh\textsuperscript{1}, Steven J. Kiddle\textsuperscript{2} and Jennifer K. Quint\textsuperscript{1}

Abstract

Rate of FEV\textsubscript{1} decline in COPD is heterogeneous and the extent to which inhaled corticosteroids (ICS) influence the rate of decline is unclear. The majority of previous reviews have investigated specific ICS and non-ICS inhalers and have consisted of randomised control trials (RCTs), which have specific inclusion and exclusion criteria and short follow up times. We aimed to investigate the association between change in FEV\textsubscript{1} and ICS-containing medications in COPD patients over longer follow up times.

MEDLINE and EMBASE were searched and literature comparing change in FEV\textsubscript{1} in COPD patients taking ICS-containing medications with patients taking non-ICS-containing medications were identified. Titles, abstract, and full texts were screened and information extracted using the PICO checklist. Risk of bias was assessed using the Cochrane Risk of Bias tool and a descriptive synthesis of the literature was carried out due to high heterogeneity of included studies.

Seventeen studies met our inclusion criteria. We found that the difference in change in FEV\textsubscript{1} in people using ICS and non-ICS containing medications depended on the study follow-up time. Shorter follow-up studies (1 year or less) were more likely to report an increase in FEV\textsubscript{1} from baseline in both patients on ICS and in patients on non-ICS-containing medications, with the majority of these studies showing a greater increase in FEV\textsubscript{1} in patients on ICS-containing medications. Longer follow-up studies (greater than 1 year) were more likely to report a decline in FEV\textsubscript{1} from baseline in patients on ICS and in patients on non-ICS containing medications but rates of FEV\textsubscript{1} decline were similar.

Further studies are needed to better understand changes in FEV\textsubscript{1} when ICS-containing medications are prescribed and to determine whether ICS-containing medications influence rate of decline in FEV\textsubscript{1} in the long term. Results from inclusive trials and observational patient cohorts may provide information more generalisable to a population of COPD patients.

Keywords: Lung function, COPD, Inhaled corticosteroids, Review

Background

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by the chronic obstruction of airflow in the airways and lungs. Evidence based clinical NICE guidelines recommend the use of inhaled bronchodilators such as long-acting beta-2 adrenergic receptor agonists (LABA) or long-acting muscarinic-receptor antagonists (LAMA) for COPD maintenance therapy [1, 2]. Currently, the addition of inhaled corticosteroids (ICS) is reserved for those who remain breathless or exacerbate despite taking short-acting bronchodilators (SABA) following NICE guidelines [3]. GOLD guidelines suggest initial treatment of ICS should be reserved for patients in GOLD group D alongside LABA if blood eosinophil levels are greater than 300 cells/μl. In addition, combination ICS (ICS/LABA) should be considered in patients who exacerbate if blood eosinophil levels are greater than 300 or 100 if they experience at least 2 moderate exacerbations or a hospitalization from AECOPD or remain...
breathless [4]. However, the use of ICS for the treatment of COPD has been debated.

FEV\textsubscript{1} is a common measure used to assess lung function and multiple studies show FEV\textsubscript{1} declines at a faster rate in smokers compared to non-smokers [5]. Randomised control trials (RCTs) have found that inhaled corticosteroids (ICS) reduce the rate of FEV\textsubscript{1} decline in people with COPD [6–9]. However, the rate of FEV\textsubscript{1} decline is heterogeneous and can vary depending on factors such as smoking status, exacerbations of COPD (AECOPD), and season [10, 11]. Most RCTs compare COPD patients on a specific ICS to those on a placebo, have specific inclusion and exclusion criteria and commonly exclude participants based on age, comorbidities and severity of disease [12]. In addition, most studies have short follow-up periods of less than 1 year. Therefore, most RCTs are not easily generalisable to the wider COPD population over the longer term.

Previous literature reviews have consisted of pre-specified ICS and non-ICS comparators [13–18] such as LAMA/LABA vs LABA/ICS or ICS, LAMA/LABA vs LABA, LAMA or LABA/ICS and more specific comparisons such as budesonide or beclomethasone vs placebo. Several large scale RCTs investigating various ICS and FEV\textsubscript{1} decline have taken place since, such as the Study to Understand Mortality and Morbidity in COPD (SUMMIT) and the Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trials, justifying the need to inform and summarise novel findings. We aimed to investigate the association between ICS or ICS-containing medications and FEV\textsubscript{1} decline compared to non-ICS-containing medications in COPD and determine whether length of follow-up influences the difference in FEV\textsubscript{1} decline between ICS and non-ICS containing groups.

Material and methods
The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42018090741. For further detail on study protocol see study protocol in Additional file 1.

Literature search
We systematically searched MEDLINE and EMBASE (up until the 25th April 2019) using the following key words:

1) COPD (Chronic Obstructive Pulmonary Disease); COAD (Chronic Obstructive Airways Disease); obstructive airflow/airway/lung/pulmonary/respiratory/bronchiectasis; emphysema; chronic bronchitis.

2) Inhaled corticosteroids; inhaled budesonide/fluticasone/beclometasone/momentasone/flunisolide/ciclesonide.

3) Forced expiratory volume; lung function; respiratory function tests; FEV\textsubscript{1}; change/rate/decline/worse/reduce/decrease/slow FEV\textsubscript{1}/lung function/lung volume.

Search terms included medical subject headings and free text words (see study protocol in Additional file 1). The Boolean operator “or” was used to search terms within the three concepts above and the operator “and” was used to combine the three concepts. Only English language literature was searched.

Selection of studies
We included studies that had recruited people with physician diagnosed COPD or an FEV\textsubscript{1}/FVC < 70% who were aged 35 or older and were current or ex-smokers. Articles were included if the exposure and comparison were ICS-containing medications and non-ICS-containing medications and if they reported a change in FEV\textsubscript{1} over time for both exposure and comparison groups. Change from baseline FEV\textsubscript{1} was defined as change in post-bronchodilator FEV\textsubscript{1}. Articles were excluded if they included people with diagnosed asthma or asthma-COPD overlap syndrome.

Two reviewers (HW and MS) independently screened all titles and abstracts following the inclusion criteria and compared initial included titles. Any inconsistencies were discussed and if necessary, a third party intervened. This was repeated for full text articles. Conference papers, non-English language papers, review articles, protocols, or systematic reviews were not included.

Data extraction, quality assessment and data synthesis
Data was extracted following predetermined criteria base on the PICO checklist. Study details included: study name; patient number; length of follow-up; study inclusion and exclusion criteria; population characteristics including recruitment method, gender, and mean age; non-ICS comparison; ICS type and dosage; crude and adjusted outcome (change in FEV\textsubscript{1}); statistical analysis; and any additional notes. Two reviewers extracted relevant data, which were compared and inconsistencies discussed.

Quality of studies was assessed using the Cochrane Risk of Bias Tool. This was developed to assess a RCT's external and internal validity [19]. This tool assesses selection bias, reporting bias, performance bias, detection bias, attrition bias, and biases not identified in the previous categories. Quality of studies were reported as high, moderate, or low bias.
A meta-analysis was performed to investigate treatment differences in change in FEV₁ between ICS and non-ICS containing medications (Additional file 1: Figure S1). Treatment differences were calculated using t-tests [20]. Due to high heterogeneity ($I^2 = 98.9\%$, $P < 0.0001$) a descriptive synthesis was performed. Data were described with regards to type of ICS-containing medications, type of comparator, length of study follow-up and population characteristics.

**Results**

Four thousand four hundred fifty-four studies were identified in MEDLINE ($n = 1319$) and EMBASE ($n = 3135$) following the electronic systematic search. After duplicate articles were excluded 3353 article titles and abstracts were screened of which, 181 articles were selected for full text screening. Seventeen articles met our inclusion criteria illustrated in the PRISMA flowchart (Fig. 1). One hundred sixty-four articles were excluded (see Fig. 1 for further details).

**Study characteristics**

All studies that met our inclusion criteria were RCTs (Table 1). Examples of RCTs that met our inclusion criteria included: ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe), TRINITY, SUMMIT and TRISTAN (Trial of Inhaled Steroids and long-acting $\beta_2$ Agonists).

Included studies were published between 1991 to 2018; spanning a 27 year period. The number of patients included in studies ranged from 24 participants [21] to 16,485 patients [6, 35]. The majority of studies had high numbers of recruited males. The percentage of females in studies ranged from 0% [30] to 46% [25] and the median percentage of females included was 25.5%. The mean age of included participants ranged from approximately 53 years [33] to 67 years [23]. The median length of follow-up ranged from 3 months [21–23] to 4 years [6, 35].

Studies differed by types of ICS and non-ICS medications. The most common comparison was placebo vs ICS. Other comparisons included LABA vs LABA/ICS, placebo vs LABA/ICS, LABA vs ICS, and LAMA vs LAMA/ICS. Tables 1 and 2 illustrate all types of ICS and non-ICS comparisons in more detail.

**Change in FEV₁**

Table 1 illustrates the change in FEV₁, by study and ordered by length of study follow-up, showing a high degree of variation between studies. A large proportion of the variation was dependent on study follow-up time and type of comparison. Change in FEV₁ in studies that had less than one year of follow-up varied between $-120$ ml (standard deviation [SD] $230$) to $+163$ ml (95% confidence intervals [CI] $80$ to $245$) over 3 months in non-ICS containing medications and between $-13$ ml (CI $-59$ to $33$) to $+239$ ml (CI $183$ to $296$) over 3 months in ICS-containing medication [21, 22, 24]. Change in FEV₁ in studies that had more than one year of follow-up varied between $-69$ ml/year to $21$ ml/year (CI $3$ to $39$) in non-ICS containing medications and between $-57$ ml/year to $85$ ml/year (CI $31$ to $110$) in ICS-containing medications [27, 33].
| Change in FEV$_1$ | Authors | Study Name | Geographic location | Follow-up (mths) | Patient N | Female (%) | Mean Age Years (SD) | Intervention (dose μg) | Change in FEV$_1$ in ml (SD or 95%CI) |
|-------------------|---------|------------|---------------------|-----------------|-----------|------------|-------------------|------------------------|---------------------------------------|
| Mean change in FEV$_1$ (ml) | Auffarth et al 1991 [21] | – | Netherlands | 3 | 24 | 0.04 | 57.0 (8.2) | Placebo | -120 (230) |
| | Cazzola et al 2000 [22] | – | Italy | 3 | 80 | 11.6 | 64.2 (6.3) | Sal (50) | 163 (80 to 245) |
| | | | | | | | Sal/FP (50/250) | 188 (89 to 287) | |
| | | | | | | Sal/FP (50/500) | 239 (183 to 296) | |
| | Lee et al 2016 [23] | – | China, Hong Kong, Indonesia, South Korea, Thailand | 3 | 577 | 43 | 66.8 (8.3) | Tio (18) | 80 (27) |
| | | | | | | Tio + bud/form (18 + 160/4.5) | 160 (29) | |
| | Bourbeau et al 1998 [24] | – | Canada | 6 | 79 | 21.5 | 66.0 (8.0) | Placebo | 0–3 months: −1 (−65 to 62) 0–6 months:12 (−61 to 85) |
| | | | | | | Bud (400) | 0–3 months: −13 (−59 to 33) 0–6 months:8 (−51 to 68) | |
| | Ohar et al 2014 [25] | – | United States, Argentina, Norway | 6.5 | 639 | 46 | 62.9 (9.2) | Sal (50) | 40 (342) |
| | | | | | | FP/Sal (250/50) | 140 (372) | |
| | Vestbo et al 2005 [26] | TRISTAN | Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Lithuania, Netherlands, New Zealand, Norway, Poland, Russia, South Africa, Spain, Sweden, Switzerland, UK | 12 | 1465 | 276 | 63.2 (8.6) | Placebo | −65 (−200 to 85) |
| | | | | | | Sal (50) | 0 (−130 to 140) | |
| | | | | | | FP (500) | 0 (−160 to 160) | |
| | | | | | | Sal/FP (50/500) | 80 (−50 to 250) | |
| Rate of FEV$_1$ change (ml/year) | Vestbo et al 2017 [27] | TRINITY | Argentina, Belarus, Bulgaria, Croatia, Germany, Hungary, Italy, Mexico, Poland, Romania, Russia, Slovakia, Turkey, UK, Ukraine | 12 | 2691 | 236 | 63.2 (8.6) | Tio (18) | 21 (3 to 39) |
| | | | | | | Fixed: Beclo/FP/gly bro (100/6/12.5) | 82 (65 to 100) | |
| | | | | | | Open: Beclo/FP/Tio (100/6/18) | 85 (31 to 110) | |
| | Wise et al 2000 [28] | Lung Health | North America, Canada | 12 | 1116 | 369 | 56.3 (6.8) | Placebo | −47 (70.8) |
| Study Name          | Study Characteristics                                                                 | Change in FEV<sub>1</sub> in ml (SD or 95%CI) |
|---------------------|----------------------------------------------------------------------------------------|-----------------------------------------------|
| Weir et al. 1999    | Triamcinolone acetonide (600)                                                           | −44.2 (688)                                  |
| Renkema et al. 1996 | Becl (750)                                                                              | −56.9 (15)                                   |
| Burge et al. 2000   | Bud (800)                                                                               | −60 (−570 to −340)                           |
| Calverley PM et al. | Bud + oral prednisolone (800/5)                                                         | −60 (−570 to −340)                           |
| Calverley et al. 2018 & Vestbo et al. 2016 | Placebo                                                                                 | −60 (−570 to −340)                           |
| Pauwels et al. 1999 | Bud (400)                                                                               | −50 (28.7)                                   |
| Vestbo 1999         | Placebo                                                                                 | −60 (−340 to −870)                           |
| Whittaker et al. Respiratory Research (2019) | FF/Vil (100/25)                                                                          | −50 (28.7)                                   |
| Change in FEV₁ | Authors | Study Name | Geographic location | Follow-up (mths) | Patient N | Female (%) | Mean Age Years (SD) | Intervention (dose μg) | Change in FEV₁ in ml (SD or 95%CI) |
|----------------|---------|------------|---------------------|------------------|-----------|------------|---------------------|-----------------------|----------------------------------|
|                | Shaker et al 2009 [36] | – | Denmark | 48 | 254 | 42 | 63.6 (7.4) | Placebo | −56 (−72 to −40) |

Notes: 2 included studies (Calverley 2018, Vestbo 2016) were analyses on the same population and reported the same change in FEV₁ estimates.

Abbreviations: FP Fluticasone propionate, FF Fluticasone furoate, Sal Salmeterol, Bud Budesonide, Becl Beclomethasone, TIO Tiotropium, Vil Vilanterol, Mom Mometasone, Form Formoterol, UMEC Umeclidinium, Gly Br Glycopyryonium bromide, Ol Olodaterol
Study follow-up time

Figure 2 illustrates change in FEV₁ in ICS and non-ICS-containing medications in studies with follow-up of one year or less. The majority of ICS point estimates show an increase in FEV₁ and 8 out of 10 studies showed that change in FEV₁ increased more or decreased slower in ICS groups compared to non-ICS groups.

Figure 3 illustrates change in FEV₁ in ICS and non-ICS-containing medications in studies with follow-up greater than one year in ml/year. All studies showed a decline in FEV₁ in both ICS and non-ICS groups, of which there was little difference in FEV₁ decline between the two groups.

The general trend in change in FEV₁ with increasing follow-up time suggests that greater increases with ICS-containing medications are seen in short term studies up to approximately one year. Longer studies greater than a year show that FEV₁ generally declines over time. All studies with greater than 1 year of follow-up were placebo vs ICS comparisons.

Inclusion and exclusion criteria

Common inclusion criteria included specific criteria regarding age, smoking status and disease severity. Specifically, the majority of studies included patients aged 40 years old or older. In terms of smoking status, the majority of studies included current or ex-smokers with at least 10 pack years history smoking. Nearly all studies included patients with an FEV₁/FVC < 70%. FEV₁% predicted criteria was commonly 30–70% predicted or < 50%.

Furthermore, 4 studies required at least one AECOPD prior to the start of follow-up. These included moderate or severe AECOPD requiring prescribed oral corticosteroids and/or antibiotics or have been hospitalised for AECOPD prior to the start of the study. One study specifically required no AECOPD prior to study start. Other inclusion criteria included MRC dyspnea scores of 2 or more, FEV₁ reversibility, and risk or history of cardiovascular disease. Additional file 1: Table S1 shows detailed inclusion criteria by study.

The most common exclusion criteria was the presence of diagnosed comorbidities including other respiratory diseases (e.g. asthma, pneumonia, URTI, LRTI) and clinically significant diseases that could affect results and patient participation (e.g. MI, HF, angina, and diabetes). Further exclusion criteria included long-term oxygen therapy, evidence of alcoholism or solvent abuse, AECOPD requiring prescription of oral corticosteroid, antibiotics, or hospitalisation prior to study start or
Quality assessment
The majority of studies were considered low risk in each of the bias domains. Reasons for considering ‘random sequence and allocation concealment’ unclear was due to no mention of a sequence generator in text or in additional files. ‘Reporting bias’ and ‘other biases’ were low risk because all outcomes mentioned in the methods were reported in the results. Similarly, no other biases were found in all studies. ‘Performance and detection bias’ was considered unclear in the study by Cazzola and colleagues [22] because the authors failed to report whether and how the study participants and personnel were blinded during follow-up and outcome assessment. ‘Performance and detection bias’ was considered high risk in the study by Lee and colleagues [23] as participants and personnel were not blinded during the study. The study by Shaker and colleagues [36] was considered to have unclear ‘attrition bias’ because there was no indication whether only participants with complete follow-up were used to measure change in FEV₁. High risk ‘attrition bias’ was observed in 4 studies. This was because only participants with complete follow-up (i.e. completed the study and did not dropout) were included in the analysis. See Additional file 1: Figure S2 and Quality Assessment for quality assessment by risk of bias domain and support for judgment.

Discussion
This systematic review investigated the change in FEV₁ with ICS-containing medications compared to non-ICS-containing medications in COPD patients over the short and long term. Of the 17 studies that met our inclusion criteria, all were RCTs. We found that the majority of studies with less than a year follow-up reported increases in FEV₁, with the general trend favouring ICS medications compared to non-ICS medications. Studies with more than a year follow-up generally reported a decline in FEV₁ with little evidence of a treatment difference between ICS and non-ICS containing medications.

Length of study follow-up
Our main finding suggests that initiating ICS medications improves lung function compared to non-ICS medications however, over long periods of time lung function starts to decline.

| Follow-up time (months) | Study | Non-ICS-containing medications | ICS-containing medications | Rate of FEV₁ decline (95% CI) |
|-------------------------|-------|---------------------------------|---------------------------|-------------------------------|
| 3 months                | Auffarth 1991 |                                |                           | -120.0 (-300.0 to 20.0)      |
|                         | Lee 2016 |                                |                           | 10.00 (50.0)                 |
|                         | Cazzola 2000 |                                |                           | 163.0 (50.0 to 273.0)        |
|                         | Bourbeau 1998 |                              |                           | 10.00 (50.0)                 |
| 6 months                | Bourbeau 1998 |                              |                           | 12.00 (50.0 to 60.0)         |
|                         | Okh 2014 |                                |                           | 8.00 (50.0 to 60.0)          |
|                         | Pauwels 1999 |                               |                           | 40.0 (20.0 to 60.0)          |
| 12 months               | Vestbo 2005 |                               |                           | -65.0 (-200.0 to 60.0)       |
|                         | Vestbo 2017 |                               |                           | 21.0 (0.0 to 42.0)           |
|                         | Wise 2000 |                                |                           | -47.0 (-200.0 to 70.0)       |

Fig. 2 Change in FEV₁ (ml) in studies with follow-up of one year or less. Studies are ordered by follow-up time. Note: Confidence intervals were not shown if the study did not report them or they were unable to be calculated.
function declines at a similar rate in both ICS and non-ICS medications. This may be due to an initial acute bronchodilation, [37] or subtle improvements in care in both arms shortly after recruitment. The decline in FEV₁ in studies greater than a year is seen in both ICS and non-ICS containing medications and raises the question of whether ICS-containing medications are similar to non-ICS medications over long periods of time with respect to their effect on lung function. In addition, the studies that reported a significant difference between the changes in FEV₁ favouring ICS-containing medications were studies that were less than 1 year in duration.

**Type of ICS-containing medications and comparators**

We found that in terms of rate of change of FEV₁ per year, the majority of studies compared: i) placebos to monotherapy ICS; ii) LABA to LABA/ICS; iii) placebo to LABA/ICS; iv) LABA to monotherapy ICS; and v) LAMA to LAMA+LABA/ICS.

Previous literature suggests that ICS/LABA has better outcomes in COPD compared to the use of ICS monotherapy or LABA monotherapy. ICS/LABA is associated with reduced rate of AECOPD, improved FEV₁ and improved patient health status compared to its individual components [38]. Barnes and colleagues showed that monotherapy ICS does not suppress inflammation in COPD [39, 40]. Further studies show that the anti-inflammatory effect of ICS is greater in the presence of beta agonists and help increase the number of beta-receptors and improve bronchodilation from LABA [41, 42]. Four studies in our systematic review included ICS/LABA as the ICS comparison arm. FEV₁ improved in ICS/LABA groups compared to its non-ICS comparator whereas monotherapy ICS showed a decline in FEV₁, similar to its non-ICS comparator. However, all studies investigating monotherapy ICS compared to a non-ICS medication had a follow-up greater than one year and all but one study investigating ICS/LABA had a follow-up of less than one year. All studies that compared ICS/LABA to LABA or ICS/LAMA to LAMA showed that FEV₁ improved more in ICS combination groups compared to LABA or LAMA. Therefore, whilst improvement in FEV₁ was seen in LABA and LAMA groups, the addition of ICS improved lung function further, highlighting the initial beneficial effect of ICS.

Furthermore, recently it has been suggested that the use of LAMA/LABA is preferential over ICS/LABA in COPD patients. This may be due to the synergistic effect of LABA and LAMA which activate both adrenergic and cholinergic pathways maximizing bronchodilation [43, 44]. A recent systematic review investigated the use of LAMA/LABA compared to ICS/LABA and found that compared to ICS/LABA, patients on LAMA/LABA had improved health status, decreased moderate or severe AECOPD, and decreased use of rescue medications [13, 16, 45]. Unfortunately, studies including LAMA/LABA were not included in the final synthesis as they did not
meet our inclusion criteria so we were unable to investigate its effect on lung function compared to ICS/LABA.

Interestingly, the latest GOLD guidelines state that ICS/LABA use should be considered if blood eosinophils are greater than 300 cells/μl in patients who exacerbate more frequently, severely, and who are more breathless [4]. Studies have shown that patients with high blood eosinophils who initiate ICS respond better in terms of lung function compared to those with low blood eosinophils [46]. On the other hand, observational studies have shown no association over longer follow-up periods [47]. As the studies we included did not stratify by eosinophils we were unable to look into this further however, further literature reviews and meta-analyses should explore this further.

Strengths and limitations
This is an extensive literature update comparing the change in FEV_1 between ICS-containing medications and non-ICS containing medications over time. ICS-containing medications were compared with non-ICS-containing medications in order to be as inclusive as possible and highlight differences in ICS type as well as length of follow-up and other study characteristics. The majority of studies included in this review had few biases and were of good quality. In addition, clinical trials with large patient populations such as TRISTAN, TRINITY, ISOLDE, and SUMMIT were included in this review.

One limitation of this systematic review is that ICS monotherapy was included even though it is not currently licensed in the UK [3, 48]. This is due to the risk of developing pneumonia and no improvement in lung function decline or risk of mortality compared to that of LABAs [49–51]. Over time prescribing ICS monotherapy has decreased [52] and it is advised by NICE that ICS monotherapy should not be used for treatment of COPD [48]. The majority of studies included reported a change in lung function in patients on ICS monotherapy, but 7 of the 12 studies were published in 2000 or earlier. The remaining studies that included ICS monotherapy were published between 2001 and 2018. These studies were either conducted in the United States or were multicenter studies that included centers in countries across Europe, Africa, and the Americas. Changes in FEV_1 reported in these studies should therefore be interpreted with caution depending on the prescribing location.

Furthermore, whilst differences in change in FEV_1 between ICS-containing medication and non-ICS-containing medications were seen, they were not always significant. This could have been due to small numbers of recruited patients. In addition, not all studies reported a treatment difference and it therefore unclear whether these differences are statistically significant as well as clinically significant. In those that did report statistical treatment differences, not all were clinically significant or vice versa. It has previously been suggested by the American Thoracic Society and the European Respiratory Society that a minimal important difference in FEV_1 between two treatments ranges from 100 ml to 140 ml [53]. However, this is with regards to pharmacological trials and individual FEV_1 measurements rather than a rate. In addition, it is important to note that clinically important differences in the real world may be different to those seen from RCTs.

Moreover, the results from included studies consist of mostly crude changes in FEV_1. Whilst it is important to observe the range of crude changes with regards to ICS and non-ICS containing medications, they could be skewed by baseline FEV_1. Milder patients with a higher baseline FEV_1 may have more lung function to lose compared to a more severe patient with a lower baseline FEV_1 [54]. Using a measure of change that accounts for baseline FEV_1 may be more informative, such as percent change from baseline.

In addition, all studies included were RCTs and had many inclusion and exclusion criteria. All studies included patients with moderate to very severe COPD. Other common inclusion/exclusion criteria consisted of specific pack year smoking history and no other significant comorbidity. Whilst RCTs are important due to their valuable methodological design, they are typically not representative of the wider population of COPD patients, many of whom have comorbidities. Therefore, the representativeness of the results included in this review should be noted. Observational and general practice studies are needed to identify changes in lung function in a more representative COPD population with a wider degree of disease severity and comorbid conditions.

Lastly, we observed a high level of heterogeneity between studies and therefore, a network meta-analysis was not performed. This limited our ability to make conclusions on rate of change in FEV_1 by ICS and non-ICS comparisons.

Conclusion
The findings from this systematic review suggests that in COPD patients, initiating ICS medications improves lung function compared to non-ICS medications. However, over long periods of time lung function declines at a similar rate for both ICS and non-ICS medications. Further studies that are more generalizable to the wider population of COPD patients are needed in order to investigate the association between ICS and FEV_1 decline further. Additionally, studies with a longer follow-up are needed to observe the long term effect of ICS on lung function.
Additional file

Additional file 1. Systematic review protocol. Figure S1: Meta-analysis of treatment differences between ICS-containing medications and non-ICS-containing medications, stratified by follow-up time; Table S1: Inclusion and exclusion criteria of included studies; Figure S2: Quality assessment of included studies. Quality assessment.

Abbreviations

COPD: Chronic obstructive pulmonary disease; FEV1: Forced expiratory volume in 1 s; ICS: Inhaled corticosteroids; LABA: Long active beta agonist; LAMA: Long acting muscarinic antagonist

Acknowledgements

Not applicable.

Author’s contributions

HW- literature search, reviewed titles and full text articles, extracted data, analysed data, writing. MS- reviewed titles and full text articles, contributed to data extraction. DJ, SK, and JQ- critical revision of the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable (no funding).

Availability of data and materials

Not applicable.

Ethics approval

Not applicable.

Consent for publication

Not applicable.

Competing interests

Miss Whittaker reports grants from GlaxoSmithKline, outside the submitted work. Mr. Sheikh has no competing interests. Dr. Jarvis reports grants from MRC, grants and other from BI, grants and other from Chiesi, other from Teva outside the submitted work.

Author details

1National Heart and Lung Institute, Imperial College London, Emmanuel Kaye Building, 1b Manresa Road, London SW3 6LR, UK. 2MRC Biostatistics, University of Cambridge, Cambridge, UK.

Received: 8 July 2019 Accepted: 25 November 2019

Published online: 04 December 2019

References

1. NICE. Chronic obstructive pulmonary disease in over 16s: diagnosis and management | https://www.nice.org.uk/guidance/cg101. Accessed 4 Apr 2019.

2. GOLD. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2018. [Cited 2019 April 4]. Available from: https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_VMS.pdf.

3. NICE. Chronic obstructive pulmonary disease in over 16s: diagnosis and management 2018. [Cited 2019 April 4]. Available from: https://www.nice.org.uk/guidance/ng115.

4. GOLD. Global Initiative for Chronic Obstructive Lung Disease 2019. [Cited 2019 April 4]. Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-VMS.pdf. Accesssed 4 Apr 2019.

5. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1:1645–8.

6. Vestbo J, Anderson JA, Brook RD, Calverley PMA, Celli BR, Crim C, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. Lancet. 2016;387(10030):1817–26.

7. Sutherland ER, Almers H, Aysa NT, Venn AJ, Martin RJ. Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: a metaanalysis. Thorax. 2003;58:937–41.

8. Lapperre TS, Snoeck-Stroband JB, Gosman MME, Jansen DF, van Schadewijk A, Thilagens HA, et al. Effect of fluticasone with and without Salmeterol on pulmonary outcomes in chronic obstructive pulmonary disease. Ann Intern Med. 2009;151:517–27.

9. Calverley PM, Anderson JA, Brook RD, Crim C, Gallot N, Kilbride S, et al. Fluticasone furoate, vilanterol and lung function decline in patients with moderate COPD and heightened cardiovascular risk. Am J Respir Crit Care Med. 2017;197(1):47–55.

10. Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, et al. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med. 2011;365(13):1184–92.

11. Taskhin DP. Variations in FEV1 decline over time in chronic obstructive pulmonary disease and its implications. Curr Opin Pulm Med. 2013;19(2):116–24.

12. Woodcock A, Boucot I, Leather DA, Crawford J, Coller S, Bakerly ND, et al. Effectiveness versus efficacy trials in COPD. How study design influences outcomes and applicability. Eur Respir J. 2018;51(2):1701531.

13. Rodrigo GJ, Price D, Anzueto A, Singh D, Altman P, Badger G, et al. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2017;12:907–22.

14. Rogliani P, Calzetta L, Braidot F, Cazzola M, Clini E, Pelia G, et al. LABA/LAMA fixed-dose combinations in patients with COPD: a systematic review. Int J Chron Obstruct Pulmon Dis. 2018;13:3115–30.

15. Miravitlles M, Urrutia G, Mathoudakis AG, Arcochea J. Efficacy and safety of tiotropium and olodaterol in COPD: a systematic review and meta-analysis. Respir Res. 2017;18(1):16.

16. Horita N, Miyazawa N, Tornam K, Inoue M, Keneko T. Long-acting muscarinic antagonist+long-acting beta agonist versus long-acting beta agonist+inhaled corticosteroid for COPD: A systematic review and meta-analysis. Respiratory (Carlton, Vic). 2015;20(8):1153–9.

17. Rodrigo GJ, Castro-Rodriguez JA, Plaza V. Safety and efficacy of combined long-acting beta-agonists and inhaled corticosteroids vs long-acting beta-agonists monotherapy for stable COPD: a systematic review. Chest. 2009;136(4):1029–38.

18. Van Grunsven PM, Van Schayck CP, Derenja JP, Kerstjens HAM, Remker TEJ, Postma DS, et al. Long term effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a meta-analysis. Thorax. 1999;54:147–14.

19. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

20. Altman DG. Practical statistics for medical research. London: Chapman and Hall; 1991.

21. Auffarth B, Postma DS, De Monchy JGR, Van Der Mark TW, Boorsma M, Koeter GH. Effects of inhaled budesonide on spiroometric values, reversibility, airway responsiveness, and cough threshold in smokers with chronic obstructive lung disease. Thorax. 1991;46(5):372–7.

22. Cazzola M, Di Lorenzo G, Di Penna F, Calderaro F, Testi R, Centanni S. Additive effects of salmeterol and fluticasone or theophylline in COPD. Chest. 2000;118(6):1576–81.

23. Lee SD, Xie CM, Yunus F, Itoh Y, Ling X, Yu WC, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium compared with tiotropium alone in patients with severe or very severe COPD: a randomized, multicentre study in East Asia. Respir Res. 2016;21(1):119–27.

24. Bourbeau J, Rouleau MY, Boucher S. Randomised controlled trial of inhaled corticosteroids in patients with chronic obstructive pulmonary disease. Thorax. 1998;53(1):15–22.

25. Rodrigo GJ, Price D, Anzueto A, Singh D, Altman P, Badger G, et al. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. Respir Res. 2017;18(1):196.

26. Whittaker et al. Respiratory Research (2019) 20:277

27. Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist
therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. Lancet (London, England). 2017; 389(10082):1919–29.

28. Wise R, Connell J, Weinmann G, Scanlon P, Skeans M. Effect of inhaled tiotropium on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med. 2000;343(26):1902–9.

29. Weir DC, Bale GA, Bright P, Sherwood BP. A double-blind placebo-controlled study of the effect of inhaled beclometasone dipropionate for 2 years in patients with nonasthmatic chronic obstructive pulmonary disease. Clin Exp Allergy. 1999;29(Suppl 2):125–8.

30. Renkema TEJ, Schouten JP, Koeter GH, Postma DS. Effects of long-term treatment with corticosteroids in COPD. Chest. 1996;109(3):1156–62.

31. Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. Br Med J. 2000;320(7245):1297–303.

32. Calverley PMA, Spencer S, Willits L, Burge PS, Jones PW. Withdrawal from treatment as an outcome in the ISOLDE study of COPD. Chest. 2003;124(4):1350–6.

33. Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Pride NB, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society study on chronic obstructive pulmonary disease. N Engl J Med. 1999;340(25):1948–53.

34. Vestbo J, Sorensen T, Lange P, Brin A, Tone P, Vlaskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 1999;353(9167):1819–23.

35. Calverley PMA, Anderson JA, Brook RD, Crim C, Gallot N, Kilbride S, et al. Fluticasone furoate, vilanterol, and lung function decline in patients with moderate chronic obstructive pulmonary disease and heightened cardiovascular risk. Am J Respir Crit Care Med. 2018;197(1):47–55.

36. Shaker SJ, Dirksen A, Ulrik CS, Stavngaard T, Laursen LC, et al. The effect of inhaled corticosteroids on the development of emphysema in smokers assessed by annual computed tomography. COPD. 2009;6(2):104–11.

37. Babu KS, Kastelik JA, Morjaria JB. Inhaled corticosteroids in chronic obstructive pulmonary disease: a pro-con perspective. Br J Clin Pharmacol. 2014;78(2):282–300.

38. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775–89.

39. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. Eur Respir J. 2003;22(4):672.

40. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. Nat Rev Immunol. 2008;8(3):183–92.

41. Usmani OS, Ito K, Manecheoteswaran K, Ito M, Johnson M, Barnes PJ, et al. Glucocorticoid receptor nuclear translocation in airway cells after inhaled combination therapy. Am J Respir Crit Care Med. 2005;172(6):704–12.

42. Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting β2-agonists and corticosteroids. Eur Respir J. 2002;19(1):182.

43. Tashkin DP, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease. Respir Res. 2013;14(1):9.

44. Lal C, Strange C. A review of current and developing fixed-dose LABA/LAMA combinations for treating COPD. Expert Opin Pharmacother. 2017;18(17):1833–43.

45. Rogglini P, Brando F, Califeta L, Cazzola M, Cini EM, Pelaia G, et al. LAMA/ LABA fixed combinations for COPD management: A systematic comparative review. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS; 2018; 197(MeetingAbstracts).

46. Barnes NC, Sharma R, Letts S, Calverley PM. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. Eur Respir J. 2016;47(5):1374–82.

47. Whittaker HR, Mullerova H, Janus D, Barnes NC, Jones PW, Compton CH, et al. Inhaled corticosteroids, blood eosinophils, and FEV1 decline in patients with COPD in a large UK primary health care setting. Int J Chron Obstruct Pulmon Dis. 2019;14:1063–73.

48. NICE. Chronic Obstructive Pulmonary Disease: beclometasone, formoterol and glycopyrronium (Trimbow) 2018. [Cited 2019 August 02]. Accessed from: https://www.nice.org.uk/advice/es17/resources/chronic-obstructive-pulmonary-disease-beclometasone-formoterol-and-glycopyrronium-trimbow-pdf-1158120380869.

49. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax. 2013;68(11):1029–36.

50. Janson C, Johansson G, Stallberg B, Lisspers K, Olsson P, Keininger D, et al. ICS and risk of pneumonia in Swedish COPD patients: The ARCTIC study. Eur Respir J. 2016;48:PA3946.

51. Park HY, Man SF, Sin DD. Inhaled corticosteroids for chronic obstructive pulmonary disease. BMJ. 2012;345:e6843.

52. Gruffydd-Jones K, Brusselle G, Jones R, Miravitlles M, Baldwin M, Stewart R, et al. Changes in initial COPD treatment choice over time and factors influencing prescribing decisions in UK primary care: in UK primary care: a real-world, retrospective, observational. NPJ Prim Care Respir Med. 2016;26:16002.

53. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. Am J Respir Crit Care Med. 2014;189(3):250–5.

54. Tantucci C, Modina D. Lung function decline in COPD. Int J Chron Obstruct Pulmon Dis. 2012;7:95–9.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.