Narrative review

The effectivity of inhaled corticosteroids in COPD

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Abstract
ICS (inhaled corticosteroids) often are used in COPD patients. But there are many controversies about the effect of ICS in COPD. It is unclear, for one thing, if the beneficial conclusions of ICS in COPD in earlier studies, are due to the inclusion of asthma in these studies. This narrative review aims to collect and assess the available evidence of the effects of ICS in COPD and the special focus of this review is to determine whether or not asthma has been properly excluded in the studies. There are a lot of ways to exclude asthma but not all of them are sufficient enough. The main focus in this review is on how to exclude asthma in ICS alone, combination therapy and triple therapy. ICS in COPD are not very effective. Positive results may be due to the inclusion of asthma or clinical features of asthma in COPD, also called ACOS. The more asthma is included, the more positive the effect of ICS in COPD is. This is due to the pathology of the different diseases asthma and COPD. More research is needed in ICS and COPD as well as in combination therapy and triple therapy.

Introduction
Chronic Obstructive Pulmonary disease (COPD) is a disorder which is characterised by persistent airflow obstruction, associated with an increased inflammatory reaction in the respiratory tract and lungs (1). COPD has become a major problem for worldwide health. The number of COPD patients is growing, in 2030 it is expected to be the 4th leading cause of death (2). But there are ways to prevent and treat COPD. Active and passive smoking are the major risk factors for COPD, so prevention of COPD should be focussed on prevention of smoking (3). COPD can be treated with bronchodilators and with inhaled corticosteroids (ICS). Generally, inhaled corticosteroids are glucocorticoids that cause a reduction in lung inflammation. ICS have been shown to improve symptoms, lung function and quality of life. Another advantage is the reduction of exacerbations in patients with a more severe airflow limitation, which means a FEV1 less than 60% of predicted. These effects have been found in a huge number of randomized, placebo-controlled clinical trials of various designs and durations. A side effect of ICS is the increased risk of pneumonia and if you stop using ICS it can lead to exacerbations (4). ICS can be used alone or in combination with long-acting bronchodilator...
therapy with Long-acting beta-adrenoceptor agonist (LABA) or a triple inhaled therapy in which a Long-acting muscarinic antagonists (LAMA) is added to LABA and ICS. Indeed, many trials studying the effects of ICS in COPD have been done with various combinations of bronchodilators as co-medication. One important confounder in COPD studies is the inclusion or exclusion of asthma in the study population. ICS are the cornerstone of drug therapy in asthma with proven effects on symptoms, lung function, exacerbation frequency and even survival. Therefore, when studying the effects of ICS in COPD, patients with (suspected) asthma need to be excluded adequately. COPD can coexist with asthma which is called Asthma-COPD Overlap Syndrome (ACOS) but these are different diseases. In all these studies there is a difficulty in the diagnosis of COPD because it may resemble asthma. This leads to studies which includes both asthma and COPD, not properly excluding asthma resulting in the end to a variety of conclusions because of the different clinical features. There are many controversies about the effect of inhaled ICS in COPD. It is unclear, however, if the beneficial conclusions of ICS in COPD in earlier studies, are due to the inclusion of asthma in these studies. This narrative review aims to collect and assess the available evidence of the effects of ICS in COPD and the special focus of this review is to determine whether or not asthma has been properly excluded in the studies. The main focus in this review is on how to exclude asthma, this is studied in ICS alone, combination therapy and triple therapy.

**Differences of COPD and asthma**

A lot of studies exclude the diagnosis of asthma, but there are varieties in the way they do this. Both disorders come with symptoms like dyspnoea, wheezing, cough and sputum production and attacks, usually called exacerbations and are characterized by inflammation of the respiratory tract but there are fundamental differences in COPD and asthma. The inflammation in asthma is mainly eosinophilic and for COPD this is neutrophilic. The number of macrophages is increased in COPD, this results in more CD4+ and CD8+ T cells in the lungs. Also lymphocytes are increased especially the Tc1, Th1, Th17 an ILC3 cells. In asthma mast cells and DCs are involved which are not considered important in COPD. These differences are not that distinct, as patients with severe asthma or smoking asthmatic patients can also have a neutrophilic inflammation (5). Also the other way around, COPD patients are found to have Th2 or ILC2 eosinophils (6). Those inflammatory cells release inflammatory mediators which are in COPD: lipid mediators, cytokines, chemokines and growth factors (7). All those differences in the pathology lead to other reactions of corticosteroids. In asthma corticosteroids reduce inflammation by provoking the recruitment of the enzyme histone deacetylase 2 (hDAC2) which leads to activated inflammatory genes. Those genes cause a deacetylation of hyper acetylated genes and supress in this way the inflammation. In COPD corticosteroids are not very able to reduce the inflammation. This may be due to the decreased activity and expression of hDAC2 in COPD patients. The reason for this is the increase in oxidative and nitrate stress (5). The inflammatory processes are very complex. There is a lot that is not understood yet and more research is needed (8). The way COPD and asthma respond to corticosteroids is different. This is why it is important to properly exclude asthma when studying the effects of ICS in COPD. As seen in asthma other cells and mediators are involved which react a lot better on corticosteroids than the cells and mediators involved in COPD. This means the population of COPD patients, which also contains insufficient exclusion of asthma, will show a greater effect on ICS than the population where asthma is excluded sufficient. This could result from studies with a polluted population which show more divergent effects than in a homogenous population with only COPD. There are many ways to exclude asthma in studies. The most used one is by excluding patients with a (current) diagnosis of asthma. But you should always take into account is if the diagnosis is right. The blurred lines between asthma and COPD are difficult to distinguish even for physicians. Also non-COPD respiratory disorders are often excluded. Less frequently used ways to exclude asthma are blood eosinophilia, clinical features of asthma, self-reported history, symptoms of asthma, allergic rhinitis, or allergic eczema. Another way found in a study is by excluding patients who regularly used bronchodilators or corticosteroids. But this is not an adequate way of excluding asthma. Because not only people who have medication for asthma have asthma. If you are uninformed of having the disease then you do not have medication for asthma. The effects of those different ways of excluding asthma on ICS in COPD will be shown in the next section.
**ICS alone**

The effect of ICS in COPD is a subject which contains a lot of controversies. The way asthma is excluded has an big impact on the outcome. In this section we will compare studies that have attempted to exclude patients with (what may well have been) asthma and their effect on the outcome. In this review most recent and key studies are chosen. A small study showed no treatment effect of ICS on FEV1 and exacerbations. The study duration was 2 years. Asthma was excluded by case of blood eosinophilia, positive skin test results for allergy, or increased serum levels of total IgE. Results are explained by the clear COPD population. Studies which included COPD patients with substantial reversibility of airflow limitation, blood or sputum eosinophilia, atopy and those with wheezing as a predominant symptom show effects of ICS because those are asthmatic symptoms (9). Even a high does not appear to be effective, no difference was found in FEV1. Asthma was excluded by history of allergic asthma during childhood or as an adult (10). A study included smoking COPD patients using ICS showed no effect on long-term decline in lung function. Patients were excluded by subjects with a history of asthma, allergic rhinitis, or allergic eczema. Attempt was to exclude the history of asthma or any other atopic disease or with reversible airflow limitation (11). A large double blind study, the TORCH trial, included patients with a diagnosis of COPD and excluded diagnosis of asthma and non-COPD respiratory disorders. The effect of ICS alone in COPD was not of statistical significance. A slightly higher mortality was found in patients with fluticasone alone in comparison with placebo (12, 13). There was a significant effect in the decline of the FEV1 rate showed a post-hoc analysis of the TORCH trial (14). In the GLUCOLD study asthma was excluded by the presence of asthma on the basis of a physician’s diagnosis or self-reported history, symptoms, treatment, or diagnosis of asthma. Effects of long-term therapy with ICS are reduced inflammation in bronchial biopsies and sputum in COPD. This is shown by attenuated lung function decline, airway hyper responsiveness, dyspnoea, and improved quality of life (15). The ISOLDE study showed a small improvement of FEV1 with the treatment of fluticasone. The treatment also reduced exacerbations and lower health status was measured. Non-asthmatic patients were excluded, but the way how was not mentioned (16). A study called

**ICS in combination with long-acting bronchodilator therapy**

Long-acting bronchodilators relax muscles around the airways which results in opening up the airways, thus increasing airflow. According to GOLD, a combination of an ICS with a long-acting bronchodilator is more effective than ICS alone (19). Results are better on improving lung function, health status and reducing exacerbations. In this section we will compare studies that have attempted to exclude patients with (what may well have been) asthma. Studies used ICS in combination with long-acting bronchodilator therapy. A study with the combination of salmeterol/fluticasone compared with salmeterol monotherapy showed a reduced frequency of moderate/severe exacerbations in COPD patients. Only the diagnosis of asthma was excluded (20). In another study, a history of asthma and/or seasonal allergic rhinitis before the age of 40 were exclusion criteria.
Treatment with Budesonide/formoterol resulted in reduced exacerbations and increased FEV1 by 9-15% (21). Treatment with fluticasone–salmeterol compared to tiotropium therapy showed no difference in the number of exacerbations. However the ICS/LABA combination did improve lung function, quality of life, and hospitalization rates in moderate to severe COPD patients. One exclusion criteria was diagnosed asthma before 40 years of age (22). Another study used the same treatment of salmeterol and fluticasone. The results of the combination treatment led to better control of symptoms and lung function. In risk of side-effects was no difference in use alone or combination. This study recommends using the combination treatment for patients with COPD. An exclusion criteria was respiratory disorders other than COPD (23). In a study no difference in exacerbation rate between salmeterol/fluticasone propionate and tiotropium was found. But there was a small significant positive effect on health status. Any respiratory disorders other than COPD were excluded (24). The TORCH trial, mentioned earlier, researched also the effects of salmeterol and fluticasone together. The combination showed reduced exacerbations, and improvements in health status and FEV1 were found. Patients with a diagnosis of COPD were included and patients with the diagnosis of asthma and non-COPD respiratory disorders excluded (12, 13). The TORCH data are included in a meta-analysis. There was no significant effect found of ICS in combination with long-acting bronchodilator on mortality (25). In the SUMMIT study there was not an increase in mortality with patients who took fluticasone. Inhaled therapy improved lung function and fluticasone furoate, alone or in combination with vilanterol, was associated with a reduction in the rate of decline in FEV1. The combination of fluticasone furoate and vilanterol does not affect overall survival or cardiovascular outcomes. The trial excluded respiratory disorders other than COPD, in which way was not mentioned (26). A trial had 691 patients using fluticasone propionate and salmeterol. Improved lung function and reduced the severity of dyspnoea compared was found in the study. The way asthma was excluded was by just excluding the diagnosis of asthma.

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Used ICS</th>
<th>Way of excluding asthma</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renkema, 1996</td>
<td>2 years</td>
<td>Budesonide 1,600 μg</td>
<td>Case of blood eosinophilia, positive skin test results for allergy, or increased serum levels of total IgE</td>
<td>No effect on FEV1 and exacerbations</td>
</tr>
<tr>
<td>Bourbeau, 1998</td>
<td>6 months</td>
<td>Budesonide 1600 μg</td>
<td>History of allergic asthma during childhood or as an adult</td>
<td>No effect on FEV1</td>
</tr>
<tr>
<td>Pauwels, 1999</td>
<td>3 years</td>
<td>Budesonide 400 μg</td>
<td>History of asthma, allergic rhinitis, or allergic eczema</td>
<td>No effect on FEV1</td>
</tr>
<tr>
<td>Calverley, 2007</td>
<td>3 years</td>
<td>Fluticasone, 500 μg</td>
<td>Diagnosis of asthma and non-COPD respiratory disorders</td>
<td>Not of statistical significance, slightly higher mortality</td>
</tr>
<tr>
<td>Laperre, 2009</td>
<td>30 months</td>
<td>Fluticasone, 500 μg</td>
<td>Presence of asthma on the basis of a physician’s diagnosis or self-reported history, symptoms, treatment, or diagnosis of asthma</td>
<td>Attenuated lung function decline, airway hyperresponsiveness, dyspnoea, and improved quality of life</td>
</tr>
<tr>
<td>Burge, 2000</td>
<td>3 years</td>
<td>Fluticasone, 500 μg</td>
<td>Non-asthmatic patients</td>
<td>Small improvement of FEV1, reduced exacerbations and lower health status</td>
</tr>
<tr>
<td>The Lung Health Study research group, 2000</td>
<td>3 years</td>
<td>Triamcinolone, 1200 μg</td>
<td>Patients who regularly used bronchodilators or corticosteroids</td>
<td>No reduced decline in the FEV1. Declines in airway reactivity and reduced respiratory symptoms</td>
</tr>
<tr>
<td>Yang, 2012</td>
<td>1,2,3 years</td>
<td>5 types in the trials: BUD, BDP, FP, TAA and MF</td>
<td>Clinical features of asthma</td>
<td>No decline of FEV1 or mortality</td>
</tr>
</tbody>
</table>
The treatment did not increase the risk of side effects in patients. The rate of exacerbations was not decreased in improved lung function and quality of life in COPD propionate/salmeterol with also tiotropium. It resulted are not found (30). A randomized controlled study used 62% over tiotropium alone. Details of excluding asthma ICS/LABA combi reduced the rate of exacerbations by found over tiotropium alone. Adding tiotropium to the outcomes. A study used budesonide/formoterol added It might help lung function and patient reported interaction of corticosteroid and muscarinic receptors could result in larger effects of ICS corticosteroids (19). It does not work because of the marked reduction in hDAC2. But hDAC2 is required so corticosteroids can switch off the inflammatory genes (33). But how is it possible that positive effects are found? This is because COPD is a heterogeneous disease, there are different components of the disease. ICS might work better on some components than others, but there is no evidence for this (34). ICS has also a positive effect on COPD patients with clinical characteristics of asthma like for example increased sputum eosinophils. But those patients suffer from Asthma-COPD Overlap Syndrome (ACOS), which might also have positive treatment effects of ICS. This is because of those clinical characteristics of asthma. ICS is an effective drug in asthma. So the reason of some positive effects might be due to the wrong way of excluding asthma. All asthma features have to be excluded to have an adequate idea about what ICS does in COPD. This is also confirmed by this review. A study excluded asthma by case of blood eosinophilia, positive skin test results for allergy, or increased serum levels of total IgE. There was no effect of ICS on FEV1 and exacerbations (9). Another study excluded less asthma strictly by only excluding patients

**Triple inhaled therapy**

Triple inhaled therapy is ICS plus LABA plus LAMA. LAMA is a long-acting muscarinic antagonists. The interaction of corticosteroid and muscarinic receptors could result in larger effects of ICS corticosteroids (19). It might help lung function and patient reported outcomes. A study used budesonide/formoterol added to the LAMA tiotropium. An improvement in FEV1 was found over tiotropium alone. Adding tiotropium to the ICS/LABA combi reduced the rate of exacerbations by 62% over tiotropium alone. Details of excluding asthma are not found (30). A randomized controlled study used propionate/salmeterol with also tiotropium. It resulted in improved lung function and quality of life in COPD patients. The rate of exacerbations was not decreased. The treatment did not increase the risk of side effects like pneumonia. The study states triple-inhaled therapy of FSC (500/100 μg per day) plus tiotropium is beneficial for COPD treatment. Asthma was excluded by a history of physician-diagnosed asthma or a chronic respiratory disorder other than COPD that was clinically significant (31). Another randomized control trial used the same treatment of fluticasone-propionate/salmeterol with tiotropium. Also improved lung and no increase in adverse effects are confirmed. Excluded was clinical diagnosis of respiratory disorder other than COPD (32). The study of Aaron concluded there was no advantage of adding LAMA to LABA/ICS. One exclusion criteria was diagnosed asthma before 40 years of age (22). More research is needed on this combination of ICS plus LAMA plus LABA. A lot is still unknown. The effects of excluding asthma properly in this treatment will be very small. This is because the contribution of the ICS to the observed effects becomes smaller with the combination of LAMA and LABA.

**Conclusion**

The effects of ICS in COPD are not the same in every study, there is a broad range of results. The reason why ICS in COPD does not work is because of the pathology. It does not work because of the marked reduction in hDAC2. But hDAC2 is required so corticosteroids can switch off the inflammatory genes (33). But how is it possible that positive effects are found? This is because COPD is a heterogeneous disease, there are different components of the disease. ICS might work better on some components than others, but there is no evidence for this (34). ICS has also a positive effect on COPD patients with clinical characteristics of asthma like for example increased sputum eosinophils. But those patients suffer from Asthma-COPD Overlap Syndrome (ACOS), which might also have positive treatment effects of ICS. This is because of those clinical characteristics of asthma. ICS is an effective drug in asthma. So the reason of some positive effects might be due to the wrong way of excluding asthma. All asthma features have to be excluded to have an adequate idea about what ICS does in COPD. This is also confirmed by this review. A study excluded asthma by case of blood eosinophilia, positive skin test results for allergy, or increased serum levels of total IgE. There was no effect of ICS on FEV1 and exacerbations (9). Another study excluded less asthma strictly by only excluding patients
who regularly used bronchodilators or corticosteroids. This study resulted in no decline in the FEV1, but declines are found in airway reactivity and reduced respiratory symptoms (17). Also the ISOLDE study found a small improvement of FEV1 and reduced exacerbations. Asthma was only excluded by excluding non-asthmatic patients and probably the cause of the results (16). Another exclusion criteria that is often used is the diagnosis of asthma. But the studies are not very clear about how they exactly exclude asthma, in some they state the decision is made by a physician. This makes it an optimistic way of excluding asthma. A trial of 55 studies concluded that there was no decline of FEV1 or mortality (18). This leads to the conclusion: The more asthma is excluded the less effect of ICS in COPD is found (Table 1). If you add another medicine or two it the effect of properly excluding asthma will become less. About ICS in combination with long-acting bronchodilator therapy is still a lot unclear. A lot of studies are contradicting but it might be better than ICS alone. Also about the combination of ICS plus LABA is still a lot unclear. Also other factors in COPD research are in important for comparing the studies like duration, treatment, dosage and different outcome measurements. The duration time could influence the results. A duration of a couple week is less reliable than a study of 2 years. The different ICS used could also lead to differences in outcome. Fluticasone and Budesonide are difficult to compare, also dosage difference could influence outcome. The outcome could be measured differently for example mortality or FEV1. All those difference makes it difficult to compare studies.

**Recommendations**

To have a reliable idea about what ICS does in COPD asthma should be excluded rigorously. The best way to do this may be excluding most of the clinical asthmatic features. This means excluding asthma in any possible way. The diagnosis of asthma should be excluded but also the history of asthma. But also the risk factors for

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Used ICS (2x daily)</th>
<th>Way of excluding asthma</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kardos, 2006</td>
<td>44 weeks</td>
<td>Salmeterol 50 µg and fluticasone 500 µg combination</td>
<td>Diagnosis of asthma</td>
<td>Reduced frequency of moderate/severe exacerbations</td>
</tr>
<tr>
<td>Szafranski, 2003</td>
<td>12 months</td>
<td>Budesonide 200 µg and formoterol 4.5 µg</td>
<td>History of asthma and/or seasonal allergic rhinitis before the age of 40</td>
<td>Reduced exacerbations and increased FEV1 by 9-15%</td>
</tr>
<tr>
<td>Aaron, 2007</td>
<td>1 year</td>
<td>Tiotropium, 18 µg once daily, plus salmeterol 25 µg</td>
<td>Diagnosed asthma before 40 years of age</td>
<td>Improved lung function, quality of life, and hospitalization rates</td>
</tr>
<tr>
<td>Calverly, 2003</td>
<td>12 months</td>
<td>Salmeterol 50 µg and fluticasone 500 µg</td>
<td>Respiratory disorders other than COPD</td>
<td>Improved control of symptoms and lung function</td>
</tr>
<tr>
<td>Wedzicha, 2008</td>
<td>2 years</td>
<td>Salmeterol 50 µg and fluticasone 500 µg or tiotropium bromide 18 µg</td>
<td>Any respiratory disorders other than COPD</td>
<td>Small significant positive effect on health status</td>
</tr>
<tr>
<td>Calverley, 2007</td>
<td>3 years</td>
<td>50 µg Salmeterol and Fluticasone 500 µg</td>
<td>Diagnosis of asthma and COPD respiratory disorders</td>
<td>Reduced exacerbations, and improvements in health status and FEV1 were found</td>
</tr>
<tr>
<td>Vestbo, 2016</td>
<td>2 years</td>
<td>Fluticasone 100 µg and Vilanterol 25 µg</td>
<td>Respiratory disorders other than COPD</td>
<td>No increase in mortality, reduction in the rate of decline in FEV1</td>
</tr>
<tr>
<td>Mahler, 2002</td>
<td>6 months</td>
<td>Salmeterol 50 µg and fluticasone 500 µg</td>
<td>Diagnosis of asthma</td>
<td>Improved lung function and reduced the severity of dyspnoea</td>
</tr>
<tr>
<td>Nannini, 2012</td>
<td>8 - 146 weeks</td>
<td>Fluticasone/Salmeterol and Budesonide/Formoterol</td>
<td>Diagnosis of asthma, cystic fibrosis, bronchiectasis, thoracic surgery or other lung diseases.</td>
<td>Beneficial reduction of exacerbations</td>
</tr>
<tr>
<td>Nannini, 2013</td>
<td>4 - 156 weeks</td>
<td>Fluticasone/Salmeterol, Budesonide/Formoterol and Mometasone/Formoterol</td>
<td>Diagnosis of asthma and other lung diseases.</td>
<td>Improved results of FEV1, quality of life and symptoms but probably not significant</td>
</tr>
</tbody>
</table>
COPD like childhood bronchitis and childhood respiratory diseases have to be excluded. Clinical features of asthma like blood eosinophilia should be excluded. Allergies should be excluded by for example increased serum levels of total IgE. COPD could also have a genetic cause, so also family asthma should be excluded. All the previous improvements are needed to properly exclude asthma. Research is needed on the topic ICS in COPD because a lot is still unclear. As discussed the way excluding asthma should be taken into account but also other factors like duration, treatment, dosage and different outcome measurements are important.

References


