CHEST

POINT:

Should an Attempt Be Made to Withdraw Inhaled Corticosteroids in All Patients With Stable GOLD 3 ($30\% \leq FEV_1 < 50\%$ Predicted) COPD? Yes

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PODCAST

ABBREVIATIONS: GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

> "One of the first duties of the physician is to educate the masses not to take medicine."
> (Sir William Osler, *Aphorisms*, 1961)

Inhaled corticosteroids (ICSs) are overused to an unjustified degree in patients with COPD. Over the past two decades they have been the dominant treatment option for COPD.[1] A recent analysis of a large primary care database in the United Kingdom examined the first maintenance therapy prescription for 29,815 patients with GOLD (Global Initiative for Chronic Obstructive Lung Disease) A/B COPD (based on the GOLD 2016 classification) and excluding patients with recorded asthma. Contrary to guidelines, an average 63% received an inhaled corticosteroid-based regimen as their initial therapy.[2]

ICS treatment for the majority of patients with COPD makes little biological sense. ICS is effective against eosinophilic airway inflammation, but neutrophilic inflammation is the dominant "endotype" in patients with severe COPD.[3-5] Neutrophils are not only resistant to the antiinflammatory effects of ICS, but there is increasing evidence that the combination of neutrophils, bacteria, and ICS results in harm.[4-6] ICS disables some neutrophil antimicrobial responses, leading to increased airway bacterial load with potential implications for increased pneumonia or exacerbation risk.[4-6] The converse is that for the minority of patients with COPD who have eosinophilic inflammation, which is not associated with bacterial airway infection, ICS can be highly beneficial.[4-7] This argues for a personalized medicine approach whereby ICS is withdrawn in the majority with neutrophilic disease, where there will be minimal benefit, and continued in those who have eosinophilic disease and a proportion who experience objective benefit after stepping up from long-acting β_2-agonist/long-acting muscarinic antagonist (LABA/LAMA).[3] Such personalized approaches should be the future of COPD treatment.[3]

The recent GOLD strategy has therefore rightly relegated the role of ICS to that of an add-on therapy to combined bronchodilators in patients with frequent exacerbations (GOLD D).[8] The complete absence of ICS as an option for patients with GOLD B COPD (those with symptoms but without frequent exacerbations) is recognition that ICS have only limited effects on lung function and are not an effective therapy for breathlessness.[8,9] Studies comparing ICS/LABA with LABA/LAMA in breathless patients have consistently shown that combined bronchodilators should be the preferred option.[8,9]

If these recommendations are adhered to, this should mean a greatly reduced role for ICS, but what to do with the large numbers of patients with COPD who are currently treated with ICS/LABA or "triple therapy"? It must be right, in view of the long-term safety issues associated with ICS, and the limited evidence of efficacy compared with combined bronchodilators, that all patients are at least considered for withdrawal. This is certainly the view of GOLD that incorporates the option of ICS withdrawal into the 2017 GOLD D algorithm (Fig 1).[8]

I recognize this is an area of controversy. The counterargument to the above position is that ICS are effective drugs in reducing exacerbations and that

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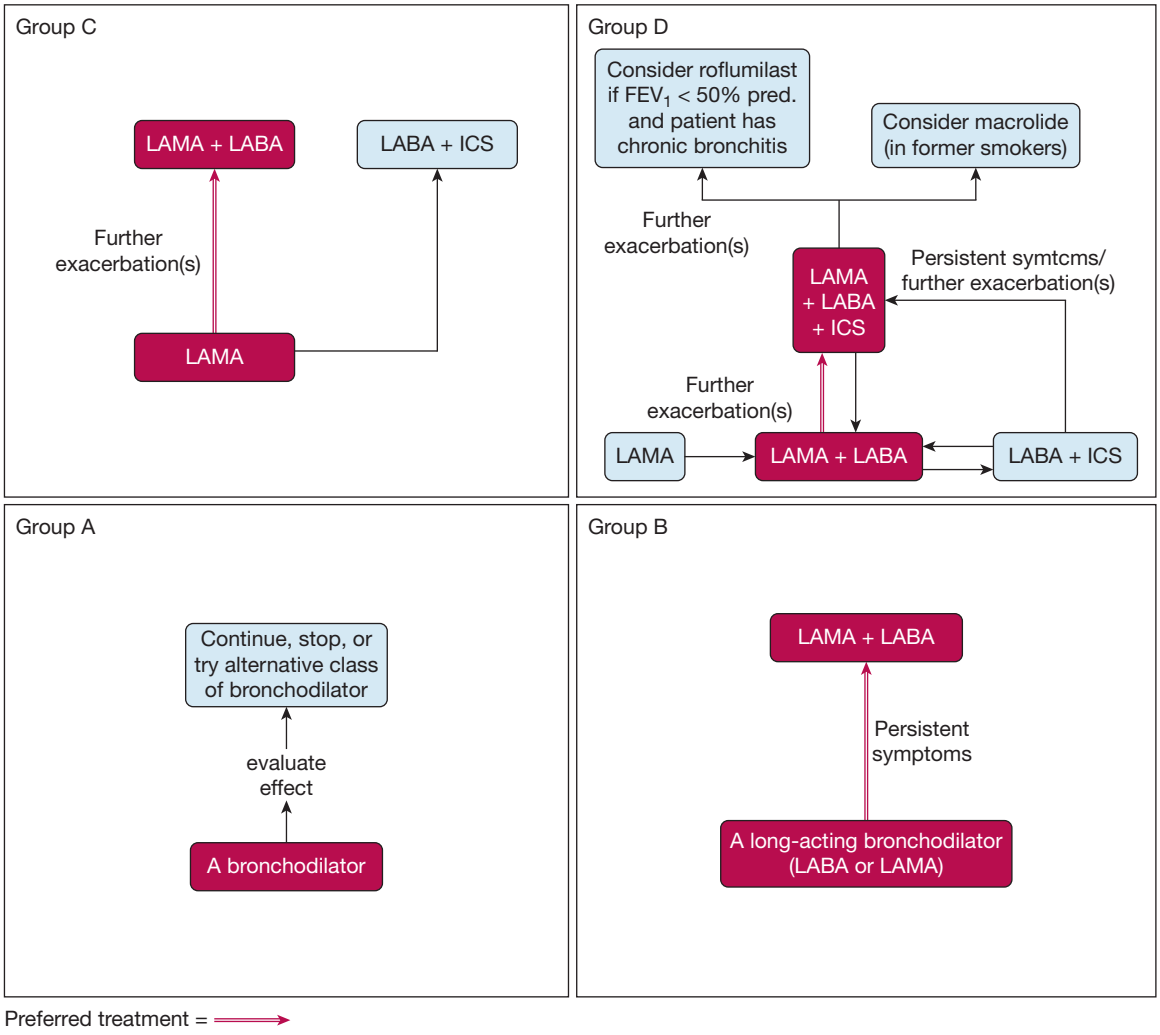

Figure 1 – *Current GOLD treatment recommendations. (Reproduced with permission from Vogelmeier et al.[8]) GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist.*

withdrawal of ICS will result in an unacceptable increase in the frequency of exacerbations in some patients. Others have argued that while ICS may be limited in their effectiveness, once established ICS suppress the adrenocortical axis and therefore withdrawal exposes patients to the dangers of adrenal insufficiency.[10] Below, I will address these issues of efficacy and safety of ICS withdrawal.

First, the efficacy of ICS in COPD is widely overestimated. The Cochrane review of combined ICS/LABA vs LABA, which represents the majority of the evidence supporting the use of ICS in COPD, shows a pooled effect (rate ratio) of 0.76 (95% CI, 0.68-0.84), indicating a 24% reduction in the frequency of exacerbations.[11] It is important to note this is compared with LABA monotherapy, a treatment that is not recommended for patients with a history of exacerbations. The largest study contributing to this meta-analysis is TORCH (Towards a Revolution in COPD Health), which contributes a rate ratio of 0.88 (95% CI, 0.81-0.96), or a 12% reduction in exacerbations.[11] Thus the exacerbation reduction benefit of ICS, even compared with an inappropriately weak comparator, is very modest (Fig 2).[11]

A comparison against a single agent, tiotropium, failed to show a benefit in terms of exacerbations,[12] and it has been clearly demonstrated that ICS/LABA is less effective than LABA/LAMA for the prevention of exacerbations, with no patient subgroup in the FLAME (Effect of Indacaterol Glycopyronium vs Fluticasone Salmeterol on COPD Exacerbations) study apparently having benefit from ICS/LABA compared with bronchodilators.[13] Rates of pneumonia were also higher in ICS/LABA users compared with LABA/LAMA users,

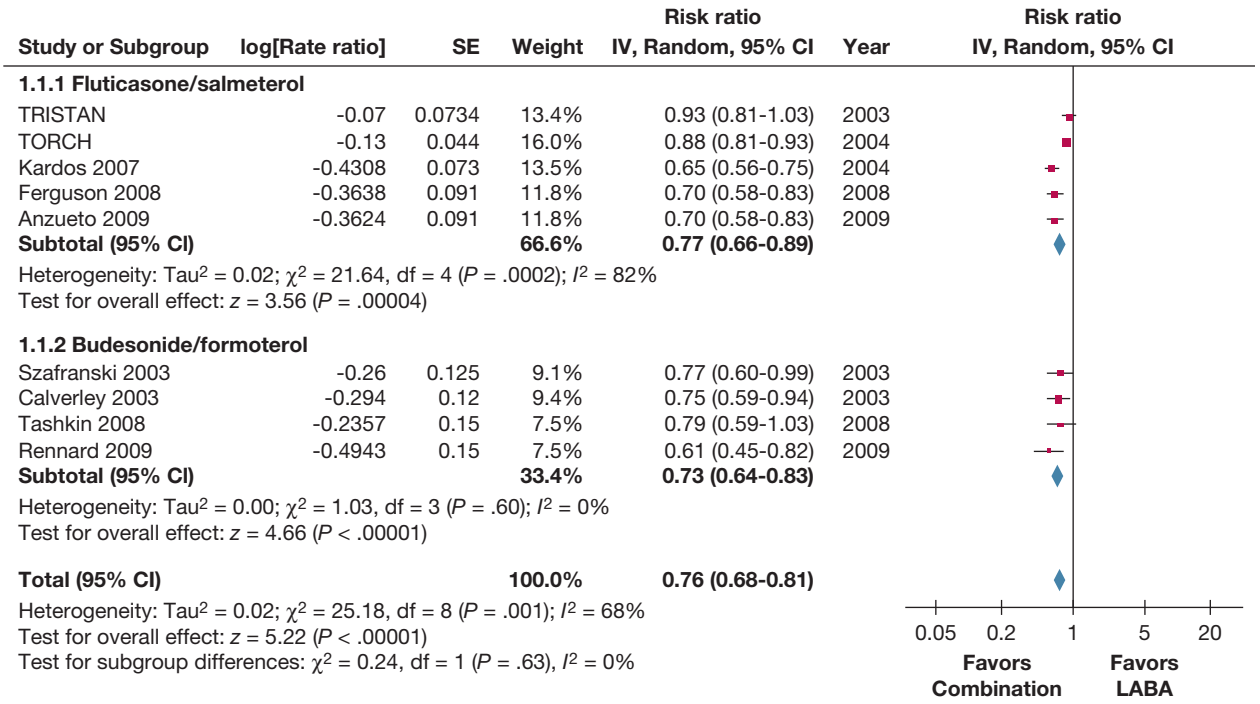

Figure 2 – *Summary of the effectiveness of ICS/LABA vs LABA on exacerbation reduction in COPD. (Reproduced with permission from the Cochrane meta-analysis [Nannini et al[11]].) See Figure 1 legend for expansion of abbreviations.*

giving a compelling combination of superior efficacy and superior safety in favor of the bronchodilator combination.[13]

In my view, there is no justification for the use of ICS/LABA in preference to LABA/LAMA on the basis of current evidence.

So what about "triple therapy"? Until recently, there was very little evidence, although secondary data from a trial of beclomethasone/formoterol vs formoterol, which allowed patients to continue using tiotropium, found a 29% reduction in exacerbations in those taking beclomethasone/formoterol plus tiotropium vs formoterol plus tiotropium.[14] A secondary subgroup analysis is, however, a very poor basis on which to support one of the most frequently used treatment options in COPD. We will soon have the results of the IMPACT (Informing the Pathway of COPD Treatment) study, which has compared triple therapy vs ICS/LABA and LABA/LAMA, and the TRIBUTE (Two-Arm Parallel Group Study of Fixed Combination of CHF 5993 vs Ultibro in COPD Patients) study, which compared beclomethasone/formoterol/glycopyrronium vs indacaterol/glycopyronium.[15] A recent press release of the IMPACT study data suggested that "triple therapy" reduced moderate or severe exacerbations by 25%, from 1.21 to 0.91 per year—a 25% reduction ($P < .001$).[16] This certainly suggests that in a large population, the addition of ICS to LABA/LAMA results in a reduction in exacerbations. Is this reduction so clinically important that we should not consider withdrawal in those patients currently receiving triple therapy? We must await the full publication to fully understand these results, but my rudimentary statistics calculate a number needed to treat of three to four, in a population experiencing approximately one exacerbation per year. This can be very simply translated for patients; on average, such a drug might prevent one moderate exacerbation every 4 years of treatment. I am aware of no quantitative or qualitative study that has examined whether patients would value such a level of benefit in exchange for the well-recognized and documented adverse effects of inhaled corticosteroids. I suspect many would happily first see whether their symptoms and exacerbations can be controlled with a bronchodilator-based regimen.

Regarding the safety of ICS withdrawal, there are now a number of randomized controlled trials that inform us on this issue.[17-19] The largest and most well-known is the WISDOM (Withdrawal of Inhaled Steroids During Optimized Bronchodilator Management) study, which included 2,485 patients randomized after a 6-week run-in period to either a gradual withdrawal of fluticasone over

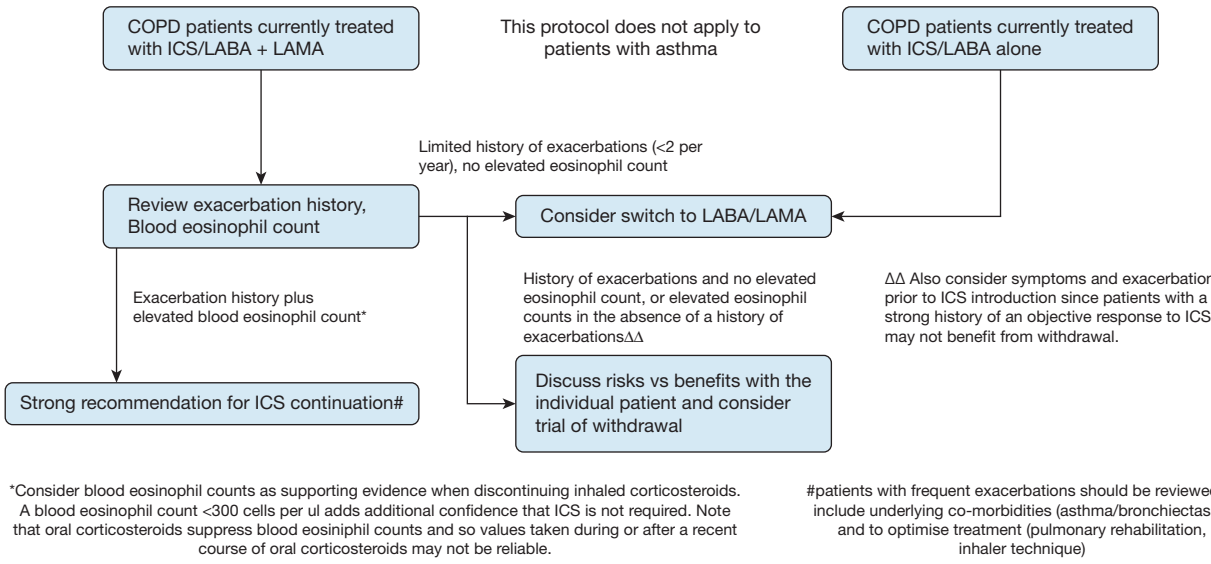

Figure 3 – *A schematic representation of how ICS withdrawal can be operationalized in practice. The majority of patients treated with ICS/LABA could be converted to LABA/LAMA, with those still exacerbating while receiving this regimen being escalated according to GOLD recommendations. Patients receiving triple therapy should be evaluating using exacerbation history and supported by blood eosinophil count and clinical judgment. See Figure 1 legend for expansion of abbreviations.*

3 months (with background LABA and LAMA) or continued treatment with triple therapy. The results showed no significant increase in the frequency of exacerbations. The criticisms of WISDOM are valid, including that the gradual withdrawal meant that the total follow-up time off ICS was only 9 months. Nevertheless, it demonstrated that ICS withdrawal was safe and not associated with an increase in exacerbation frequency. Subsequent analysis found that an increase in exacerbations was only evident in patients with eosinophil counts > 300 cells/μL, representing 448 patients (18% of the original cohort). When this was further analyzed by Vogelmeier et al,[18] only those with a combination of raised eosinophils plus a history of frequent exacerbations (> 1/y) appeared to have an increase in events postwithdrawal (n = 86, or 3.5% of the original cohort).

The INSTEAD (Indacaterol: Switching Nonexacerbating Patients With Moderate COPD From Salmeterol/Fluticasone to Indacaterol) study randomized patients with moderate COPD to either ongoing ICS/LABA or LAMA monotherapy.[19] The key point in this study was that ICS withdrawal was immediate, with no weaning. No difference in outcomes between groups was seen, and there were no reported issues with adrenal insufficiency. The idea that ICS withdrawal is a risk because of symptomatic adrenal insufficiency therefore appears to have no validity. Indeed, virtually all modern inhaler trials in COPD include patients treated with ICS, and will involve a run-in period where ICS is withdrawn. If ICS withdrawal in clinical practice were somehow dangerous, modern COPD trials would be unethical. Finally, on this subject of adrenal insufficiency, recent data using the Inhaler Compliance Assessment (INCA) device, which uses sound recordings to monitor drug compliance (n = 244) in patients treated with ICS/LABA, found that only 22% of patients took their medications as prescribed, and actual adherence after taking into account inhaler technique was 6%. If stopping ICS is somehow dangerous, then it should never be prescribed because patients are constantly discontinuing their ICS through lack of adherence.[20]

There is therefore a clear basis in real-life data, clinical trial data, and in pathobiology, to consider ICS withdrawal in patients with COPD. Figure 3 presents a very simple concept of how this could be done in clinical practice using exacerbation history and the blood eosinophil count to support clinical judgment.

In a sense, the fact that we are having this debate illustrates some of the problems we have psychologically as respiratory physicians with getting over this issue of ICS. It is inconceivable that we would have a debate over whether it would be appropriate to withdraw roflumilast or macrolides in patients who were not achieving benefit or in those who were experiencing adverse events, but these drugs have a similar impact on exacerbations as

ICS.[8] We must stop thinking of ICS as somehow "special," a cornerstone of COPD treatment, when it is clearly just one drug among many that may reduce exacerbations in a small subgroup of patients.[3] The future of COPD treatment is to use all of our medical therapies in a judicious way, following the principles of personalized medicine and optimizing the often neglected nonpharmacological treatments such as pulmonary rehabilitation.[3]

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COUNTERPOINT:

Should an Attempt Be Made to Withdraw Inhaled Corticosteroids in All Patients With Stable GOLD 3 ($30\% \leq FEV_1 < 50\%$ Predicted) COPD? No

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PODCAST

Inhaled corticosteroids (ICS) have been accepted by successive Global Initiative for Chronic Obstructive Lung Disease (GOLD) documents as being effective

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