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Statement of Interest: None declared.

REFERENCES

DOI: 10.1183/09031936.00078510

From the authors:

We agree with M.A. Puhan’s letter regarding the need for full reporting of important clinical end-points and appropriate statistical analysis in randomised controlled trials in chronic obstructive pulmonary disease, the need for which is demonstrated by our robust meta-analysis on cardiovascular outcomes [1].

First, the manufacturers of other inhaled bronchodilators should provide comprehensive listings of adverse events similar to those available for salmeterol–fluticasone. The present systematic review is limited by the paucity of data on budesonide, in a similar manner to our previous analysis on the outcome of pneumonia [2]. However, the subsequent availability of data on budesonide allowed us to conduct appropriate intention to treat meta-analysis on pneumonia, without censoring participants [3]. This analysis demonstrated no conclusive differences between inhaled fluticasone and budesonide on the risk of pneumonia.

Secondly, the concerns about the low absolute incidence of cardiovascular events in the trials are unfounded. The low absolute incidence is unlikely to have significant impact on measures of relative treatment effect in our meta-analysis, because there were sufficient numbers of trial participants and cardiovascular events for us to ascertain reasonably precise estimates (narrow 95% confidence intervals) of the cardiovascular effects of inhaled corticosteroids.

Thirdly, any potential misclassification of outcomes is likely to be non-differential, and would not affect our point estimates, although it may result in some imprecision, because all the randomised controlled trials in our analysis were double-masked.

Finally, we strongly agree with M.A. Puhan that the practice of medicine should be evidence based. The ‘positive’ opinions of inhaled corticosteroids proffered by academics should be critically examined for the hierarchy of evidence, whether they are based on randomised controlled trials or ‘expert’ opinion. These should also be critically evaluated in light of the pervasive issue of publication bias towards positive results in pharmaceutical company-sponsored research of inhaled corticosteroids [4].

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Statement of Interest: None declared.

REFERENCES

DOI: 10.1183/09031936.00089310

From the authors:

M.A. Puhan raises several issues that are frequently used to argue against the use of inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD). First, he implicitly equates hormone replacement (HRT) and celecoxib therapies with the use of ICS in COPD. This is neither fair nor justified based on the existing literature. Unlike these drugs, ICS have
been vigorously evaluated through many large randomised controlled trials (RCTs). Over the past 20 yrs, clinical trials involving >7,000 patients (and 17,000 person-yrs of observation) have unequivocally demonstrated the benefits of ICS therapy in ameliorating symptoms, reducing exacerbations and improving health status in COPD [1, 2]. In combination with long-acting β2-agonists (LABAs), ICS further reduce exacerbations and enhance quality of life of patients with COPD and may even reduce mortality [3, 4]. In contrast, the use of HRT was driven largely by observational studies [5] and celecoxib by short-term (<6 month) clinical trials powered on (arthritic) symptom-based end-points, rather than hard outcomes such as mortality [6]. Thus, the comparison of ICS with these two drugs is unfair and needlessly raises anxiety over the safety of ICS, which when used appropriately are safe [3]. Secondly, M.A. Puhan indicates that our endorsement of the effectiveness of ICS is based just on one (selective) study. We would like to clarify that our conclusion is grounded on data from not just one but many high-quality RCTs, involving >7,000 patients. Collectively, these trials indicate that, compared with the standard treatment (at the time the RCTs were conducted), ICS unequivocally alleviate patient symptoms, enhance their quality of life and reduce the risk of exacerbations [1, 2]. Thirdly, M.A. Puhan indicates that ICS produce no additional benefits when compared with LABAs alone. This statement, however, is not supported by high-quality RCT data. The trials reported by Anzueto et al. [7] involving 797 patients and Kardos et al. [8] involving 994 patients with COPD showed unequivocally that the addition of fluticasone to salmeterol compared with salmeterol alone improved patient symptoms and health status, and resulted in a 30–35% reduction in the rate of exacerbation and hospitalisation over 1 yr. Withdrawal of ICS from patients with COPD, on the other hand, leads to a 50% increase in exacerbations and significant worsening of symptoms [9, 10]. Thus, the totality of data clearly indicates that ICS, especially in combination with LABA, enhance patient-based outcomes in COPD. Finally, we disagree with M.A. Puhan that network meta-analyses can provide a definitive answer to the role of ICS in COPD. There already exists a rich body of high-quality RCT data on ICS in COPD. What we need in the future are mechanistic as well as clinical studies that, by using sophisticated phenotyping and genotyping platforms, will allow clinicians to easily identify patients who will and will not benefit from ICS therapy. Until then, the practising physician can be assured that, in general, by treating their patients with moderate to severe disease, who also have exacerbations, poor quality of life or symptoms, with an ICS-based therapy that they are enhancing the outcomes of these patients.

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Support Statement: D.D. Sin is a senior scholar with the Michael Smith Foundation for Health Research (Vancouver, BC, Canada) and a Canada Research Chair in COPD.

Statement of Interest: Statements of interest for both authors can be found at www.erj.ersjournals.com/misc/statements.dtl

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DOI: 10.1183/09031936.00097710