M.A. Puhan

Dept of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.

Correspondence: M.A. Puhan, Dept of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Mail Room 5010, Baltimore, MD 21205, USA. E-mail: mpuhan@jhsph.edu

Statement of Interest: None declared.

REFERENCES

- 1 Loke YK, Kwok CS, Singh S. Risk of myocardial infarction and cardiovascular death associated with inhaled corticosteroids in COPD. *Eur Respir J* 2010; 35: 1003–1021.
- 2 Sin DD, Man SF. Steroids in COPD: still up in the air? *Eur Respir J* 2010; 35: 949–951.
- 3 McGarvey LP, John M, Anderson JA, *et al.* Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007; 62: 411–415.
- 4 Puhan MA, Schunemann HJ. How to increase the value of randomised trials in COPD research. *Eur Respir J* 2009; 34: 552–558.
- 5 Hill KP, Ross JS, Egilman DS, *et al.* The ADVANTAGE seeding trial: a review of internal documents. *Ann Intern Med* 2008; 149: 251–258.
- 6 Steinman MA, Bero LA, Chren MM, *et al.* Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Ann Intern Med* 2006; 145: 284–293.
- 7 Puhan MA, Bachmann LM, Kleijnen J, *et al.* Inhaled drugs to reduce exacerbations in patients with chronic obstructive pulmonary disease: a network meta-analysis. *BMC Med* 2009; 7: 2.
- 8 Nannini LJ, Cates CJ, Lasserson TJ, *et al.* Combined corticosteroid and long-acting beta-agonist in one inhaler *versus* long-acting beta-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007; 4: CD006829.

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].

S. Singh* and Y.K. Loke#

*Johns Hopkins University School of Medicine, Baltimore, MD, USA. #University of East Anglia, School of Medicine, Health Policy and Practice, Norwich, UK.

Correspondence: S. Singh, Johns Hopkins University School of Medicine, Division of General Internal Medicine, Joint Appointment in International Health, Center for Public Health and Human Rights, Johns Hopkins Bloomberg School of Public Health, 1830 E. Monument St, Rm 8063, Baltimore, MD 21287, USA. E-mail: ssingh31@jhu.edu

Statement of Interest: None declared.

REFERENCES

- 1 Loke YK, Kwok CS, Singh S. Risk of myocardial infarction and cardiovascular death associated with inhaled corticosteroids in COPD. *Eur Respir J* 2010; 35: 1003–1021.
- 2 Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. *Arch Intern Med* 2009; 169: 219–229.
- 3 Singh S, Loke YK. Risk of pneumonia associated with long-term use of inhaled corticosteroids in chronic obstructive pulmonary disease: a critical review and update. *Curr Opin Pulm Med* 2010; 16: 118–122.
- 4 Liss H. Publication bias in the pulmonary/allergy literature: effect of pharmaceutical company sponsorship. *Isr Med Assoc J* 2006; 8: 451–454.

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 β_2 -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.

D.D. Sin and S.F.P. Man

Dept of Medicine, Division of Respiriology, The University of British Columbia and The UBC James Hogg Research Center at

the Providence Heart and Lung Institute, St. Paul's Hospital, Vancouver, BC, Canada.

Correspondence: D.D. Sin, UBC James Hogg Research Center, Providence Heart and Lung Institute, St Paul's Hospital, Room #368A, 1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada. E-mail: don.sin@hli.ubc.ca

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

REFERENCES

- 1 Sin DD, Wu L, Anderson JA, *et al.* Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. *Thorax* 2005; 60: 992–997.
- 2 Yang IA, Fong KM, Sim EH, *et al.* Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007; 2: CD002991.
- 3 Kliber A, Lynd LD, Sin DD. The effects of long-acting bronchodilators on total mortality in patients with stable chronic obstructive pulmonary disease. *Respir Res* 2010; 11: 56.
- 4 Nannini L, Cates CJ, Lasserson TJ, *et al.* Combined corticosteroid and long-acting beta-agonist in one inhaler *versus* placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007; 4: CD003794.
- 5 Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. *N Engl J Med* 2003; 348: 645–650.
- 6 Emery P, Zeidler H, Kvien TK, *et al.* Celecoxib *versus* diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet* 1999; 354: 2106–2111.
- 7 Anzueto A, Ferguson GT, Feldman G, *et al.* Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. *COPD* 2009; 6: 320–329.
- 8 Kardos P, Wencker M, Glaab T, *et al.* Impact of salmeterol/fluticasone propionate *versus* salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 175: 144–149.
- 9 van der Valk P, Monninkhof E, van der Palen J, *et al.* Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. *Am J Respir Crit Care Med* 2002; 166: 1358–1363.
- 10 Wouters EF, Postma DS, Fokkens B, *et al.* Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. *Thorax* 2005; 60: 480–487.

DOI: 10.1183/09031936.00097710