From the authors:

We would like to thank J.E. Hansen for his detailed response to our recently published analysis regarding prevalence of bronchoreversibility in subjects enrolled in the National Emphysema Treatment Trial [1]. J.E. Hansen raises a concern that the American Thoracic Society (ATS)/European Respiratory Society (ERS) definition of bronchoreversibility is too restrictive in that it requires both an absolute forced expiratory volume in 1 s (FEV_1) $\geqslant$200 mL and a 12% increase in FEV_1 to qualify as a positive test, which may underestimate bronchoreversibility in a patient population with very low lung function. J.E. Hansen has asked us for a reanalysis of the data with this in mind. If we use the ATS criteria for bronchoreversibility, 121 (22.2%) subjects met these criteria at least once during the period of evaluation. If we choose a 12% absolute increase in FEV_1 alone as our definition for bronchoreversibility, 452 (83%) subjects met this criterion at least once during the period of evaluation. As J.E. Hansen suspected, the number of subjects meeting this less restrictive criterion is significantly higher, although possibly too high, making the clinical utility less clear. As J.E. Hansen pointed out, identifying the ''perfect'' measure for bronchoreversibility is not an easy task and perhaps should depend on the subject population being studied. The data we present in our paper helps us to better understand the prevalence of bronchoreversibility in the severe emphysema patient population, but the choice of definition for bronchoreversibility should ultimately be determined by the definition that best discriminates patients as they relate to clinically meaningful outcomes.

M.K. Han and F.J. Martinez
Pulmonary and Critical Care, University of Michigan, Ann Arbor, Michigan, MI, USA.

Correspondence: M.K. Han, Pulmonary and Critical Care, University of Michigan, 1500 E Medical Center Dr, 3916 Taubman Center, Ann Arbor, MI, USA. E-mail: mrking@umich.edu

REFERENCES

1 Han MK, Wise R, Mumford J, *et al*. Prevalence and clinical correlates of bronchoreversibility in severe emphysema. *Eur Respir J* 2010; 35: 1048–1056.

DOI: 10.1183/09031936.00104510

Inhaled corticosteroids: a controversial add-on treatment in COPD

To the Editors:

LOKE *et al.* [1] provide an excellent meta-analysis of the risk of cardiovascular events (CVEs) associated with inhaled corticosteroids (ICSs) in patients with chronic obstructive pulmonary disease (COPD) [1]. In their editorial, SIN and MAN [2] point out that the incidence of CVEs was very low, and I am also concerned that the available trials do not provide a definitive answer because of the way in which CVEs were ascertained. The only trial that explicitly ascertained CVEs as a cause of death and verified them using an adjudication committee was the TOwards a Revolution in COPD Health (TORCH) trial [3]. Indeed, a much higher rate of fatal CVEs was found than in all of the other trials, which cannot alone be explained by the long observation period of 3 yrs. In consequence, the meta-analyses are largely driven by the TORCH trial, whereas most other trials contribute little to the analyses. This may well be because CVEs were not rigorously captured, as pointed out by SIN and MAN [2], which is a common problem for secondary outcomes [4]. The authors may want to discuss whether or not the low incidence of CVEs in the other trials is a consequence of different study populations, insufficient CVE ascertainment or incomplete reporting of CVEs, and whether the latter two may be differential for treatment groups. In addition, I wonder whether they see any opportunity for assessing whether selective and/or differential reporting of CVEs could be present in some of the trials.

Although I agree with the editorial that current data do not provide a definitive answer regarding the role of ICSs, I largely disagree with some of the statements supporting their role. First, history shows that blockbuster or widely prescribed drugs are not necessarily effective or safe drugs (*e.g.* hormone replacement therapy, celecoxib or antibiotics for sinusitis or acute otitis media). Secondly, there is ample evidence that various forms of pharmaceutical marketing are effective in influencing physicians through opinion leaders, seeding trials and continuing medical education [5, 6]. Thirdly, the cited ''unequivocal evidence'' for the effectiveness of ICSs is selectively chosen and based on single observational studies or randomised trials. Additionally, the question as to whether ICSs are superior over placebo is not really relevant because ICSs are used as an add-on treatment to long-acting bronchodilators, and rarely without them. Current meta-analyses and network meta-analyses do not suggest a great additional value of ICSs in reducing exacerbations or improving health-related quality of life to a clinically meaningful extent unless the COPD is very advanced [7, 8]. Research should further explore ICSs but focus on the comparisons relevant for practice. Important clinical end-points should be carefully ascertained and fully reported so that future (network) meta-analyses provide more definitive answers regarding the role of ICSs in COPD patients.

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