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CORRESPONDENCE

Comorbidities in COPD

To the Editors:

We read with great interest the recent review article by BARNES and CELLI [1] outlining the systemic manifestation of chronic obstructive pulmonary disease (COPD) and the potential benefits of statin therapy in the management of COPD. In this article, the authors propose that statins may have a dual role in reducing pulmonary and systemic inflammation, through inhibition of cell signalling molecules (Ras, Rho and Rac). Attenuation of pulmonary inflammation would result from inhibition of inflammatory cell migration and associated cytokine release into lung tissue. Attenuation of systemic inflammation would result from a reduction in pulmonary inflammation (reduced ''spill over'' into the systemic circulation) and inhibition of interleukin (IL)-6 and C-reactive protein synthesis from the liver and other tissues [2]. We suggest the pharmacological and clinical benefits of statins in COPD [3] may be even greater than described in this review.

With respect to the possible inhibition of pulmonary inflammation, a recent systematic review of observational studies showed that patients with COPD taking statins had consistently better outcomes than those not taking statins [4]. Benefits included less COPD exacerbations (30% reduction), lower mortality from chest infections (40–50% reduction), a slower decline in forced expiratory volume in 1 s (FEV_1) and lower all-cause mortality (50% reduction). In addition to these findings, we have shown that three large observational studies consistently show a reduced risk of lung cancer in those taking statins (30–50% reduction) [3]. The latter benefit is of considerable importance as lung cancer accounts for the greatest proportion of deaths (33%) in patients with COPD [5]. Moreover, along with other studies, we have recently shown that as many as 70% of patients with lung cancer have pre-existing COPD [6]. If statins confer a chemopreventive action as suggested, then widespread use of statins in patients with COPD might, along with reduced smoking rates, reduce the incidence of lung cancer in the near and long term. The mechanism for this chemopreventive effect has been elucidated in studies showing that statins not only inhibit the pulmonary inflammatory and remodelling processes underlying COPD [1, 3], but also inhibit (or even reverse) subsequent epithelial mesenchymal transition, recognised in pre-clinical studies as the precursor to lung malignant transformation [7, 8].

The second important implication from this review article stems from the hypothesis that systemic inflammation in patients with COPD (''spill over'' effect) is associated with the development of coronary artery disease (CAD) and can be modified by statin therapy [1]. The former would explain why reduced FEV_1 has been shown to be a strong predictor of CAD, comparable to cholesterol level and independent of smoking history [3]. Given the strong relationship between COPD and CAD, and that CAD is a common cause of death in patients with COPD (23%) [5], it could be argued that COPD patients might benefit from statin therapy for this reason alone. In our review we showed that about 20–30% of patients with COPD are currently taking statins [3], although many more may benefit from this therapy.

Lastly, in their review, BARNES and CELLI [1] voice concerns that statins may have a detrimental effect on skeletal muscle. However, elevated IL-6 is an important factor underlying skeletal and respiratory muscle dysfunction or wasting [9]. As statins inhibit IL-6 synthesis in both the liver and other tissues (including inflammatory cells in the lung), then they could potentially improve muscle function. Such a finding was reported in a small randomised control trial where exercise tolerance in patients with COPD was improved by >50% in those receiving statin therapy for 6 months compared with placebo [10].

We conclude that the recently published review by BARNES and CELLI [1] highlights the need to look beyond the lungs in treating patients with COPD [1]. Specifically, they suggest that addressing co-existing systemic inflammation may result in a considerable improvement in morbidity and mortality. In contrast, limiting COPD treatment to symptom control with bronchodilators might appear analogous to limiting treatment of CAD to sublingual glyceryl trinitrate. We suggest that considerable clinical and pre-clinical data exist to show that statins inhibit pulmonary inflammation through mechanisms that explain all of the respiratory benefits reported to date. Although randomised control trials are needed to confirm and quantify these pulmonary effects, there is no doubt that statins reduce systemic inflammation, reduce mortality and, thus, have potential in the management of COPD.

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From the authors:

We thank R. Young and co-workers for their constructive comments on our review [1] and we fully agree with them on the potential benefits of statins in chronic obstructive pulmonary disease (COPD) patients. The new information they provide about the potential for statins in reducing lung cancer is particularly important, as this is one of the most common causes of death amongst COPD patients, particularly in those with severe disease. The potential anti-inflammatory effects of statins highlighted in our review might account for the reduction in cancer, although it is possible that statins have additional effects on the signalling pathways which lead to epithelial cancers [1]. For example, lovastatin inhibits the growth of lung cancer cell lines *in vitro*, in part, by increasing activity of the tumour suppressor protein p53 and the cell-cycle check-point inhibitors $p21^{WAF}$ and $p27^{KIP}$ [2]. Although the pleiotropic effects of statins provide a convincing scientific rationale for their potential benefit in COPD patients, a note of caution should be applied as the evidence for the benefits of statins is derived solely from observational studies that may have a selection bias. For example, patients with a better prognosis or who receive more intense medical attention may be more likely to be selected for statin therapy. What is needed now is a large, long-term, randomised placebo-controlled study investigating the addition of statins to usual therapy across a range of COPD disease severity; measuring disease progression, exacerbations, comorbidities and all-cause mortality. However, the high costs of such a study and the availability of generic statins mean that such a trial may be difficult to fund. In the meantime, further research investigating the molecular mechanisms of action of statins may be useful in identifying novel targets for the development of new treatments for COPD and its comorbidities [3]. It should also be remembered that there are differences between statins in the range of pleiotropic effects, thus it may not be appropriate to analyse all statins together.

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Statement of Interest: A statement of interest for P.J. Barnes can be found at www.erj.ersjournals.com/misc.statements.dtl

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Penetrating missile pulmonary embolisation

To the Editors:

We read with interest the review by JORENS *et al.* [1] highlighting the causes, diagnosis and treatment of nonthrombotic pulmonary embolism. Certainly, particulate material embolisation, especially from an iatrogenic source, is becoming more common. In fact, another well recognised source of embolisation of cyanoacrylate glue and lipiodol is following endoscopic injection of gastric or oesophageal varices [2, 3]. Embolisation of foreign material related to military trauma or weapons ammunition has become more topical with the presence of worldwide military conflicts in recent years [4]. The management of these patients can be very challenging given the presence of multiple injuries and contaminated wounds. Following adequate resuscitation, total body computed tomography (CT) imaging is often advocated to guide and prioritise treatment for the most life-threatening condition. The CT images in figure 1 show a 36-yr-old male injured by a