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Statins Have No Role in Pulmonary Disease Mortality

To the Editor:

A clarion call is a risk factor for sunrise as sure as a statin prescription is one for higher-than-minimal cholesterol, dyslipidemia being the on-label prescribing rationale for a statin. It is therefore surprising that neither Frost et al[1] nor the accompanying "clarion call" editorial[2] (April 2007) mentioned the word *cholesterol* when suggesting that statins may have a role regarding mortality and morbidity in pulmonary diseases. The type of studies[1,2] discussed or referenced cannot prove cause and effect, yet the authors proposed statins as a potential promising agent for influenza, COPD, and even bird flu.

The authors did not discuss baseline cholesterol, previously shown to be inversely associated with pulmonary diseases, where, in men, a statistically significant inverse association was found between serum cholesterol and hospitalizations for pneumonia/influenza.[3] A risk reduction of approximately 25% for deaths from miscellaneous respiratory diseases per SD cholesterol increase (1.19 mmol/L) has been shown[3]; the 16% reduction in women did not reach statistical significance.

The authors[1,2] proposed randomized trials, but prescribing information for ezetimibe/simvastatin (Vytorin; Merck/Schering-Plough Pharmaceuticals; North Wales, PA; Table 8)[4] already reports such data (*ie*, a 1.92-times increased incidence of influenza plus upper respiratory tract infections in the simvastatin group, vs placebo [$p < 0.05$]).

Statin use selects the healthy user or unselects the unhealthy low-cholesterol patient; and while the authors[1] attempted to address mortality, total mortality is still the "hard nut" for statins to "crack," with only simvastatin claiming such short-term benefit, such as in the Heart Protection Study,[5] and this in men only. The article by Frost and colleagues[1] simply reported a healthy-user effect because we know that "low cholesterol" is no benefit in all-cause mortality[6,7] or in the respiratory diseases discussed.[3]

Eddie Vos, M Eng
Sutton, QC, Canada
Luca Mascitelli, MD
Udine, Italy

The authors have no conflicts of interest to disclose.

Correspondence to: Luca Mascitelli, MD, Sanitary Service, Comando Brigata alpina "Julia," Via S. Agostino, 8, Udine 33100, Italy; e-mail: lumasci@libero.it

DOI: 10.1378/chest.07-1157

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Response

To the Editor:

We appreciate the concern that our results[1] contradict a previous study by Iribarren et al[2] that found an association between elevated blood lipid levels and reduced hospitalization and mortality from pneumonia/influenza and COPD. However, their study used a cross-sectional design, a weaker design for evaluating causal associations. Also, most of the results were not statistically significant and were inconsistent across strata of gender and age. They concluded that their results might be spurious or even secondary to reverse causality. If high blood lipid levels are protective against morbidity and mortality from COPD and influenza/pneumonia, then the lipid-reducing effect of statins should have resulted in higher rates of hospitalization and mortality in our statin users.

Drs. Vos and Mascitelli also suggest that randomized trials have already been completed. However, the prescribing information for ezetimibe/simvastatin did not demonstrate an association between simvistatin use and the incidence of influenza in a clinical trial.[3] Among those receiving simvistatin, 24 of 1,234 patients (1.9%) had influenza diagnosed, compared with 3 of 311 patients (1.0%) who received placebo ($p = 0.33$, Fisher exact test). Lower respiratory infections were not reported.

We are unable to rule out residual confounding by a "healthy-user" effect due to our limited data. However, we do not believe that it can completely account for the very strong protective effect that we identified, especially in preventing deaths associated with COPD. In our study, like many other observational studies of the effects of statin use, statin users compared to nonusers were somewhat older and had more comorbidities. This is a seemingly paradoxical finding when implicating a healthy-user effect. One of the reasons we recommend randomized clinical trials to study the pleiotropic effects of statins in COPD and influenza is to help prevent confounding by a possible healthy-user effect.

Floyd Frost, PhD
Lovelace Respiratory Research Unit
Albuquerque, NM

The author has no conflict of interest to disclose.

Correspondence to: Floyd Frost, PhD, Lovelace Respiratory Research Unit, 2425 Ridgecrest Dr SE, Albuquerque, NM 87108; e-mail: ffrost@lrri.org
DOI: 10.1378/chest.07-1474

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Mechanism of Statin-Associated Mortality Reduction in COPD

To the Editor:

We read with interest the article by Frost et al (April 2007)[1] reporting reduced mortality in COPD patients prescribed statins. The antiinflammatory properties of these drugs hold exciting promise in respiratory disease, especially COPD, in which there is heightened systemic inflammation associated with increased cardiovascular morbidity.[2] There are currently no randomized trials of statins in COPD, and the mechanism underlying any mortality benefit remains unexplained. We recently performed a study[3] of systemic biomarkers in patients with COPD, and have now analyzed these data with respect to the presence of cardiovascular disease (CVD) and prescription of statins on plasma interleukin (IL)-6 and C-reactive protein (CRP).

Plasma biomarkers were assayed in samples from 90 patients with stable COPD (mean age, 70.1 years [SD, 8.2 years]; median FEV_1, 1.00 L (range, 0.74 to 1.33 L); median FEV_1, 43.9% of predicted (range, 27.5 to 56.8% of predicted).[3] Self-reported CVD (angina, myocardial infarction, cerebrovascular disease, and/or peripheral vascular disease) and prescription of statins were recorded at clinic visits within 6 months of the samples (available in 87 of 90 patients).

Sixteen patients (18%) had CVD, of whom 7 patients (44%) were receiving statins. Of the 71 patients (82%) without CVD, 12 patients (17%) were receiving statins. Age, FEV_1, exacerbation frequency, and inhaled steroid dose did not vary between patients with and without CVD, or who were and were not prescribed statins.

As expected, in COPD patients not receiving statins, those with CVD had a higher plasma IL-6 concentration than those without CVD: median, 3.02 pg/mL vs 1.49 pg/mL ($p = 0.022$). Furthermore, patients with COPD and CVD who were prescribed statins had lower plasma IL-6 concentrations than those not receiving these drugs: 1.43 pg/mL vs 3.02 pg/mL ($p = 0.031$). However, plasma IL-6 concentrations were not significantly different in COPD patients without CVD in the presence or absence of statins: 1.11 pg/mL vs 1.49 pg/mL ($p = 0.187$). There were no differences with respect to CRP.

In conclusion, while statins were associated with reduced plasma IL-6 concentration in patients with COPD and comorbid CVD, this may not be true in patients without CVD. This observation may be important in the interpretation of clinical trials of statins in patients with COPD.

John R. Hurst, MD
Academic Unit of Respiratory Medicine
University College
London, UK
Gerry Hagan, MD
GlaxoSmithKline
Greenford, UK
Jadwiga A. Wedzicha
Academic Unit of Respiratory Medicine
University College
London, UK

Dr. Hurst has no conflict of interest to declare. Dr. Hagan is employed by GlaxoSmithKline. Dr. Wedzicha has received honoraria and research funding from GlaxoSmithKline.

Correspondence to: John R. Hurst, MD, Academic Unit of Respiratory Medicine, University College, London, UK; e-mail: jrhurst@lineone.net
DOI: 10.1378/chest.07-1435

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Response

To the Editor:

We very much appreciate the additional data presented by Hurst et al that may be relevant to our previously published article.[1] They present a very interesting hypothesis that should be testable. We found no evidence of reduced influenza-related morbidity among statin users, even though there was a reduced risk of death. We did not, however, stratify by whether the patients had preexisting cardiovascular disease (CVD). We are currently evaluating whether statin users and nonusers have similar comorbidities and mortality risks prior to initiation of statin therapy. Using these additional data, we may be able to examine whether people with or without a history of diagnosed CVD were differentially affected by statin therapy, as suggested by Hurst et al. Unfortunately, perhaps because statins are used to reduce CVD risks, statin users commonly have CVD comorbidities.

Floyd Frost, PhD
Lovelace Respiratory Research Unit
Albuquerque, NM

The author has no conflict of interest to disclose.

Correspondence to: Floyd Frost, PhD, Lovelace Respiratory Research Unit, 2425 Ridgecrest Dr SE, Albuquerque, NM 87108; e-mail: ffrost@lrri.org
DOI: 10.1378/chest.07-1570