5.3 days for non-users. This bias unquestionably explains the phenomenal 92% reduction in mortality associated with short acting β agonists as over 95% of subjects used the agents and the magnitude of the bias is directly proportional to the frequency of exposure.[3]

Secondly, bias was introduced if β blockers are less likely to be used in the fatal hospitalisation of a patient with COPD who is in the final stages of the disease. Indeed, if these drugs are withheld in the context of palliative care, the rate of death in patients exposed to β blockers will be underestimated, which will make β blockers appear protective.

Thirdly, selection bias was likely introduced by the way the cohort was defined. The cohort of 825 subjects was formed using the last hospitalisation for a COPD exacerbation that occurred during the period 1999–2006. There were, however, approximately 2120 hospitalisations that occurred during this period (calculated from table 1 of the paper). By selecting the last hospitalisation, the cohort necessarily overrepresented the hospitalisations resulting in death. Basic tenets of epidemiology propose instead to use either the first hospitalisation to define the cohort, or to use all hospitalisations, albeit with a data analysis complicated by the correlated nature of hospitalisations occurring in an individual patient. Selection bias is amplified if β blockers are likely to be withheld in fatal hospitalisations.

Another important source of selection bias was introduced by identifying study subjects according to death summaries citing COPD as the probable cause of death. As death from cardiovascular causes is frequent in patients with COPD,[4] and as patients prescribed a β blocker, and therefore with cardiovascular disease, are less likely to have COPD listed as the cause of death,[5] subjects with COPD receiving a β blocker who died were systematically less likely to be included. As a result, a significant number of deaths exposed to β blockers was likely left out, leaving only eight such subjects in the study, thus leading to the appearance of a protective effect of β blockers. The presence of this bias is further suggested by the trend towards a protective effect of calcium channel blockers (odds ratio 0.76).

Observational studies are essential to complement information from randomised controlled trials. However, when such studies suggest astounding benefits that are inconsistent with trial data and use methods that are known to introduce well recognised biases, their results regrettably must be considered unfounded.

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Competing interests: None declared.

Accepted 29 June 2008

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Authors' response

We thank Suissa and Ernst for their important comments regarding our paper and the design of observational studies. They raise several methodological concerns that call into question the validity of the results and highlight the many limitations of observational studies, including ours. It is certainly possible that immortal time bias and selection bias may have confounded our results and inflated the mortality benefit we observed with β blocker use; however, we strongly disagree that the results are inconsistent with clinical trial data as no randomised studies examining the effect of β blockers on COPD exacerbations or mortality exist. In fact, our results are entirely consistent with the few randomised studies of cardioselective β blocker use in COPD patients which suggest no harmful effects on lung function,[1] and with the majority of observational studies of β blocker use in patients with COPD which suggest benefit.[2–5]

Our study included a number of controls to appropriately account for confounding. Principally among them was the finding that in contrast with β blockers, calcium channel blockers were not associated with a beneficial effect on mortality, arguing against a healthy user bias. Drs Suissa and Ernst point out that there was a trend towards a protective benefit with calcium channel blockers but this was not significant and the effect size was far smaller than that observed with β blockers. We should point out that the pharmacy billing dataset did not include the date patients were charged for β blockers and thus we could not eliminate immortal time bias. However, because β blockers are much more likely to be instituted during the chronic care of the patient with COPD, rather than during the hospitalisation itself, this effect is likely reduced.

As suggested, we did examine the data using the first hospitalisation as the index event and found similar results to those we report. This approach supports the conclusions in the manuscript but does not allow for the inclusion of exacerbation frequency as a measure of disease severity which we viewed as critical to the analysis. Although our methodology for subject selection is not immune to bias, we did not select patients for inclusion based on a death summary citing COPD as the cause of death, as is suggested. We included all patients admitted with a primary diagnosis of COPD or a secondary diagnosis of COPD with a primary diagnosis of respiratory failure regardless of their hospital outcomes. Importantly, it is highly unlikely that β blocker use among patients with COPD with cardiovascular disease whose lung disease was not severe enough to warrant inclusion in the discharge summary as a primary or secondary diagnosis would be harmful.

Suissa and Ernst are correct to highlight the limitations of our observational study. However, the systematic withholding of β blockers from patients with COPD is not supported by published data, and we found no evidence of harm even among this inpatient population. Our results highlight the need for a randomised trial in the outpatient setting to definitively examine this issue.

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Predicting development and progression of COPD

Albers and colleagues[1] recently concluded that "Lung function below the normal range and early respiratory signs predict the development and progression of COPD". We have some concerns about the data. Table 2 in their article lists 151 subjects