COMMENTS

LONG-TERM USE OF PROTON PUMP INHIBITORS AND COMMUNITY-ACQUIRED PNEUMONIA: ADVERSE EFFECT OR BIAS?

To the Editor: We read with a greater interest the study of long-term proton-pump inhibitor (PPI) use and the risk of community-acquired pneumonia (CAP) in older adults by Zirk-Sadowski and colleagues.[1] Using electronic medical record data of individuals aged 60 and older in England, the authors examined the rate of CAP after 1 year of PPI use using a prior event rate ratio (PERR) approach, an analytical method used to minimize potential confounding. With a reported PERR-adjusted hazard ratio (HR) of 1.82 (95% confidence interval (CI)=1.27–2.54), the authors concluded that long-term PPI use was associated with greater risk of CAP.

Although it is possible that long-term PPI use increases the risk of CAP, it is likely that the observed association is the result of bias. As reported in Figure 1 of the study by Zirk-Sadowski and colleagues, the risk of CAP was greatest in the treated population immediately before receiving their first PPI prescription (the index date). These results suggest that the greater risk of CAP is likely to be due not to the pharmacological effect of the PPI itself but to the indication for its use, namely the underlying gastroesophageal reflux disease (GERD). Existing biological evidence suggests that GERD itself may increase the risk of pneumonia,[2] a hypothesis that is consistent with the incidence rates presented in this study. Although the PERR approach adjusts for time-fixed confounding, it does not control for time-varying confounding, such as worsening GERD over time.

Although there is existing literature that supports an association between PPI use and CAP,[3] recent studies in this area have demonstrated that it is likely that this purported adverse drug reaction is the result of confounding by indication. As part of the Canadian Network for Observational Drug Effect Studies,[4] we conducted a multi-database cohort study with inclusion restricted to new users of nonsteroidal antiinflammatory drugs to allow for examination of prophylactic PPI use rather than use to manage the symptoms of GERD.[5] Using this approach, we found that PPI use was not associated with risk of hospitalization for CAP (HR=1.05, 95% CI=0.89–1.25). In a more recent retrospective cohort study that also included a self-controlled case series analysis and a PERR analysis[6], the cohort analysis supported an association (incidence rate ratio (IRR)=1.67, 95% CI=1.55–1.79), but the other analyses suggested that this association was not causal. As in the study by Zirk-Sadowski and colleagues, the self-controlled case series found a higher risk of CAP before PPI initiation (IRR in the 30 days before =1.92, 95% CI=1.84–2.00) than after initiation (IRR in the 30 days after =1.19, 95% CI=1.14–1.25), and the PERR analysis suggested no greater risk (IRR=0.91, 95% CI=0.83–0.99). The authors concluded that it was likely that any greater risk observed was the result of confounding. Although both studies included short-term PPI use, the observed greater risk of CAP immediately before starting PPIs is consistent in both studies, and the biological effects of GERD on the risk of pneumonia are unlikely to differ in these populations.

Ultimately, given the greater risks of osteoporotic fractures[7,8] and *Clostridium difficile* infection[9,10] associated with the use of PPIs, we agree with Zirk-Sadowski and colleagues that the safety of the long-term use of these drugs requires monitoring. Nevertheless, although older adults using PPIs over the long term are at greater risk of CAP, it is likely that their underlying GERD, rather an adverse reaction caused by the long-term use of PPIs, is the cause of this greater risk.

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See the Reply by Ble et al

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REPLY TO: PROTON PUMP INHIBITORS AND LONG-TERM RISK OF COMMUNITY-ACQUIRED PNEUMONIA IN OLDER ADULTS

To the Editor: We thank Filion[1] and Schreiber[2] for their interest in our research on proton pump inhibitors (PPIs) and long-term risk of community-acquired pneumonia (CAP) in older adults.[3]

Our study was a retrospective analysis of routine primary care data including a representative sample of community-dwelling older adults,[4] which would be a challenge in prospective studies. Filion and colleagues suggest that the association between PPI exposure and the longer-term risk of CAP seen in our study is unlikely to be causal but more likely the consequence of the confounding effect of gastroesophageal reflux disease (GERD), a condition treated with PPIs and potentially associated with risk of pneumonia.

We accept that analyses could be subject to time-dependent unmeasured confounding and acknowledge that GERD may increase the risk of pneumonia and that the severity of GERD varies over time. However, the prevalence of GERD in the study was only 0.2% in controls and 5% in PPI-treated participants (as shown in Supplementary Table 1),[3] and the reported results of greater likelihood of CAP with longer-term PPI treatment were significant across indication groups. In addition, we performed sensitivity analyses, which included propensity scoring and inverse probability weighted–adjusted models to reduce the effect of potential confounders, including adjustments for GERD as a known potential confounder. These analyses were supportive of the main results.

According to Figure 1,[3] the risk of CAP was greatest in the treated population immediately before receiving their first PPI prescription. We agree that these findings, consistent with those reported previously,[5] suggest that the short-term risk of CAP—in the first months after PPI prescription—is due to the indication for prescription rather than the pharmacological effect of PPIs, but unless we assume the unlikely occurrence of all CAP being the first clinical manifestation of previously unrecognized GERD, the most probable reason for PPI prescription in this setting is CAP itself or a health condition leading to CAP. In vulnerable older adults, it is not uncommon to use PPIs for prevention purposes, for example after acute medical or surgical stress perceived as potentially jeopardizing gastric integrity. Nevertheless, although the reported increase in CAP risk in the first months after initiation of a PPI is likely to be the consequence of the health condition for which the PPI was prescribed, the higher CAP risk during the second year after PPI initiation (the subject of our article) is less likely to be the consequence of the acute condition for which the PPI had been prescribed more than 1 year earlier, and we therefore cannot exclude an untoward pharmacological effect of the drug. In conclusion, the observed short- and long-term increase in CAP risk after PPI prescription should not necessarily be seen as consequences of the same phenomenon.[2]

Schreiber points out that, in our study, people treated with PPIs had many more comorbidities than those not treated with PPIs and observes that this greater burden of disease—and consequent greater vulnerability—is ultimately due to greater CAP risk in the treated group. More importantly, in his opinion, no statistical adjustment will sufficiently address such a confounding effect, and he concludes that "the only legitimate way to estimate pneumonia risk is to prospectively compare similar groups of individuals taking and not taking PPIs." Prospective cohort studies would be 1 of several ways of studying such effects. Another possibility would be to test the hypothesis in randomized trials; these in turn could take a form of between-person or cross-over studies. We would agree that there is a hierarchy of evidence.

Other studies of PPIs, including Othman et al.,[4] have used the same statistical method (prior event rate ratio (PERR)) and the same dataset (Clinical Practice Research Datalink) in similar populations (age, sex, year of prescription matched cases and controls) to adjust for substantial baseline differences between groups. Nevertheless, as opposed to what we have shown for longer-term CAP risk, these authors found that the difference in CAP risk in the first months after PPI treatment initiation in PPI-treated and nontreated subjects was no longer significant when adjusted for the difference in CAP risk before initiation of PPIs. Another study used PERR to adjust for baseline differences between groups in people taking PPIs.[5] Moreover, sensitivity analyses performed to check the robustness of our results, using substantially different statistical methods (propensity score, inverse probability-weighted models) on different subgroups of people (e.g., age, comorbidity), achieved strikingly similar

This letter comments on the letters by Ayele et al and Richard Schreiber