Proton pump inhibitors (PPIs) are among the most commonly prescribed medicines in the world and are used for a variety of indications, including peptic ulcer disease, gastroesophageal reflux disease, dyspepsia, and prevention of gastrointestinal bleed during antiplatelet therapy. A number of adverse effects, from Clostridium difficile infection to chronic kidney disease, have previously been observed with long-term use of PPIs. In addition, a link between long-term PPI use and increased cardiovascular risk has been suggested although not definitively established. In this issue of *Mayo Clinic Proceedings*, Bell et al have identified an association between PPI use, in an exposure-dependent manner, and adverse cardiovascular outcomes, defined as development of stroke, coronary heart disease, or heart failure. Specifically, the authors identified a hazard ratio of 2.11 (95% CI, 1.50 to 2.72) for patients with more than 5.1 years of cumulative PPI exposure in comparison to patients without PPI exposure, after adjustment for covariates. This finding was driven by heart failure events, showing a hazard ratio of 2.21 (95% CI, 1.51 to 3.23) for those with more than 5.1 years of PPI exposure. The authors hypothesize that long-term exposure to PPIs may pathologically promote the development of cardiovascular disease (CVD).

The study has a number of strengths in design. First, it evaluates a longitudinal patient cohort through the Atherosclerosis Risk in Communities Study (ARIC), which included extensive collection of data on potential covariates, maintenance of a high follow-up rate, and inclusion of a community-based population. The authors also performed a thorough analysis to account for confounding variables, including analyses to demonstrate consistency of their finding. In particular, the authors’ results were consistent even after removal of patients who had ever reported symptoms of angina, such that patients with angina thought to have acid reflux who were treated with PPIs did not confer an additional bias. Moreover, the authors performed an insightful and unique assessment for lifetime PPI exposure. The beginning of the ARIC study also largely preceded the widespread use of PPIs, eliminating the risk of prior PPI exposure. It is also worth noting that the design of a large, prospective randomized trial of PPI-naïve patients who are observed during multiple years of therapy would be challenging, particularly given the variety of clinical scenarios in which PPIs are used and common application.

There were also several limitations to the findings of the study. In a biracial patient demographic, findings may not be extendable to non-White and non–African American populations. In addition, a number of assumptions were made in calculating total PPI exposure time, which used a “last-observation-carried-forward” technique. Specifically, the authors assumed that a PPI was taken continuously if it was reported on consecutive visits and that if data were absent at 1 visit, the most recent ascertainment was still assumed to hold true. This was most significant for the approximately 9-year period between visit 4 and telephone follow-up in 2006, during which 87% of patients did not have PPI use ascertained. Furthermore, the mechanism for potential PPI-induced increase in CVD has not been elucidated, and the authors offer limited insight into the pathophysiology. Specifically, the mechanism for increased heart failure events, which was the primary driver of the combined end point, is not clear, although PPI-induced reduction of myocardial contractility was proposed.

Most notably, a major limitation is that causality inference is limited because of the observational, retrospective nature of the
study. Nonetheless, certain features of this study do strengthen the case for causality, with particular attention to those delineated by the Bradford Hill criteria. First, the authors found a considerable 2-fold increase in the primary outcome in patients who took PPIs for more than 5 years compared with those who did not have PPI exposure. Because patients who developed CVD before the “baseline” assessment (visit 5 of ARIC) were excluded, the degree of increased risk could, in fact, be higher. Second, the link between PPIs and CVD has been suggested in prior retrospective analyses, which suggests reproducibility. Third, the increase in risk in an exposure-dependent manner strengthens the case for a cause and effect association. Therefore, although not definitively established, certain features of the study lend credence to a possible causal relationship. In any case, the findings in the article of Bell et al support an initiative for prompt discontinuation of PPIs when these medications are no longer indicated.

This important implication is relevant to practice patterns that were highlighted in a recent article by Blackett et al. In their article, the authors evaluated a population of adult patients admitted across 9 intensive care units between 2014 and 2018 who were initiated on PPIs on admission. Patients with an appropriate long-term PPI indication were excluded. From their cohort of 2467 patients, the authors found that 45% of patients were continued on a PPI after floor transfer, and 27% of patients were prescribed a PPI on discharge despite lack of an outpatient indication.

The practice of initiating stress ulcer prophylaxis in critical care is common and endorsed by societal guideline committees for select critically ill patients. Although it is data driven and well intentioned, the possibility of causing harm, if it is continued on a long-term basis after resolution of the acute illness, is palpable, particularly after considering the findings from Bell et al. As Blackett et al also point out in their article, perhaps a reason for provider hesitancy is reluctance to stop a medication that the provider did not start. However, the onus stands on both hospital physicians and outpatient providers to pay careful attention to the medication reconciliation and to ensure that each ordered medication is appropriately indicated. A multidisciplinary approach with subspecialty services and rehabilitation teams in determining medication appropriateness may also be helpful, given that risk of inappropriate PPI continuation was increased for patients who had undergone endoscopy and for patients requiring rehabilitative services or residential care after discharge. Although this example focuses on the hospital and perihospital setting, it highlights an important area in which simple modifications of clinical practice may enhance long-term outcomes by avoiding the cumulative adverse effects of PPIs altogether.

Additional work remains to better understand the link between PPI use and cardiovascular risk, including identifying a mechanism for pathologic effects of PPIs and clarifying the strength of the relationship between PPIs and CVD. The role of histamine type 2 receptor antagonists will also need to be elucidated as an alternative to both short- and long-term therapy. Regardless, the outlined studies do highlight the dangers of polypharmacy and how simply overlooking a “benign” medication may, in fact, produce tangible harm. Polypharmacy itself has become increasingly common on an international scale and has been linked, albeit through mostly observational studies, to adverse events, including decline in physical and cognitive function, hospitalization, and death. It therefore behooves the modern-day physician to “do no harm” and to take caution in prescribing, refilling, and renewing unnecessary medications, PPIs as well as other medications, to provide optimal patient care.

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