Editorial



# Association between proton pump inhibitor and ischemic stroke risk remains controversial

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Proton pump inhibitors (PPIs) are widely used in gastrointestinal disease, including peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), upper gastrointestinal (GI) bleeding, and other GI disorders. PPIs are one of the most frequently used drugs in the world. Although PPIs are currently one of the most commonly used class of drugs (1), clinicians have found that PPIs may potentially increase the risk of ischemic stroke, which may be related to the interaction between PPIs and other commonly used cardiovascular drugs. Several studies (2,3) have shown an increased risk of ischemic stroke in association with PPI use, but other studies have obtained different results.

Nguyen *et al.* (4) recently investigated the relationship between ischemic stroke and PPI use. They enrolled 97,503 individuals, including 68,514 women since 2000 and 28,989 men since 2004. Individuals in both cohorts were followed up biennially until 2012 with detailed biennial questionnaires including lifestyle factors and medication use. The primary endpoint was stroke documented on the records of a neurological deficit, which could lead to a cerebrovascular accident that occurs suddenly and rapidly greater than 24 hours or until death. Over the follow-up period totaling 949,330 person-years, the authors reported 2,599 incidences of strokes. The data revealed a statistically significant difference in the age-adjusted risk of ischemic stroke [hazard ratio (HR), 1.25; 95% confidence interval (CI), 1.08–1.46]. To eliminate the influence of confounding risk factors, a subsequent multivariable model was adjusted for age, body mass index (BMI), smoking, physical activity, diet, alcohol, estrogen, multivitamins, aspirin, non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs), as well as other comorbidities, including hypertension, hyperlipidemia, diabetes, or coronary artery disease. They found that this association between PPI use and ischemic stroke weakened after multivariable adjustment in this model but remained statistically significant (HR, 1.18; 95% CI, 1.02–1.37). Considering that the clinical indications for PPI use may confound the association between PPI use and ischemic stroke, the authors performed additional analyses with adjustment for PPI use indications, including PUD, GERD, gastrointestinal bleeding, and use of histamine 2 receptor antagonists (H2RAs), in addition to the risk factors used in previous model. In this model, the association between PPI use and ischemic stroke was no longer significant (HR, 1.08; 95% CI, 0.91–1.27). In a further evaluation of the association between the duration of PPI use and ischemic stroke, no clear association was found ($P_{trend}$=0.18).

Their study has several highlights. First, it was a large-sample, prospective study with a very long-term follow-up of up to 12 years. Second, the population was recruited from two large-scale population-based cohort studies, which differs from other studies that mainly focused on the interference of clopidogrel metabolism by PPIs or only patients with high cardiovascular risk treated with aspirin, clopidogrel and ticagrelor *et al.* antiplatelet agents. The population selected in this study also avoided increased risk of ischemic stroke from cardiovascular disease itself. Third, they ascertained the participants' PPI use by self-reporting, which accounted for non-prescription PPIs and potential non-compliance. This self-reporting system could better

reflex the real PPI use. Finally, they also considered several confounding risk factors (including the usual risk factors for cardiovascular disease) and the indications for PPI use (including the history of PUD, GERD, GI bleeding, or use of H2RAs). This adjusted model demonstrated that the perceived increased stroke risk was caused by confounding, rather than by the PPI.

However, the study still has several limitations. As mentioned by the authors, this observational study is inherently susceptible to confounding bias which precludes the drawing of causal associations from such trials. Second, the PPI brand, dosage, and schedule may also have affected the results according to another study (3), but these data were not included in this study. Third, the baseline characteristics differed between the two databases, which may have therefore affected the results.

PPIs are a standard treatment for acid-related GI disorders and usually have good tolerability and safety (5). In more recent years, concern has arisen about potential interference between PPIs use and clopidogrel metabolism. Clopidogrel is an inactive prodrug, which need to be converted to an active metabolite by hepatic enzymes, mainly CYP2C19. PPIs have been shown to inhibit CYP2C19 and were therefore thought to compromise the efficacy of clopidogrel (6,7). Nonetheless, results of a placebo-controlled randomized trial showed no increased risk for adverse cardiovascular events with PPIs as compared to placebo in addition to dual antiplatelet therapy with aspirin and clopidogrel (8). PPIs are being increasingly used in both patients with and without cardiovascular risks. Most studies to date have focused on the association between PPIs and cardiovascular risks mainly in patients undergoing antiplatelet treatment because of high cardiovascular risks. Juurlink *et al.* (9) studied 2765 patients older than 66 years old administrated with clopidogrel after a stroke from all Ontario residents. They found that current use of PPIs had no relationship with an increased risk of recurrent stroke (9). However, this conclusion cannot be extended to other population because of the restrictions of the selected population. More recently however, other studies involving the general population have shown different results. Wang *et al.* (2) studied 15,378 patients from a register database in Taiwan with a 120-day follow-up. They found an association between PPI use and increased cerebrovascular risks with adjusted odds ratios of 1.77 (P<0.001) within 30 days, 1.65 (P<0.001) from 31 to 90 days, and 1.28 (P=0.025) from 91 to 180 days before the first onset of ischemic stroke. The association during long-term follow-up remains unclear.

Results may differ greatly among databases, and it is still too early to determine whether PPI use is associated with ischemic stroke. In the near future, more randomized controlled trials and meta-analyses may answer this question. Notably, some animal experiments have showed that PPI use can increase the serum concentration of asymmetric dimethylarginine, which can cause decrease of nitric oxide and thus impair endothelium-dependent vasodilatation (10). However, this effect has not been verified in the human body (11). The more detailed mechanism of the effect of PPIs on ischemic stroke remains to be fully elucidated.

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