

USE OF PROTON PUMP INHIBITORS AND RISK OF CARDIOVASCULAR EVENTS IN THE GENERAL POPULATION

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BACKGROUND Proton pump inhibitors (PPIs) are among the most commonly prescribed drugs for the management of upper gastrointestinal disorders. The beneficial effects even after short-term therapy, together with a good tolerability profile, lead to an overutilization of these drugs. Within this scenario, a potential increased risk of serious adverse drug reactions, like cardiovascular disease (CVD), could be an important source of public health concern.

AIM To estimate the risk of hospitalization for cardiovascular and cerebrovascular events in a cohort of incident PPI users.

METHODS A case-control study, nested in a cohort of incident PPIs users, was carried out using the administrative healthcare utilization databases of the Italian Lombardy region. All residents aged 18-70 years with a first prescription of PPIs from January 1, 2003 until December 31, 2007 were identified, and the date of first prescription was defined as the index date. Patients with a hospitalization for any cardiovascular events or with any anticoagulant or antiplatelet therapy within 3 years before index date were excluded. All cohort members were followed from the index date until the earliest of the following events: hospitalization for CVD, death, migration or end of follow-up (31/12/2012). Cases were members of the cohort who during follow-up were hospitalized for any cardiovascular disease. For each case, up to five controls randomly selected from the cohort were matched by gender, age at cohort entry, and index date. Exposure was evaluated as treatment duration (based on defined daily doses) and recency of the last prescription with respect to event date, defining current user (having last prescription of PPIs within 6 weeks before event date), recent user (having the last prescription of PPIs between 6 weeks and 6 months before event date), and past user (having the last prescription of PPIs 6 months before event date). Conditional logistic regression was used to model the CVD risk associated with the two measures of exposure and with the interaction term.

RESULTS In our cohort of new PPI users, we identified 18,335 cases and 91,668 controls. Cases showed a significantly higher prevalence of comorbidity than controls. In the multivariate-adjusted regression analysis, risk of CVD was significantly higher for patients with a higher treatment duration (for >6 weeks: OR 1.19, 95%CI 1.10-1.28; for 2-6 weeks: OR 1.08, 95%CI 1.00-1.16; compared to <2 weeks) and for current (OR 1.79, 95%CI 1.67-1.92) and recent users (OR 1.12, 95%CI 1.05-1.20) compared to past users. This increased risk with exposure longer than 6 weeks or with current use was confirmed in the stratified analysis for coronary (OR 1.20, 95%CI 1.10-1.31; and OR 1.13, 95%CI 1.04-1.22, respectively) or cerebrovascular events (OR 1.19, 95% CI 1.03-1.38; and OR 1.58, 95% CI 1.38-1.81). The analysis with interaction terms showed an increasing risk for recent use (OR 1.18, 95% CI 1.10-1.26), current use with exposure ≤2 weeks (OR 1.24, 95% CI 0.93-

1.67), current use with exposure 2-6 weeks (OR 1.78, 95% CI 1.50-2.12), and current use with exposure >6 weeks (OR 1.95, 95% CI 1.82-2.08), compared to past use.

CONCLUSIONS Consistent with the evidence that PPIs may adversely impact vascular function, in this study PPI use was independently associated with an increased risk of first-time cardiovascular event in the general population. These results underline the need to promote appropriate prescribing of these drugs.