

Diabetes

Long-term PPI use associated with increased risk of type 2 diabetes

Regular use of proton pump inhibitors (PPIs) increased the risk of type 2 diabetes in a cohort analysis of three large American population studies. The risk increased with longer duration of use.

The study authors used data from the Health Professionals Follow-Up study (HPFS), Nurses' Health Study (NHS), and the Nurses Health Study II (NHSII). The HPFS was established in 1986 when 51,529 American male healthcare professionals aged 40-75 years began completing questionnaires about their medical history and lifestyle. The NHS started in 1976 and recruited 121,700 female nurses aged 30-55 years. NHSII commenced in 1989, with a younger cohort of 116,430 female nurses (aged 25-42 years).

All three studies sent questionnaires to participants every two years and follow-up has continued long term.

The cohort for this study included individuals with reported PPI use and excluded those with self-reported diabetes. Specific questions about regular PPI use were included in the reporting from 2000 for the NHS, 2001 for the NHSII and 2004 for the HPFS. Regular use was defined as more than twice a week. Dose, brand or type of PPI was not specified.

The authors also reviewed the incidence of diabetes in users of H2 receptor antagonists (H2RA), which reduce stomach acid production through a different mechanism.

The study population included 176,050 women and 28,639 men.

Over 2,127,471 person-years of follow-up, there were 10,105 new diagnoses of type two diabetes. After lagging PPI use for 2 years, to address potential reverse causation, and age/study duration stratification, regular PPI users had a 74% higher risk of diabetes than non-users.

After adjustment for demographics, lifestyle, comorbidities and other medications, the risk was reduced, but still present.

- Regular use of PPIs was associated with a 24% higher risk of diabetes compared with non-users: HR 1.24 (95% CI: 1.17-1.31).

- The risk of diabetes increased with duration of PPI use: HR 1.05 (95% CI: 0.93-1.19) for 0-2 years' use, and 1.26 (95% CI: 1.18-1.35) for > 2 years' use, compared with non-users.

Regular H2RA users also showed an increased risk of type 2 diabetes, although the risks were less pronounced.

Stopping PPIs was associated with a reduction in risk of diabetes. Compared with current users, the adjusted HR for those who stopped PPIs within 2 years was 0.83 (95% CI: 0.70-0.98).

The study authors state: 'In this analysis of three large prospective cohort studies we found that regular PPI use was associated with a 24% higher risk of type 2 diabetes. The risk of diabetes was likely to increase with duration of PPI use and to decrease with time stopping PPIs.'

A recent randomised controlled trial showed a trend towards increased diabetes risk with PPI use; the increased risk was moderate and not statistically significant.¹

The authors acknowledge the limitations of the data, and that the population studied are healthcare professionals.

They suggest clinicians should be aware of a possible increased risk of type 2 diabetes when prescribing and following up PPIs in clinical practice.

The data suggests that the risk seems to rise sharply if PPIs are used for more than 2 years, so I feel that short-term use should be the preferred option.

Many of the patients taking long-term PPIs are likely to be on chronic illness registers where annual health checks for diabetes are already indicated. However, there are a substantial number of patients using the medication for GORD or non-ulcer dyspepsia, who may not be aware of the potentially increased risk of type 2 diabetes.

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Yuan J, He Q, Nguyen LH et al. Regular use of proton pump inhibitors and risk of type 2 diabetes: results from three prospective cohort studies. *Gut* 2020;0:1-8

REFERENCE

1 Moayyedi P, Eikelboom JW, Bosch J et al. Safety of proton pump inhibitors based on a large multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology* 2019;157:682-91.e2