Proton-Pump Inhibitors and Fragility Fractures in Vulnerable Older Patients

Short title: PPIs and Fragility Fractures in Older Patients

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Proton Pump Inhibitors (PPIs) taken for ≥1 year have been linked to increased fragility fracture (FF) risk, prompting the US FDA to issue a related warning.

The oldest old (≥85) and patients with co-morbidities may be at greater risk;(1) however little or no evidence has been available in these groups of vulnerable people.

In this retrospective matched-cohort study with difference-in-difference methods, we investigated the 4-year FF risk in older patients (≥60) and patients with co-morbidities.

Methods

We used the Clinical Practice Research Datalink, a database of primary care electronic medical records linked to hospital records. The sample included 86,469 patients receiving PPIs for ≥1 year and 86,469 age- and gender-matched controls, registered with a primary care practice in England between April 1997 and March 2014.

PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) were identified in the electronic prescribing data and analyzed as a class, regardless of dosage. The date of the first PPI prescription for the treated member of each matched pair was deemed the pair's index date.

FFs, were defined by hospitalization for new spine, hip, wrist, humerus, pelvis, ankle and rib fracture, coded using ICD-10. Patients with FFs within 3 months before their first PPI prescription were excluded, to avoid bias.(2)

Cox's regressions were used to compare FF risk during the 4 years before (pre-treatment period) and after (treatment period) index date. According to the Prior Event Rate Ratio (PERR) approach,(3) a difference-in-difference method, hazard ratios in the pre-treatment period were used to correct the treatment period hazard ratios. PERR was used to address both measured and unmeasured confounding, the latter being a major caveat in the interpretation of current evidence.(4)

Results were stratified by age (60-74, 75-84, and ≥85) and co-morbidity (Charlson Comorbidity Index, 0 and ≥1). Numbers needed to harm (NNHs) were also calculated.(5) Subgroups were compared using confidence intervals since interactions cannot be tested using PERR.

Results

The mean age was 71.9 (±7.9) years. FF rates in people aged ≥60 and those 60-74, 75-84, and ≥85 were 11.7, 7.3, 18.5, and 33 per 1000 person-years, respectively.

Differences at index date between treatment groups (table) were reflected by higher hazard ratios in patients exposed to PPIs in both pre-treatment and treatment periods (figure). Measured and unmeasured confounding has been addressed using PERR.

In the adjusted analysis (net estimates, figure) across the studied age-range, patients receiving PPIs were at greater risk of FF than controls (PERR adjusted Hazard Ratio 1.27: 95%CI 1.16 to 1.34) after accounting for prior differences in FF rates. The Hazard Ratio for PPI use in those aged ≥85 overlapped with that in younger groups and were similar in patients with and without co-morbidity. Sensitivity analyses excluding people with corticosteroids co-prescription and their matched pairs showed similar results (HR: 1.23, 95%CI: 1.05-1.44).

Since the hazard estimates were similar in age and co-morbidity subgroups, subgroup-specific NNHs were calculated by applying the full-sample risk estimate to subgroup-specific FF rates. (5) The NNH for FF in all patients aged ≥60 was 121 (95%CI 81 to 222) over 4 years. NNH in patients ≥85 (45, 30 to 81) was lower than that in ages 60-74 (207, 141 to 368) but similar in patients with and without co-morbidity (data not shown).

Conclusion

This observational study, using a validated method to address unmeasured confounding, confirms an approximately 30% increased FF risk in older patients receiving PPIs for ≥1 year. Although there were similar excess risks in patients aged ≥85, given the higher

absolute risk of FF in this group, only 45 patients need to be treated to harm one, suggesting that PPIs should be used with caution especially for symptomatic relief in this group. In the UK the vast majority of people aged ≥60 receive free drug prescriptions and the ≥1 year over-the-counter PPI use is therefore limited and unlikely to bias our results.

References

1. Reimer C. Safety of long-term PPI therapy. Best Pract Res Clin Gastroenterol 2013;27:443-54.

2. Uddin MJ, Groenwold RH, van Staa TP, et al. Performance of prior event rate ratio adjustment method in pharmacoepidemiology: a simulation study. Pharmacoepidemiol Drug Saf 2015;24:468-77.

3. Brophy S, Jones KH, Rahman MA, et al. Incidence of Campylobacter and Salmonella infections following first prescription for PPI: a cohort study using routine data. Am J Gastroenterol 2013;108:1094-100.

4. Laine L, Nagar A. Long-Term PPI Use: Balancing Potential Harms and Documented Benefits. Am J Gastroenterol 2016;111:913-5.

5. Barratt AL WP, Guyatt G, Simpson JM. NNT for studies with long-term follow-up. Canadian Medical Association Journal 2005;172:613-615.

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Specific author contributions: Dr Zirk-Sadowski and Dr Ble had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ble, Zirk-Sadowski, Masoli, Melzer;

Acquisition or interpretation of data: All authors

Drafting of the manuscript: All authors

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Zirk-Sadowski, Henley, Melzer, Ble

J.Z, J.A.M., W.D.S., J.D., W.H., W.H., D.M., A.B. has approved the final draft submitted.

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Table: Percent of selected characteristics at index date

*Characteristic**	Controls N=86,469	Treated N=86,469
Age group		
60-74	66.1	66.1
75-84	27.7	27.7
85+	6.3	6.3
Gender (women)	56.4	56.4
Ethnicity		
White	60.2	79.9
Non-white	1.4	2.5
Not recorded */Undisclosed*	38.5	17.5
Poorer socio-economic status (3rd-5th quintile of Index of Multiple Deprivation)	50.3	52.2
Body Mass Index		
Underweight (<18.5 kg/m^2)	1	1
Normal (18.5-24.9 kg/m^2)	17.3	18.4
Overweight (25-29.9 kg/m^2)	20.4	25.8
Obese (≥30 kg/m^2)	12.7	18.1
Unrecorded	48.5	36.8

*Characteristic**	Controls N=86,469	Treated N=86,469
Smoking status		
Never smokers	44.6	41
Ex-smokers	17.6	21.9
Current smokers	28	32.6
Not recorded	9.8	4.4
Alcohol drinking		
Never/currently not	9	10.6
Current, known amount	42.2	47.2
Heavy	9.4	12
Current, unknown amount	0.9	1
Former	2.2	3
Undetermined	36.4	26.2
Charlson Comorbidity Index (≥1)	39.8	57.6
Falls (within a year before baseline)	11.6	16.6
Anaemia	2.7	7.7
Ischemic stroke	5.5	9.3
Coronary heart disease	10.5	20.1
Osteoporosis	3.6	6
Osteoarthritis	19.9	32.6
Gastroesophageal reflux disease	0.2	4.6

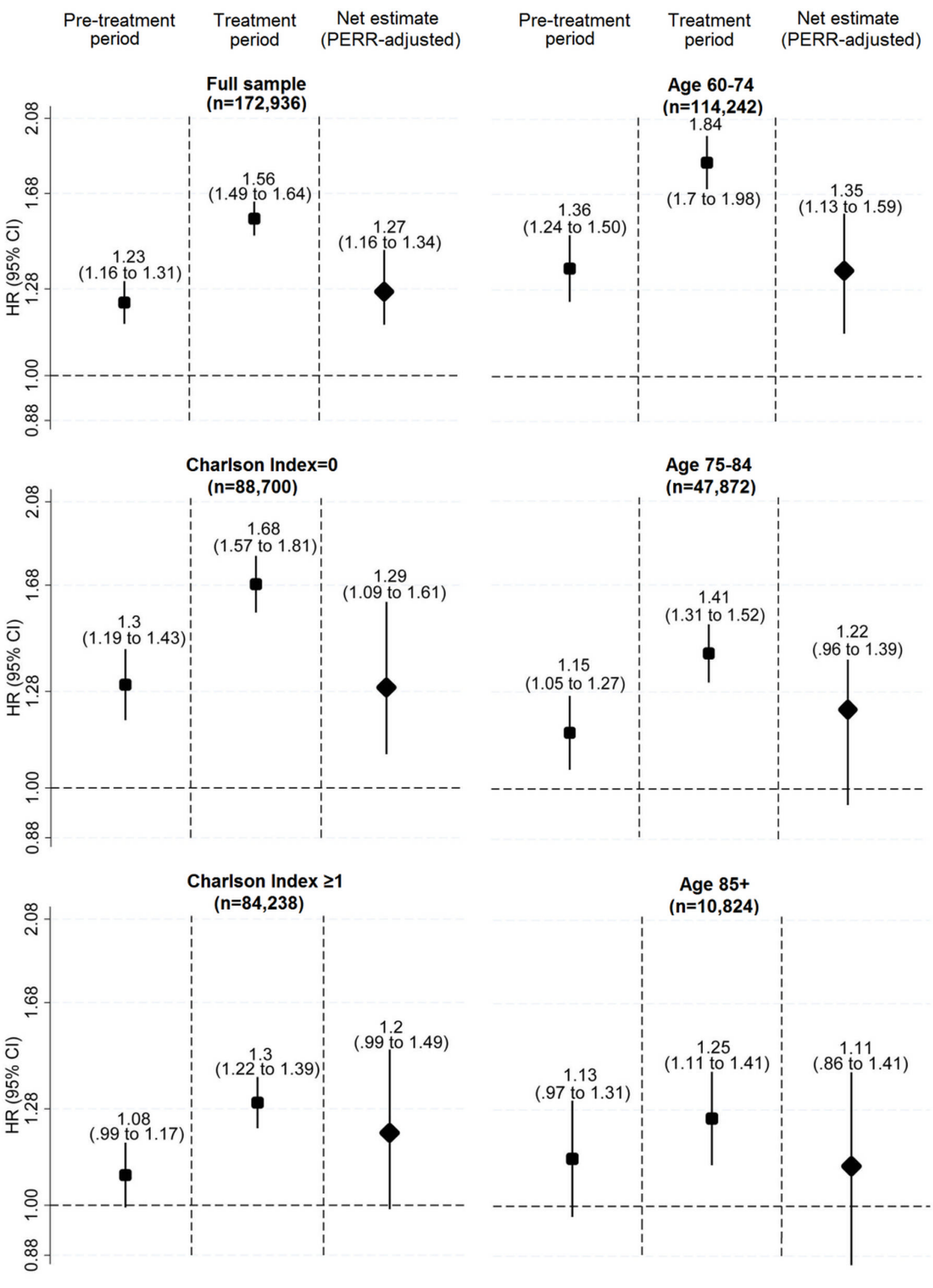
*Characteristic**	Controls N=86,469	Treated N=86,469
Vitamin D supplement	3.9	9
Corticosteroids	25.2	44.3
Oestrogen	2.2	4.4
Testosterone	0.1	0.1
Anti-thyroid drugs	0.2	0.3
Levothyroxine	6	8.6

*****All differences (except for gender and age groups) between the PPI treated and controls significant at $p<.001$ (χ^2).

Legend to the Figure

Hazard ratios for pre-treatment and treatment periods and PERR-adjusted hazard ratios for the full sample and by comorbidity and age groups (log-scale);

HR= hazard ratio; 95%CI= 95% confidence interval; PERR: Prior Event Rate Ratio. CCI= Charlson Comorbidity Index; $HR_{PERR} = HR_{Treatment\ period} / HR_{Pre\text{-}treatment\ period}$; confidence intervals for PERR analyses were calculated using bootstrapping techniques.


Pre-treatment period
Treatment period
Net estimate (PERR-adjusted)
Full sample (n=172,936)
HR (95% CI)
0.88
1.00
1.28
1.68
2.08
1.23 (1.16 to 1.31)
1.56 (1.49 to 1.64)
1.27 (1.16 to 1.34)
Age 60-74 (n=114,242)
1.36 (1.24 to 1.50)
1.84 (1.7 to 1.98)
1.35 (1.13 to 1.59)
Charlson Index=0 (n=88,700)
1.3 (1.19 to 1.43)
1.68 (1.57 to 1.81)
1.29 (1.09 to 1.61)
Age 75-84 (n=47,872)
1.15 (1.05 to 1.27)
1.41 (1.31 to 1.52)
1.22 (.96 to 1.39)
Charlson Index ≥1 (n=84,238)
1.08 (.99 to 1.17)
1.3 (1.22 to 1.39)
1.2 (.99 to 1.49)
Age 85+ (n=10,824)
1.13 (.97 to 1.31)
1.25 (1.11 to 1.41)
1.11 (.86 to 1.41)