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**ORIGINAL ARTICLE**

# Use of proton-pump inhibitors and their associated risks among frail elderly nursing home residents

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**Abstract**

*Objective*. The aim of this study is to investigate the use of proton-pump inhibitors (PPI) and their associated risks among frail elderly nursing home residents. *Design.* A cross-sectional study. *Setting.* General practice. *Subjects.* An assessment of residents (n = 1987, mean age 83.7 years) in all nursing homes in Helsinki was carried out in February 2003. Data included demographic characteristics, symptoms such as diarrhea, vomiting and constipation, use of various drugs, and medical diagnoses. *Outcome*. Coded data analysis with NCSS statistical program. Multivariate logistic regression analysis served to determine which variables were independently associated with diarrhea; variables which were statistically significant or near $p < 0.05$ in univariate analyses were included. *Results.* Altogether 433 residents were on PPIs. The factors associated with regular PPI use in univariate analyses included poor functional status, higher number of comorbidities, higher number of medications and lactose intolerance. The users had suffered from a prior ventricular or duodenal ulcer, cancer and coronary heart disease more often than the non-users. In accordance with our hypothesis, the users of PPIs more often had diarrhea (19.7%) than the non-users (12.9%) ($p < 0.001$), and they had a prior hip fracture (28.5%) more often than the non-users (19.4%) ($p < 0.001$). In logistic regression analysis the use of PPIs had an independent association with diarrhea (OR 1.60 (95% CI 1.20 to 2.15). *Conclusion.* Physicians should avoid unnecessary long-term use of PPIs, particularly among frail elderly long-term care patients.

**Key Words:** *Aged, diarrhea, family practice, hip fracture, proton pump inhibitors, risks*

Proton-pump inhibitors (PPIs) are the most effective drugs available to reduce gastric acid secretion [1]. They are widely used by primary care physicians in the effective management of many acid peptic disorders [2–4]. In addition, they are also used to reduce the risk of gastrointestinal (GI) bleeding related to the use of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin [5].

PPI use has increased dramatically over the past years [6]. Once started, these drugs are often used for longer time periods among elderly people who are vulnerable to GI bleeding and even without clear therapeutic intent [7].

In general, these drugs have been considered to be safe [8]. However, PPIs have been suggested to predispose to gastrointestinal infections [9] and even to pneumonia [10]. There are several reports showing the associations of PPIs with bacterial overgrowth as well as with *Cl. difficile* infections [9,11].

The PPI therapy may also be associated with a significantly increased risk of hip fractures [12]. It has been suggested that PPIs may interfere with calcium absorption through induction of hypochlorhydria, and may reduce bone resorption through inhibition of osteoclastic vacuolar proton pumps [13].

Nursing home patients represent the frailest sector of the elderly population, often taken care of by primary care physicians. They have multiple comorbidities and are often administered a high number of

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The well-known benefits of proton-pump inhibitors (PPIs) have led to their increased and long-term use as "all purpose" protectors of the GI tract among older patients.

- Among nursing home residents 22% were administered PPIs regularly.
- Regular PPI use was associated with diarrhea, prior hip fracture, coronary heart disease, and lactose intolerance indicating possible adverse events or their use for inappropriate therapeutic intent.
- Unnecessary long-term use of PPIs should be avoided among frail, older patients.

concomitant drugs [14,15]. Thus, they are prone to drug–drug interactions and various adverse events. In addition, few patients in nursing homes have the opportunity for a thorough reassessment of their medication after admission to a nursing home [14]. Thus, their use of those drugs intended to be used for a limited time is often extended for long durations [16].

This study aims to test the associated risks of the use of PPIs in a large sample of frail elderly people in all nursing homes in Helsinki, Finland. To our knowledge, no such extensive epidemiological study of the PPI use in the frail elderly population has yet been undertaken.

## Material and methods

We collected cross-sectional material for this study during February 2003 from all nursing homes in Helsinki, Finland, as part of a larger project investigating the nutritional status of nursing home residents [17]. Frail long-term patients are primarily treated by primary care physicians in Finland. We collected and analyzed all data anonymously. This study was approved by the Helsinki city ethics committee.

The inclusion criteria for this study were long-term residency in nursing home, sufficient information regarding demographic factors, and medication charts available. In February 2003, 1088 persons were residing in public nursing homes (n = 4), and 1336 in private nursing homes (n = 16). Of these 2424 residents, we assessed 2084; we excluded short-term residents and those who refused to participate. Of the residents assessed, 1987 had sufficient medical and demographic data for further analysis.

Trained nursing home personnel assessed the residents' health status, and retrieved data on demographic factors, regularly administered medications, and diagnoses (including prior hip fracture, lactose intolerance, and celiac disease) were retrieved from the residents' medical charts. Comorbidity was assessed by the Charlson comorbidity index, a weighted index taking into account the number and severity of comorbid conditions [18]. Each resident was assessed by the Mini Nutritional Assessment (MNA) test [19]. The overall MNA score distinguishes between elderly patients with: (i) good nutritional status ($>$ 24 points), (ii) a risk of malnutrition (17–23.5 points), and (iii) malnutrition ($<$ 17 points). The validity and reliability of the MNA is thoroughly tested, and there are several questions embedded in the scale concerning the contents of the diet such as use of vegetables and fruits and drinking habits [19]. Various gastrointestinal symptoms were charted with questions such as "Does this patient suffer from the following gastrointestinal problems: 1. diarrhea (yes/no); 2. vomiting (yes/no); 3. constipation (yes/no)?"

The point prevalence of prescribed PPIs during one day was studied. We classified residents as PPI users if their medical charts indicated a regular sequence for PPI dosage. The PPIs used by patients in this study were omeprazole (423 patients), pantoprazole (1 patient), esomeprazole (2 patients), and lansoprazole (7 patients). Use of laxatives (bulk laxatives, stimulant laxatives, osmotic agents, neuromuscular agents), and constipation-inducing drugs were classified as described [29]. We also classified other medications having diarrhea as a common side effect according to the Finnish Pharmacopoeia. They included antibiotics, metformin, non-steroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin, iron supplements, cholinesterase inhibitors, calcium supplements, and selective serotonin reuptake inhibitors (SSRI).

We studied the association between PPI use and demographic characteristics, symptoms such as diarrhea, constipation, use of other drugs, and presence of other diseases.

We analyzed the coded data with the NCSS statistical program. We compared the PPI users with the non-users and the patients who had diarrhea with those without with the chi-squared test, or with Fisher's exact test, when appropriate. We used the Mann–Whitney U-test to compare mean ages and numbers of daily drugs. We considered p-values $< 0.05$ to be statistically significant. Multivariate logistic regression analysis served to determine which variables were independently associated with diarrhea; we used those variables which were statistically significant or near $p < 0.05$ in univariate analyses.

## Results

Of the 1987 elderly residents assessed, 80.7% were female. The residents' mean age was 83.7 years. Among the participants, 433 (21.8%) were regularly administered PPIs (Table I).

The PPI users and non-users did not differ in their mean age, gender distribution, or nutritional status. The factors associated with regular PPI use in univariate analyses included poorer functional status (inability to move independently), higher Charlson comorbidity index, and higher mean number of medications. The PPI users more often received calcium supplements and vitamin D supplements than the non-users. There was a higher incidence of a prior ventricular or duodenal ulcer and cancer than among the non-users. They suffered more often from coronary heart disease and lactose intolerance than the non-users. They less often had a dementia diagnosis.

In accordance with our hypothesis, the users of PPIs more often had diarrhea (19.7%) than the non-users (12.9%) ($p < 0.001$), and they had a prior hip fracture more often than the non-users. There were no differences in how many PPI users and non-users were on low-dose aspirin or NSAIDs.

Further, we cross-tabulated the patients suffering from diarrhea and those not (Table II). The mean age of the patients with diarrhea was higher, and they had more comorbidities and a higher number of medications. In addition, they suffered more often from diabetes, celiac disease, lactose intolerance, prior ventricular or duodenal ulcer, and coronary heart disease than those not having diarrhea. They were also more frequently users of laxatives and selective serotonin reuptake inhibitors (SSRI). However, the use of antibiotics, iron supplements, cholinesterase inhibitors, metformin, or NSAIDs did not differ between the groups.

In logistic regression analysis, where age, gender, drinking habits, Charlson comorbidity index, lactose intolerance, celiac disease, chronic inflammatory bowel disease, constipation, use of laxatives, calcium supplements, and SSRIs were used as covariates, the use of PPIs had an independent association with diarrhea (OR 1.60, 95% CI 1.20–2.15; $p = 0.002$). Also Charlson comorbidity index (OR 1.16, 95% CI 1.05–1.28; $p = 0.005$) and age (OR 1.02, 95% CI 1.00–1.04; $p = 0.008$) were independent associates of diarrhea.

Table I. Characteristics of residents divided by the use of proton pump inhibitors (PPI).

| | PPI users (n = 433) | PPI non users (n = 1554) | p-value[1] |
|---|---|---|---|
| Mean age (SD[2]) | 83.8 (7.4) | 83.7 (7.8) | 0.69 |
| Females, % | 79.2 | 81.1 | 0.38 |
| Education < 7 years, % | 61.2 | 61.9 | 0.83 |
| Unable to move independently, % | 35.5 | 28.9 | 0.009 |
| Nutritional status according to the MNA[3]> 23.5 points, % | 12.5 | 10.9 | |
| 17–23 points, % | 59.4 | 60.6 | |
| < 17 points, % | 28.2 | 28.5 | 0.65 |
| Mean body mass index, kg/m$^2$ (SD[2]) | 24.0 (5.0) | 23.6 (4.9) | 0.15 |
| Mean number of medications (SD[2]) | 10.5 (3.4) | 7.2 (3.2) | < 0.001 |
| Laxatives, % | 58.9 | 54.3 | 0.09 |
| Calcium supplements, % | 40.1 | 24.9 | < 0.001 |
| Vitamin D supplements, % | 37.7 | 29.5 | 0.001 |
| Cholinesterase inhibitor, % | 6.5 | 7.4 | 0.51 |
| SSRIs[4], % | 32.8 | 24.9 | 0.001 |
| Low-dose aspirin[5], % | **43.9** | **46.7** | **0.29** |
| NSAIDs[5], % | **5.5** | **5.2** | **0.74** |
| Coronary heart disease, % | 47.4 | 34.9 | < 0.001 |
| Prior stroke or transient ischemic attack, % | 29.4 | 29.8 | 0.88 |
| Dementia, % | 56.8 | 73.0 | 0.001 |
| Prior hip fracture, % | 28.5 | 19.4 | < 0.001 |
| Diabetes, % | 20.0 | 16.9 | 0.14 |
| Cancer, % | 15.1 | 10.3 | 0.008 |
| Prior ventricular or duodenal ulcer, % | 15.0 | 3.1 | < 0.001 |
| Mean Charlson comorbidity index[6] (SD[2]) | 2.3 (1.3) | 2.1 (1.2) | < 0.001 |
| Lactose intolerance, % | 15.1 | 7.8 | < 0.001 |
| Celiac disease, % | 0.5 | 0.5 | 0.98 |
| Constipation, % | 44.2 | 44.3 | 0.98 |
| Diarrhea, % | 19.7 | 12.9 | < 0.001 |
| Frequent vomiting, % | 8.2 | 3.7 | < 0.001 |

Notes: [1]Categorial variables are tested with chi-squared test or Fisher's exact test and continuous variables with t-test or Mann–Whitney U-test. [2]SD = standard deviation. [3]MNA = Mininutritional Assessment (Vellas et al., [19]). [4]SSRIs = Serotonin Reuptake Inhibitors. [5]NSAIDs = Non Steroidal Anti-inflammatory drugs. [6]Charlson Comorbity Index (Charlson et al., [18]).

Table II. Characteristics of patients divided by having or not having diarrhea.

| | Diarrhea (n = 277) | Without diarrhea (n = 1645) | p-value[1] |
|---|---|---|---|
| Mean age (SD[2]) | 84.9 (7.2) | 83.5 (7.7) | 0.003 |
| Females, % | 82.3 | 82.3 | 0.41 |
| Nutrition and gastrointestinal symptoms, % | | | |
| Nutritional status according to MNA,[3] % | | | 0.11 |
| < 17 points | 33.2 | 27.5 | |
| 17–23.5 points | 57.8 | 60.7 | |
| > 23.5 points | 9.0 | 11.7 | |
| Mean body mass index, kg/m$^2$ (SD[2]) | 23.6 (5.0) | 23.8 (4.9) | 0.43 |
| Drinks at least 5 glasses of fluids/day, % | 55.6 | 60.4 | 0.079 |
| Eats at least two portions of fruits or vegetables/day, % | 77.1 | 75.9 | 0.66 |
| Frequent vomiting, % | 9.2 | 3.7 | < 0.001 |
| Constipation, % | 39.0 | 43.9 | 0.13 |
| Medical conditions: | | | |
| Mean Charlson Comorbidity Index[4] (SD) | 2.34 (1.2) | 2.09 (1.2) | 0.001 |
| Dementia, % | 70.4 | 69.2 | 0.70 |
| Prior ventricular or duodenal ulcer, % | 9.0 | 4.8 | 0.007 |
| Prior hip fracture, % | 25.2 | 20.4 | 0.085 |
| Cancer, % | 12.4 | 10.8 | 0.46 |
| Coronary heart disease, % | 44.3 | 36.1 | 0.0013 |
| Diabetes mellitus, % | 21.7 | 16.6 | 0.047 |
| Prior stroke or transient ischemic attack, % | 31.2 | 28.9 | 0.45 |
| Lactose intolerance, % | 28.1 | 6.4 | < 0.001 |
| Celiac disease, % | 1.5 | 0.3 | 0.009 |
| Chronic inflammatory bowel disease, % | 1.1 | 0.4 | 0.11 |
| Use of drugs | | | |
| Mean number of medications (SD[2]) | 8.6(3.6) | 7.8(3.5) | < 0.001 |
| Laxatives, % | 46.2 | 56.6 | 0.001 |
| Calcium supplements, % | 32.6 | 27.5 | 0.083 |
| Vitamin D supplements, % | 31.0 | 31.6 | 0.86 |
| Cholinesterase inhibitors, % | 6.1 | 7.3 | 0.34 |
| SSRIs, % | 31.8 | 25.9 | 0.041 |
| Iron supplements, % | 9.7 | 9.4 | 0.84 |
| Antibiotics, % | 18.4 | 16.9 | 0.54 |
| metformin, % | 4.0 | 2.6 | 0.21 |
| Non-steroidal anti-inflammatory drugs, % | 46.2 | 49.5 | 0.30 |

Notes: [1]Categorial variables are tested with chi-squared test or Fisher's exact test and continuous variables with t-test or Mann–Whitney U-test. [2]SD = standard deviation. [3]MNA = Mininutritional Assessment (Vellas et al., [19]). [4]Charlson Comorbity Index (Charlson et al., [18]).

## Discussion

This study confirms the relationship between the use of PPIs and prevalence of diarrhea in a large frail elderly population. Even in multivariate analysis, where several confounding factors affecting diarrhea were controlled for, the use of PPIs remained an independent predictor of diarrhea. The PPI users had also more often had prior hip fractures, coronary heart disease, and lactose intolerance than the non-users. The users and non-users of PPIs did not differ in how they were administered low-dose aspirin or NSAIDs. These findings indicate possible adverse events related to PPI use as well as unnecessary use without clear therapeutic intent.

Although PPIs are usually very well tolerated [21], concerns have recently been raised regarding their long-term safety. Some reports suggest that these drugs are associated with a greater risk of community-acquired pneumonia [10], *Cl. difficile* infections and diarrhea [9], and hip fractures [13]. In a systematic review there was an association between acid suppression and an increased risk of enteric infection [9]. All the studies in this meta-analysis were case-control studies with a relatively small number of participants. Our study with a large representative sample of frail elderly patients confirms these prior preliminary findings. In this frail, elderly population dependent on other people's continuous help, frequent diarrhea is a burdensome symptom causing unnecessary suffering and skin problems. The diarrhea risk of PPIs deserves more attention in this population.

Treatment with proton-pump inhibitors induces a clinical state similar to atrophic gastritis with markedly reduced gastric acid production and less pepsin activity because of high gastric pH, and is frequently

associated with bacterial overgrowth [22,23] which may be of particular importance in the elderly. Bacterial overgrowth of the small intestine can result in malabsorption of fat, carbohydrate, protein, and micronutrients and clinical manifestations of abdominal pain, diarrhea, and even malnutrition [24]. Multiple drug therapy compounds the problem of drug-associated diarrhea.

The National Institute for Clinical Excellence (NICE) has introduced guidance on the use of PPIs [25]. However, the guidelines have had little impact on clinical practice. Only 38.6% of PPI prescribing was appropriate according to NICE recommendations. The same study suggested that relief of non-specific abdominal symptoms or indeterminate chest pain was the main unapproved indication for PPI therapy [26]. These non-specific abdominal and esophageal symptoms may also explain the association of PPI use in our study with coronary heart disease, celiac disease, and lactose intolerance. Thus, the indications for PPIs in this population may be vague.

There was an association of prior hip fracture and the use of PPIs in our sample. Although the causal relationship cannot be determined in our study, this association deserves more attention. The strength of the association between PPI use and hip fracture has been shown to increase with longer duration of PPI therapy [13]. Significant hypochlorhydria could theoretically result in calcium malabsorption. It has been suggested that cumulative exposure to acid suppression therapy may be a clinically relevant measure when considering the risk of osteoporosis [27,28]. PPI therapy is associated with a significantly increased risk of hip fractures, with the highest risk seen among those receiving high-dose PPI therapy, and those on PPI therapy for more than a year [12]. For elderly patients who require long-term and particularly high-dose PPI therapy, it may be prudent to reemphasize increased calcium intake. In fact, our patients using PPIs were more often on calcium and vitamin D supplementation. This is probably explained by the fact that these patients had more often had prior hip fracture, thus requiring preventive measures against further fractures.

Our study suggests that the use of PPIs is vast and there may not be clear indications for their administration. The use of NSAIDs or low-dose aspirin did not differ between the groups, thus the PPIs were not clearly used to reduce the risk of GI bleeding related to NSAID and low-dose aspirin [5]. GPs often have the primary responsibility for preventive drug therapies, duration, and discontinuation of these treatments [29]. It has been pointed out that textbooks and recommendations often lack indications, duration of therapy, and discontinuation of treatment [29].

The strength of this study is its large sample size and representativeness of the sample including all available frail elderly nursing home residents in the city of Helsinki in Finland. The results were reliably collected due to nursing personnel's continuous follow-up of the residents' symptoms. The nursing home residents' own nurses often know their patients very well and are well acquainted with their physical conditions and symptoms, thus increasing the reliability of our symptom data. The limitation of this study is its cross-sectional nature. Our study design does not take into account the prescription sequence, which is necessary when assessing causalities.

We had a limited number of variables in this study. The potential confounding factors can be numerous among multimorbid elderly patients. For example, we did not have information on such diagnoses as irritable bowel syndrome or vitamin B12 deficiency. Neither did we have information on the fecal samples or etiologies of diarrhea of these patients. Our study showed associations between the use of PPIs and diarrhea as well as hip fractures. As with all observational studies there is a possibility that the associations observed were due to residual confounding.

## Conclusions

When prescribing PPIs physicians should consider both their benefits and their harms. The need for these drugs should be reviewed on a regular basis, and unnecessary long-term use of PPIs should be avoided. They should not be used as as "all purpose" protectors of the GI tract, and therapeutic indications should remain clear.

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**Conflict of interests**: None.

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