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ORIGINAL ARTICLE

Proton pump inhibitors and risk of hip fracture: a meta-analysis of observational studies

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Abstract

Summary We performed a meta-analysis of relevant studies to quantify the magnitude of the association between proton pump inhibitors (PPIs) and risk of hip fracture. Patients with PPIs had a greater risk of hip fracture than those without PPI therapy (RR 1.20, 95% CI 1.14–1.28, $p < 0.0001$). These results could be taken into consideration with caution, and patients should also be concerned about the inappropriate use of PPIs.

Introduction Proton pump inhibitors (PPIs) are generally considered as first-line medicine with great safety profile, commonly prescribed for gastroesophageal reflux disease (GERD) and peptic ulcer disease. However, several epidemiological studies documented that long-term use of PPIs may be associated with an increased risk of hip fracture. Although, the optimal magnitude of the hip fracture risk is still undetermined. We, therefore, performed a meta-analysis of relevant studies to quantify the magnitude of the association between PPIs and risk of hip fracture.

Methods We collected relevant articles using MEDLINE, EMBASE, Google Scholar, and Web of Science from January 1, 1990, to March 31, 2018. We included only the large ($n \geq 500$) observational studies with a follow-up duration of at least one year in which the hip fracture patients were identified by a standard procedure. Two of the authors extracted data from each included study independently according to a standardized protocol.

Results A total of 24 observational studies with 2,103,800 participants (319,568 hip fracture patients) met all the eligibility criteria. Patients with PPIs had a greater risk of hip fracture than those without PPI therapy (RR 1.20, 95% CI 1.14–1.28, $p < 0.0001$). An increased association was also observed in both low and medium doses of PPI taken and hip fracture risk (RR 1.17, 95% CI 1.05–1.29, $p = 0.002$; RR 1.28, 95% CI 1.14–1.44, $p < 0.0001$), but it appeared to be even greater among the patients with higher dose (RR 1.30, 95% CI 1.20–1.40, $p < 0.0001$). Moreover, the overall pooled risk ratios were 1.20 (95% CI 1.15–1.25, $p < 0.0001$) and 1.24 (95% CI 1.10–1.40, $p < 0.0001$) for the patients with short- and long-term PPI therapy, respectively, compared with PPI non-users.

Conclusion Our results suggest that PPI use is significantly associated with an increased risk of hip fracture development, which is not observed in H2RA exposure. Physicians should, therefore, exercise caution when considering a long-term PPI treatment to their patients who already have an elevated risk of hip fracture. In addition, patients should be concerned about the inappropriate use of PPIs; if necessary, then, they should continue to receive it with a clear indication.

Keywords Bone fracture · Gastroesophageal reflux disease · Hip fracture · Osteoporosis · Proton pump inhibitors

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Introduction

Hip fracture is considered as a serious health problem among the elderly. The economic burden of hip fracture is substantial especially in developed countries and expected to rise significantly in the near future [1]. The prevalence of hip fracture increases with age, and this number reaches a peak at the age of 75–79 years. Although, the prevalence rate varies considerably by gender, nearly 75% of hip fracture occur in women [2]. In fact, hip fracture is associated with substantial morbidity and mortality; approximately 20–30% of patients die in the first year after having this condition [3]. Recent studies have provided evidence showing that some potential risk factors, such as certain medical conditions, tendency to fall, low physical activity, and use of psychotropic/anxiolytic/hypnotic, are associated with hip fracture [4]. Furthermore, there has been a surge of interest in PPIs and a possible risk factor for loss of bone mineral and hip fracture [5, 6].

Proton pump inhibitors (PPIs) are one of the most widely prescribed medications, generally considered to be a safe medication for the treatment of gastroesophageal reflux disease, ulcers, and other gastrointestinal conditions. There is growing concern regarding the inappropriate use of PPIs in the general population. A significant amount of recent literature reported that long-term use of PPIs needs to be cautious due to its wide range of potential health risks. It is now becoming clear that long-term use of PPI is associated with an increased risk of gastric cancer [7], community-acquired pneumonia (CAP) [8], kidney disease [9], cardiovascular events [10], and dementia [11]. In contrary, Filion et al.'s [12] study findings do not support the hypothesis of an independent association between PPI use and risk of CAP. Indeed, PPI use and the risk of dementia and CAP might be limited by methodological issues and residual confounding factors [11]. Moreover, increasing epidemiological evidence suggests that PPI use is associated with an increased risk of hip fracture [13–15], but the biological mechanisms of how PPI use increased the hip fracture risk are still controversial. Moreover, researchers have also claimed that reducing the level of acidity in the stomach may lead to malabsorption of calcium which triggers the risk of hip fracture risk [16].

To our knowledge, five previously published meta-analyses [5, 17–20] have shown that PPI is associated with an increased risk of hip fracture. However, these studies included less number of observational studies and not provided an extensive subgroup analysis between the association. Herein, we report the findings of an updated comprehensive systematic review and meta-analysis of observational studies that have investigated the association between PPIs and hip fracture risk. Our aim was to gauge precisely the nature and magnitude of the association between PPIs and hip fracture risk. We also have investigated whether the duration, such as short (< 1 year), intermediate (1–2 years), and long (≥ 3 years), and various amounts of PPI dosage (low, medium, and high) are associated with an even greater risk of hip fracture or not. Indeed, previously published several literatures claimed that various duration and dosage of PPI use had a potential effect on hip fracture [17–19]. Clarification of the magnitude of the risk of hip fracture would reveal the possibility to improve clinical outcomes of PPI therapy. Additionally, a coherent evidence on the magnitude of risk associated with PPI use on the basis of duration and dosage would also assist current treatment decision.

Methods

Experimental section

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), which is based on the Cochrane's Handbook for Systematic Reviews, was used to conduct the current study [21]. A review of the written protocol was not drafted (Supplementary Table S1).

Literature review

PubMed, EMBASE, Scopus, Google Scholar, and Web of Science were searched systematically for relevant articles published between January 1990 and March 2018. The search terms included extensive-controlled following vocabularies: "Proton pump inhibitors," "PPIs," "Acid suppressants," "Omeprazole," "Pantoprazole," "Rabeprazole," "Lansoprazole," "Esomeprazole," "Observational study," "Case-control study," "Randomized control trial," and "Hip fracture" (Supplementary Table S3). There was no language and data restriction made on our primary search. Additionally, we also searched the bibliographies of included studies manually and discussed with consultants if anything is needed to be searched. We used EndNote X7 (Thomson Reuters) software to remove duplication of included studies.

Study selection criteria

Two of the authors, MMI and TNP, independently screened the titles and abstracts for inclusion of all the potential studies identified previously using the search terms. They retrieved the full-text study report/publication. All articles were, then, being considered as potentially eligible (types of study, participants, interventions, and outcome) by these two reviewers after reviewing the full text and recording the reasons for exclusion of the ineligible studies. Any disagreement in this stage was resolved by discussion and consensus with the other experts (HCY and CCW).

Studies were included if they met the following (PICO) criteria:

(i.) *Types of studies*

We initially included an observational study (cohort, case-control, etc.) reported as full text, abstract only, and unpublished data.

(ii.) Types of participants

(a) Adults (aged 18 years or greater) with any hip fracture at baseline, confirmed by the International Classification of Disease Code (ICD), radiology, or other standard protocol.
(b) Participants more than 500.

(iii.) Types of interventions

The experimental intervention was PPI use for at least one month or greater. We included any study with at least one-year follow-up period. A valid control group included one of the following subsets of participants.

(a) with no PPI treatment or placebo treatment;
(b) undergoing no anti-reflux surgery or endoscopy anti-reflux treatment;
(c) other kinds of gastric therapy: histamine H2-receptor antagonist or antacid.

Only oral treatment at any dosage was considered.

(iv.) Types of outcome measures

Primary outcomes: Development of hip fracture after PPI therapy at any terms.
Secondary analysis: Development of hip fracture after short-term (< 1 year), intermediate (1–2 years), and long-term (≥ 3 years) PPI therapy. Additionally, various types of dosage (low, medium, and high) were considered to make the current study more comprehensive.
Sensitivity analysis: Development of hip fracture after H2RA therapy (excluding PPIs).

Data extraction and quality assessment

Data abstraction was conducted by the same two authors who used a predefined, standardized protocol and data collection instrument. They entered the data into Review Manager software (RevMan-5) and checked for accuracy. The following information is obtained from the extracted data: (a) method—study design, total duration of the study, number of study centers and location, study setting, date of study; (b) participants—number of participants, mean age, age range, gender, percentage of gender, diagnostic criteria, inclusion criteria, exclusion criteria; (c) interventions—intervention, comparison, concomitant medications, comorbidities (Supplementary Table S5); (d) outcome—primary and secondary outcomes. Two review authors (MMI, TNP) independently extracted outcome data from the included studies. We resolved disagreements by consensus or by involving the main investigator (YCL).

Additionally, the risk of bias was also assessed by the two review authors. The methodological quality of the included observational studies was assessed based on a modified version of the Newcastle-Ottawa Scale (NOS) which is recommended by the Cochrane's Collaboration (Supplementary Table S2). NOS uses a star system (maximum of nine stars) to assess a study in three areas, such as the selection of participants, comparability of study groups, and the ascertainment of outcomes of interest. We considered a study as a low risk and a high risk if it receives a score of ≥ 7 (high quality) and < 7 stars (low quality), respectively (Supplementary Table S4).

Statistical analyses

The primary outcome of interest of this meta-analysis was the risk of hip fracture among individual with PPIs compared with the risk of hip fracture among those without PPIs. The summary risk ratio (RR) with 95% CI from HRs and ORs was calculated to measure the magnitude of hip fracture with PPIs. ORs approximated RRs since fracture is a sufficiently lower event (< 5% per year), and most of the case-control study used an open-cohort sampling design. However, DerSimonian and Laird random effects model was used to pool the results that were considered both within- and between-study variation [22]. Risk ratio > 1 indicates an increased risk of hip fracture and < 1 indicates a decreased risk of hip fracture. We assessed statistical significance using the 95% CIs. If the 95% CI did not include the neutral value of 1, we considered the risk to be statistically significant. The forest plots were drawn to evaluate the possibility of statistical heterogeneity. An I^2 value was used to assess the statistical heterogeneity which provided an estimate of the percentage of variability among the included studies. An I^2 value at 0–25%, 25–50%, 50–75%, and more than 75% represents very low, low, medium, and high heterogeneity, respectively [23, 24]. The results from all included studies were pooled, and an overall estimate of effect size was evaluated using a random effects model which helps to provide exact heterogeneity among studies. The funnel plot and Egger's regression test were used to evaluate publication bias. In the secondary analysis, we evaluated the risk of hip fracture with PPI exposure periods, such as short term (< 1 year), intermediate (1–2 years), and long term (≥ 3 years), and various amounts of PPI dosage (low, medium, and high). In addition, a sensitivity analysis (H2RA use and hip fracture risk) was conducted to identify other gastric medication use and hip fracture risk. Moreover, the subgroup was also calculated based on

individual PPI users, region, study design, and methodological quality. All the statistical tests were two-sided and used a significance level of p value ≤ 0.05. The comprehensive meta-analysis (CMA, V-2) was used for all statistical analysis.

Results

Study characteristics

A total of 1253 relevant studies were identified in the initial search. Of these, 1100 articles were excluded for duplication, and 123 out of 153 studies were excluded based on predetermined eligibility criteria during title/abstract review. The remaining 30 articles went through full-text reviews. However, 24 [1, 13–15, 25–43] unique observational studies ultimately met all of our study inclusion criteria. Figure 1 shows the article selection diagram for this meta-analysis.

The study characteristics of the included 24 articles are summarized in Table 1. In this meta-analysis, nine studies have cohort study design [20, 21, 30, 34, 40–42, 44] and fifteen studies have case-control study design [1, 19, 29, 31–33, 35–39, 43, 45–47]. Moreover, nine studies were conducted in North America [19, 30, 34, 39, 41–44], ten in Europe [1, 20, 29, 32, 33, 36, 37, 45–47], and five in Asia [21, 31, 35, 38, 40]. A total of 2,103,800 participants were included in this meta-analysis, of these 319,568 were hip fracture patients. All studies provided information about the age limit of the study participants (> 18 to > 85 years) and gender information, except for one study [47]. The range of women participant's inclusion was 0 to 100%. Only five studies analyzed individual PPI use and hip fracture risk. Additionally, eight studies provided information about the impact of dosage and hip fracture risk. In all the studies, results of the hip fracture risk were adjusted to age, gender, co-medication, and comorbidity, but in more than half of the studies, results were not adjusted to smoking status, alcohol consumption, and previous history of any site fracture.

Primary analysis

PPI use and hip fracture risk

Twenty-four studies evaluated PPI use and the risk of hip fracture. The overall pooled risk was RR 1.20 (95% CI 1.14–1.28, $p < 0.0001$) in the random effects model with moderate heterogeneity ($I^2 = 70.65\%$, $\tau^2 = 0.011$, $p < 0.0001$). Figure 2 shows the overall risk of hip fracture patients with PPIs.

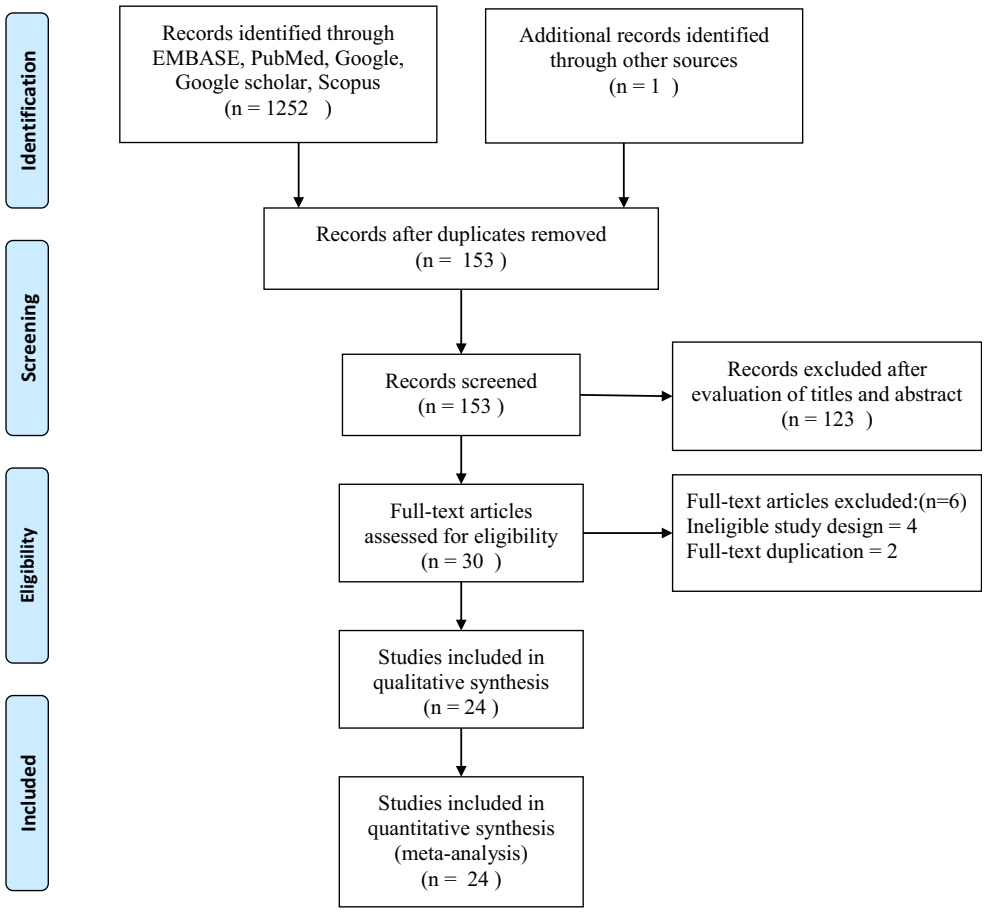

Fig. 1 PRISMA flow diagram for study selection

Table 1 Characteristic of observational studies reporting the effects of PPI use and hip fracture risk

Study	Year	Country	Age (yrs.)	% Women	Study period	Study design	Total participant	Hip fracture	OR/HR (95% CI)	NOS quality score
Adams	2014	USA	> 45	0	1991–2006	C-C	13,548	6774	1.13 (1.01–1.27)	7
De Vries	2009	UK	> 40	56	1998–2006	Co	468,251	848	1.22 (1.10–1.37)	8
Chen	2016	Taiwan	> 20	44	2000–2010	Co	31,358	114	0.79 (0.53–1.18)	8
Vestergaard	2006	Denmark	43	51	1996–2000	C-C	498,617	124,655	1.45 (1.28–1.65)	6
Ding	2014	USA	> 65	81	1999–2002	Co	25,276	816	1.32 (1.01–1.71)	7
Lee	2013	Korea	> 65	74	2005–2006	C-C	123,352	24,710	1.34 (1.24–1.44)	8
Pouwels	2011	Netherlands	> 18	73	1991–2002	C-C	33,104	6763	1.20 (1.04–1.40)	6
Khalili	2012	USA	44–79	100	2000–2008	Co	79,899	893	1.36 (1.13–1.63)	6
Targownik	2008	Canada	> 50	70	1996–2004	C-C	63,081	15,792	1.09 (0.88–1.34)	7
Chiu	2010	Taiwan	> 50	58	2005–2006	C-C	2481	1241	2.11 (1.45–3.07)	6
Yang	2006	UK	> 50	80	1987–2003	C-C	148,942	13,556	1.44 (1.30–1.59)	6
Kaye	2008	UK	50–79	72	1995–2005	C-C	12,021	4414	1.00 (0.70–1.30)	6
Lai	2017	Taiwan	65–> 85	60.3	2000–2013	C-C	14,416	7208	0.96 (0.76, 1.22)	8
Lenihan	2017	USA	40–63	51	2007–2011	C-C	15,806	231	1.39 (1.04–1.84)	7
Lin	2018	Taiwan	53–79	37.3	2000–2012	Co	10,596	665	1.18 (1.00–1.38)	8
Fraser	2013	Canada	> 25	70	1995–2007	Co	9423	1295	1.75 (0.94–3.26)	9
Yu-SOF	2008	USA	> 65	100	1986–2007	Co	5327	1410	1.16 (0.80–1.68)	8
Yu-MrOS	2008	USA	> 65	0	2000–2007	Co	5742	489	0.62 (0.26–1.46)	8
Corley	2010	USA	> 18	65	1995–2007	C-C	164,223	33,752	1.30 (1.2–1.39)	7
Gray	2010	USA	50–79	100	1993–2005	Co	161,806	1500	1.00 (0.71–1.40)	8
Reyes	2013	Spain	> 50	77	2007–2010	C-C	1056	698	1.24 (0.93–1.65)	6
Soriano	2014	UK	40–89	75	2000–2008	C-C	30,958	10,958	1.09 (1.01–1.17)	7
T-Kiiskinen	2018	Finland	< 65–> 85	75	2005–2011	C-C	24,053	19,235	1.12 (1.03–1.22)	8
Abrahamsen	2013	Denmark	N/A	N/A	2000	C-C	166,206	41,551	1.13 (1.05–1.21)	7

OR, odd ratio; HR, hazard ratio; C-C, case-control; Co, cohort; NOS, The Newcastle-Ottawa Scale

Secondary analysis

Hip fracture risk with PPI duration

The impact of duration of PPI therapy (short-, intermediate, and long-term PPI exposure) and the risk of hip fracture was also assessed. Short-term use (< 1 year) of PPI was significantly associated with 20% increase risk of hip fracture (RR 1.20, 95% CI 1.16–1.25, $p < 0.0001$; heterogeneity $I^2 = 19.10\%$, $\tau^2 = 0.011$, $p = 0.27$). However, intermediate and long-term exposure of PPI have almost similar risk of hip fracture (RR 1.23, 95% CI 1.07–1.41, $p = 0.003$; heterogeneity $I^2 = 70.81\%$, $\tau^2 = 0.014$, $p = 0.01$ and RR 1.24, 95% CI 1.10–1.40, $p < 0.0001$; heterogeneity $I^2 = 68.58\%$, $\tau^2 = 0.010$, $p = 0.002$, respectively) (Fig. 3).

Hip fracture risk with PPI dosage (low, medium, and high)

The magnitude of hip fracture risk with different types (low, medium, and high) of PPI dosage was separately evaluated. A low, medium, or high dose of PPIs was associated with 17, 29, and 30% increased risk of hip fracture, respectively. The overall pooled risk ratio was RR 1.17, 95% CI 1.05–1.29, $p = 0.002$; heterogeneity $I^2 = 56.13\%$, $\tau^2 = 0.01$, $p = 0.025$ for the low dose; RR 1.29, 95% CI 1.14–1.44, $p < 0.0001$; heterogeneity $I^2 = 82.49\%$, $\tau^2 = 0.02$, $p < 0.0001$ for the medium dose; and RR 1.30, 95% CI 1.20–1.40, $p < 0.0001$; heterogeneity $I^2 = 33.58\%$, $\tau^2 = 0.003$, $p = 0.16$ for the high dose (Fig. 4).

Sub-group analysis

Subgroup analyses were conducted to examine the influence of individual PPI use, study design, methodological quality, and region on the risk of hip fracture and to estimate whether these characteristics could be the possible sources of heterogeneity (Table 2).

The impact of different types of PPI use and risk of hip fracture was examined. There was an increased risk of hip fracture with Rabeprazole (RR 1.27, 95% CI 1.05–1.53, $p = 0.01$; heterogeneity $I^2 = 12.07\%$, $\tau^2 = 0.005$, $p = 0.33$), Pantoprazole (RR 1.13, 95% CI 0.93–1.37, $p = 0.19$; heterogeneity $I^2 = 90.75\%$, $\tau^2 = 0.031$, $p < 0.0001$), and Omeprazole (RR 1.13, 95% CI 1.05–1.22, $p = 0.001$; heterogeneity $I^2 =$

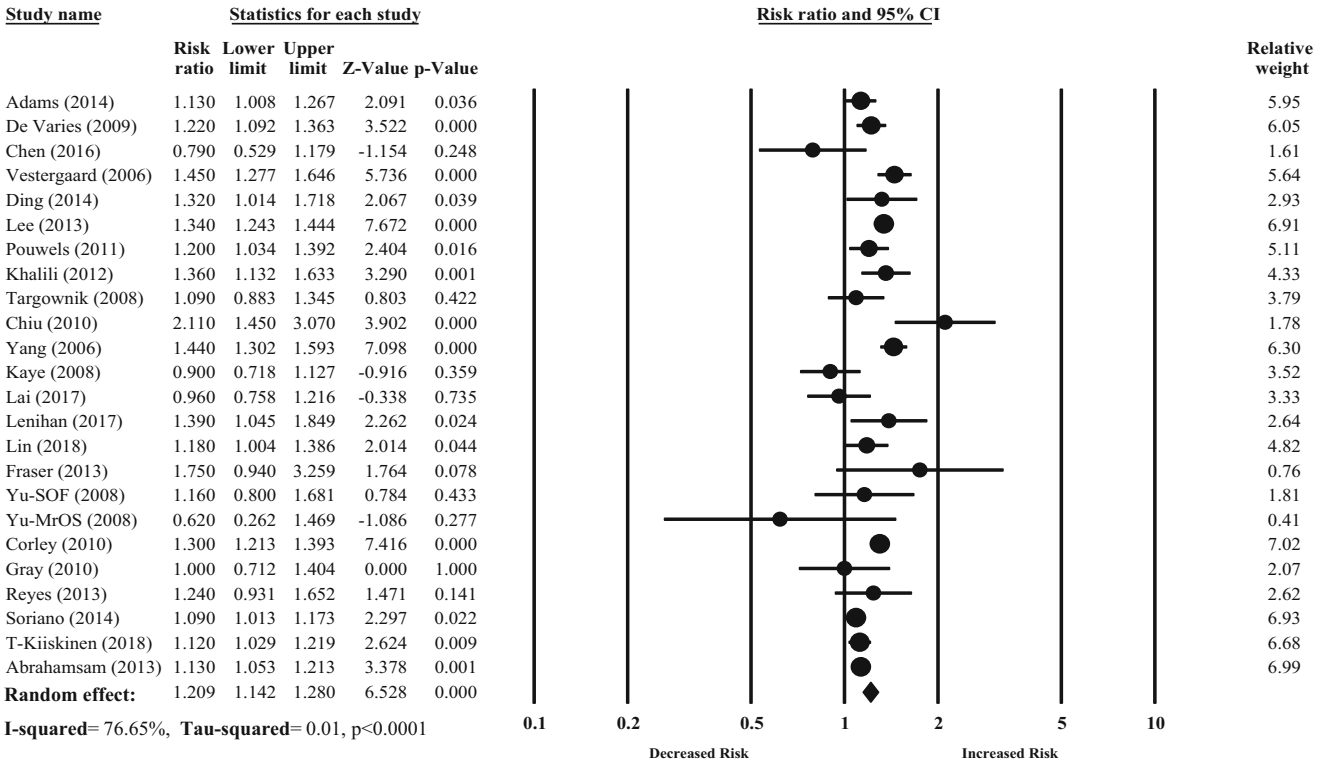

Fig. 2 Proton pump inhibitor use and risk of hip fracture

30.10%, $\tau^2 = 0.002$, $p = 0.22$), but no association was observed in Esomeprazole (RR 0.93, 95% CI 0.73–1.17, $p = 0.54$; heterogeneity $I^2 = 00.00\%$, $\tau^2 = 0.00001$, $p = 0.90$) and Lansoprazole (RR 1.08, 95% CI 0.97–1.21, $p = 0.14$; heterogeneity $I^2 = 00.00\%$, $\tau^2 = 0.0001$, $p = 0.94$).

Fifteen case-control and nine cohort studies evaluated the risk of hip fracture with PPI use. The overall risk of hip fracture of case-control studies was RR 1.21, 95% CI 1.13–1.30, $p < 0.0001$. The overall risk of hip fracture of cohort studies was RR 1.19, 95% CI 1.08–1.32, $p = 0.001$.

The pooled risk ratio for hip fracture in patients with PPIs in the high methodological-quality articles was RR 1.17, 95% CI 1.10–1.30, $p < 0.0001$. In contrary, the pooled risk ratio for hip fracture in patients with PPIs in the low methodological-quality articles was RR 1.32, 95% CI 1.15–1.50, $p < 0.0001$.

The risk of hip fracture in patients with PPIs was higher in North America (RR 1.22, 95% CI 1.13–1.33, $p < 0.0001$). However, there were 20 and 19% increased risk of hip fracture in a patient with PPIs compared with non-PPI users in the region of Asia (RR 1.20, 95% CI 0.98–1.48, $p = 0.07$) and Europe (RR 1.19, 95% CI 1.10–1.29, $p < 0.0001$), respectively.

Sensitivity analysis

In order to evaluate hip fracture with H2RA therapy, the magnitude of hip fracture risk was also assessed. The pooled risk ratio was 1.03 (95% CI 0.85–1.26, $p = 0.70$) in the random effects model. Supplementary Figure S1 shows the risk of hip fracture with H2RA therapy.

Publication bias

Supplementary Figure S1 shows the funnel plot that indicates the existence of some publication bias. The Egger's regression test of the funnel asymmetry showed no observed significant publication bias (p value = 0.75).

Discussion

Main findings

Our current meta-analysis provides an evidence for the significant association between PPI use and hip fracture risk. Indeed, patients who used PPIs for more than 3 years had a 24% increased risk of hip fracture compared with non-users. We also observed that short-term (< 1 year) and intermediate (1–2 years) users had a higher risk of hip fracture. To evaluate the potential dose-response relationship, we stratified PPI use into three categories and observed a statistically significant trend between the dose and the risk of hip fracture. The risk appeared to be even greater in patients with the

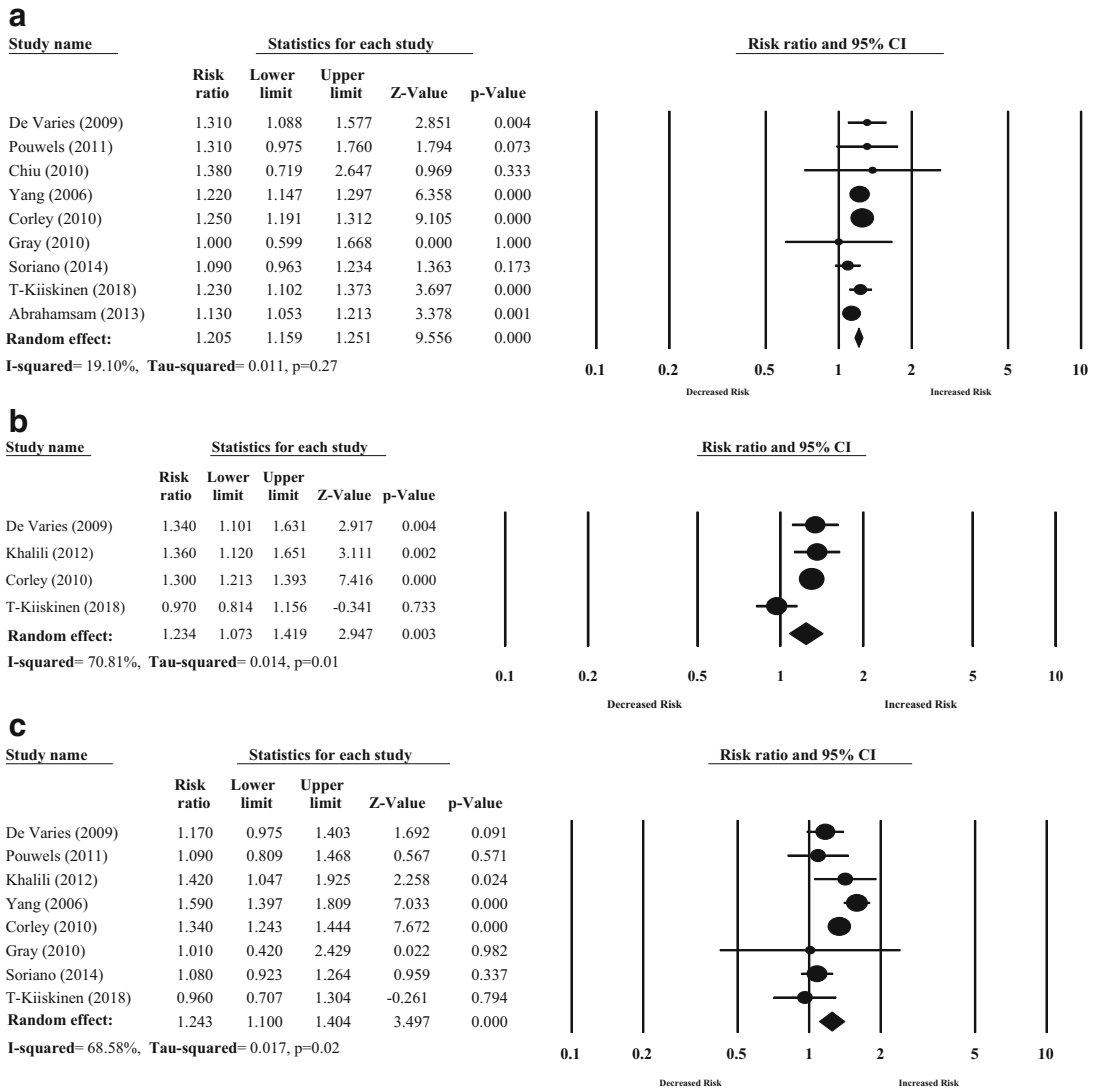

Fig. 3 Increased risk of hip fracture based on PPI exposure periods: (**a**) short term, (**b**) intermediate, and (**c**) long term

higher dose. In contrary, no association was observed between H2RA use and hip fracture among studies examining participants taking H2RA therapy alone. This is, in fact, the largest and most updated meta-analysis that aims at investigating the role of PPI therapy in hip fracture risk. Our findings confirm and extend the results from the previously published literature by providing an extensive statistical analysis and a clear evidence that hip fracture risk of individuals with PPI therapy is higher than that of individual without PPI therapy. The summary risk was also evaluated from the fully adjusted results of all included observational studies. Moreover, the NOS scale was used to assess the methodological quality of the included studies, and the overall pooled risk analysis in various subgroups helped to make a better quality of the overall body of the evidence and to strengthen their association.

Biological plausibility

There is no exact explanation of how PPIs increased the risk of hip fracture. However, the association between PPI use and hip fracture risk is probably related to factors independent of osteoporosis. Several convincing biological plausibilities have already been proposed that PPIs may increase the risk of hip fracture incidence. First, PPI is mainly responsible for calcium absorption impairment which is thought to affect calcium homeostasis. Therefore, the reduction of calcium in the bone tissue decreases its mineral density [16]. Second, PPIs impair gastric acid secretion which can lead to decreased calcium solubility and its subsequent absorption. Indeed, impaired gastric acid secretion also lessens the absorption of folate and vitamin B_{12} and increases homocysteine levels and the risk of atherosclerosis in the skeletal end arteries [37]. Third, PPI use is associated with increased gastrin secretion which

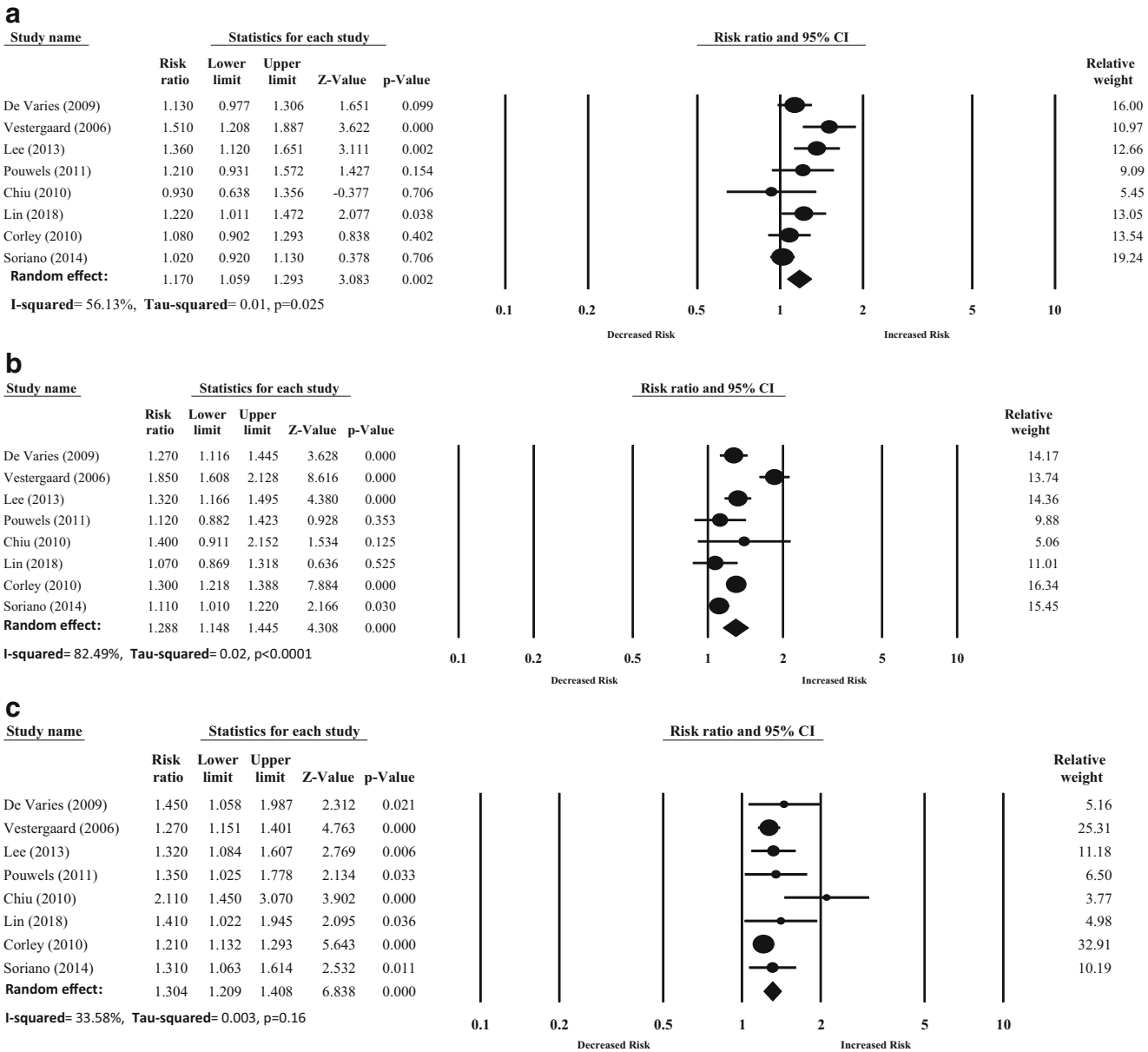

Fig. 4 Increased risk of hip fracture with PPI dosage: (**a**) low, (**b**) medium, and (**c**) high

eventually contributes to the dietary calcium release impairment, controlling calcium levels in the blood and, thereby, calcium absorption further leading to compensatory secondary hyperparathyroidism. Furthermore, thyroid secretion of calcitonin and parathyroid hormone (PTH) is associated with the stimulation of bone osteoblastic activity, decreased bone mass, and increased hip fracture [44]. Bone tissue is indeed reformed and reshaped by the combined action of osteoclasts and osteoblasts that maintain an adequate mass and structure [45]. Recent biological studies have provided evidence showing that PPIs could be responsible for the acid vesicle activation of the osteoclasts. However, in vitro studies have reported that PPIs inhibit gastric H^+-K^+-ATPase; a significantly lower abundance of vacuolar type of H^+-ATPase therefore causes osteoclast [46]. The vacuolar H^+-ATPase proton pump is to be found in the bone-apposed plasma membrane of the osteoclast. However, inhibition of V-ATPase by PPIs may control the secretion of hydrogen ions which might cause aberrant osteoclast-mediated bone resorption and osteoporosis [47]. Furthermore, in an in vivo ovariectomized rat study, Joo et al. [48] evaluated the effect of long-term PPIs (30 mg/kg for 8 weeks) on bone turnover and analyzed the signaling pathway involved in osteoclast differentiation and bone resorption/formation. PPI with a low-calcium diet was responsible for osteocalcin reduction and elevation of serum C-terminal cross-linked telopeptides of type I collagen in the rat. Also, Kocsis et al. [49] reported that PPI administration (20 mg/day with short term) did not significantly influence the

Table 2 Risk of hip fracture in patients with PPIs in the subgroup meta-analysis

Study	Pooled estimate			Test of heterogeneity			
	Number of study	RR (95% CI)	*p* value	τ^2	I^2	*p* value	Model
All studies	24	1.20 (1.14–1.28)	< 0.0001	0.011	70.65	< 0.0001	RE
Study design							
Cohort	9	1.19 (1.08–1.32)	0.001	0.006	29.69	0.181	RE
Case-control	15	1.21 (1.13–1.30)	< 0.0001	0.01	79.09	< 0.0001	RE
Methodological quality							
High quality	17	1.17 (1.10–1.3)	< 0.0001	0.006	60.63	0.001	RE
Low quality	7	1.32 (1.15–1.50)	< 0.0001	0.02	74.39	0.001	RE
Region							
Europe	9	1.19 (1.10–1.29)	< 0.0001	0.011	79.25	< 0.0001	RE
North America	10	1.22 (1.13–1.33)	< 0.0001	0.004	29.83	0.171	RE
Asia	5	1.20 (0.98–1.48)	0.07	0.03	90.49	< 0.0001	RE
Individual drugs							
Omeprazole	5	1.13 (1.05–1.22)	0.001	0.002	30.10	0.221	RE
Esomeprazole	3	0.93 (0.73–1.17)	0.54	0.00001	00	0.90	RE
Lansoprazole	4	1.08 (0.97–1.21)	0.14	0.0001	00	0.94	RE
Pantoprazole	5	1.13 (0.93–1.37)	0.19	0.031	90.75	< 0.0001	RE
Rabeprazole	4	1.27 (1.05–1.53)	0.01	0.005	12.07	0.33	RE

τ, tau; RR, risk ratio; RE, random effect

biochemical parameters of osteoclast and osteoblast function, such as urinary calcium excretion, serum total alkaline phosphatase activity, and collagen type 1 cross-linked C-telopeptide, in any age or gender group of pediatric patients. Similarly, long-term PPI treatment (12 weeks) was not responsible for altering the level of iPTH, ionized calcium, vitamin D, osteocalcin, or serum C-terminal cross-linked telopeptides of type I collagen in the healthy adults (aged 18–50 years) [50]. It is therefore clear that the effect of PPIs on bone metabolism is more evident in elderly individuals (aged more than 50 years) than that of younger individuals.

Comparison with other studies

The results of the current comprehensive meta-analysis are consistent with previously published five systematic reviews and meta-analyses [5, 17–20]. Ngamruengphong et al. [17] included 10 studies with 223,210 fracture patients, and the risk of hip fracture was higher in patients with PPIs (OR 1.25, 95% CI 1.14–1.37) compared with non-users. They reported that the available evidence of the impact of PPIs and risk of hip fracture is conflicting and inconsistent. Moreover, the overall level of evidence was very low as assessed by the GRADE approach. Similarly, Ye et al. [18], Elaine et al. [5], and Zhou et al. [19] showed that PPI use moderately increased the risk of hip fracture (OR 1.24, 95% CI 1.15–1.34; RR 1.30, 95% CI 1.19–1.43; RR 1.26, 95% CI 1.16–1.36, respectively). However, they did not support a causal relationship between PPIs and hip fracture, although the effects of duration (short term and long term) and dosage (lower and higher) of PPI use were also evaluated. Lastly, Hussain et al. [20] suggest that PPI use is associated with an increased risk (26%) of hip fracture. These five systematic reviews and meta-analyses commented on the possibility that this finding was due to residual confounding factors. In contrary, our study included 24 observational studies with larger number of participants and conducted extensive subgroup analysis (regional effect, methodological quality, individual PPIs) than previously published studies. The findings of our study were pooled from adjusted results of all included studies which would help to reduce potential confounding factors. Additionally, some possible biological mechanisms on how PPIs may cause hip fracture have also been provided.

Clinical implications

Gastroesophageal reflux disease (GERD) affects approximately 20% of the US general population (GP); 20–40% of Western adult populations report chronic heartburn or regurgitation symptoms [51]. However, it is associated with a substantially impaired health-related quality of life and accounts for a large burden on the financial resources of Medicare. PPIs are more widely used first-line treatment to reduce gastric acid secretion, and concern has been raised regarding the utilization of PPIs [52]. Findings of our study also support that PPI use is associated with an increased risk of hip fracture. It is also worth mentioning that the current evidence regarding the

association of PPI use and the risk of hip fracture is predominantly based on observational studies. However, an observed association in the observational studies often triggers "false alarms" [53] due to inappropriate study design or confounding factors due to poorly adjusted study variables applied to included observational studies. Due to heterogeneous data, variable study design, variability of clinical diversity, and risk bias, it is always uncertain whether existing association is true or not [11]. However, it is also important to note that there is no hard and fast rule by which to judge causation to this epidemiological association. This is why physicians should make a reasonable judgment about this evidence and properly evaluate the evidence objectively to discern the likelihood that any reported association might actually be causal. Indeed, physicians are generally asked for the inappropriate treatment of individual patients with GERD and peptic ulcer disease. Therefore, apart from short-term duration, PPI maintenance therapy is recommended in certain disease, such as gastroesophageal reflux disease (GERD) and Zollinger-Ellison syndrome (e.g., erosive esophagitis or Barrett's esophagus).

Additionally, there is also growing concern regarding the safety issues of using PPIs without prescription. A significant proportion of patients are taking PPIs unnecessarily for conditions or symptoms for which they would not have been expected to provide benefit. Moreover, many patients are taking PPI treatment for appropriate indications and receiving PPI therapy excessively on high daily doses on a long-term basis. However, emerging evidence including our findings also suggests that PPI could be considered in the lowest effective dose and for the shortest possible time. This meta-analysis also provides an evidence to re-think about the unnecessary prescription of PPIs in patients who may not need PPI therapy. These study findings have provided an opportunity to discuss potential risk of PPI therapy with patients who require a more risk-benefit analysis, such as those at higher risk of hip fracture (e.g., elderly patients and patients already in the early stage of hip fracture).

Strengths and limitations

Our meta-analysis has several strengths. First, it is the first meta-analysis that included a large number of studies and reported PPIs and hip fracture risk. Second, it examined the magnitude of the association in great detail, stratified by duration (short, intermediate, and long), dose (low, medium, and high), study design, methodological quality, and different categories of PPIs. Third, this meta-analysis included studies from three continents that make the study more diverse, reliable, and robust. However, our study also has several limitations. First, this meta-analysis is based on the findings of epidemiological studies; therefore, it could have some sort of confounding factors in the individual studies that make summary estimate potentially misleading. Although all included studies had had an adjusted result, it is not enough to reduce all residual confounding factors. For example, observational studies do not give the answer to the question of whether the observed positive association is due to the effects of PPIs or other conditions. Patients with bad health status and older age are also more prone to develop hip fracture than healthy users. Selection of patient solely relies on diagnostic codes in medical records or claims data to measure comorbidities, but they always fail to take the severity of the comorbidities into consideration [54]. Second, there was a sort of heterogeneity across the studies in the main analysis of hip fracture incidence. However, this could be explained partly by different study designs, regional effects, various methods, and partly due to the duration of PPI therapy. Third, our findings are not able to explore other possible sources of variability, although a higher number of studies were included in this meta-analysis. The random effects model was used to reduce heterogeneity among studies. Finally, in the subgroup analysis, we did not have enough information to classify the studies or patients based on gender, age group, smoking status, or alcohol consumption due to lack of information in the included studies.

Conclusion

Our comprehensive meta-analysis suggests that PPI use is associated with an increased risk of hip fracture but no association is observed in H2RA exposure. Our findings add to the increasing evidence in currently available literature through the breadth of our search, the inclusion of updated research, and extent of analysis. Physicians should, therefore, exercise caution when prescribing long-term PPIs to those patients at higher risk for hip fracture, especially patients aged more than 50 years. However, patients having Zollinger-Ellison syndrome and gastroesophageal reflux disease, who are already having enormous benefit to this therapy, should not discontinue this medication solely on the basis of hip fracture risk. Physicians should only prescribe rational PPI therapy where it is clearly indicated but always start at the lowest dose and need to check patients' symptom and bone mineral on a timely basis. Since a meta-analysis of observational studies cannot clarify a causal effect, it is, therefore, important to conduct randomized controlled studies to confirm or refute our findings.

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Compliance with ethical standards

Conflicts of interest All the authors (Tahmina Nasrin Poly, Md. Mohaimenul Islam, Hsuan-Chia Yang, Chieh Chen Wu, Yu-Chuan (Jack) Li) declare that they do not have any conflict of interest.

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