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Systematic Review with Meta-Analysis: Fundic Gland Polyps and Proton Pump Inhibitors

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Abstract

Background: A causal association between proton pump inhibitor (PPI) use and fundic gland polyps has been suggested but the data are conflicting.

Aim: The aim of this study was to clarify the relationship through a meta-analysis of the existing data.

Methods: A systematic retrieval and selection of records was performed. The main inclusion criteria were original studies reporting the prevalence of fundic gland polyps in PPI users or the reverse, compared to controls. Key outcomes were the odds ratios (OR) for fundic gland polyp prevalence in association with PPI use, prevalence of PPI use amongst subjects with fundic gland polyps, and fundic gland polyp prevalence amongst PPI users. Statistical analysis was performed using Mix 2.0 Pro.

Results: The initial search using electronic databases and manual searching retrieved 338 peer-reviewed articles and abstracts. Twenty articles met all inclusion and exclusion criteria, with a total of 40,218 subjects included. The meta-analysis of twelve studies revealed an increase in fundic gland polyps amongst PPI users compared to controls (OR 2.46, 95% CI 1.42-4.27, p = 0.001), particularly among individuals taking PPIs for at least 6 months (OR: 4.71, 95% CI 2.22-9.99, p < 0.001) or 12 months (OR: 5.32, 95% CI 2.58-10.99, p < 0.001).

Conclusions: PPI usage is associated with a significantly increased prevalence of fundic gland polyps, and there is a trend for this to increase with longer length of PPI exposure. However, the meta-analysis is limited mainly to cohort studies.

Introduction

Since the introduction of the proton pump inhibitors (PPIs), there have been a number of reports suggesting their association with one particular type of gastric polyp, the fundic gland polyp.

Gastric polyps are usually found incidentally at upper gastrointestinal tract endoscopy, since they are rarely symptomatic and so an indication for endoscopy. The true incidence of gastric polyps in the general population is not well known, and available data tend to come from endoscopy populations that are being investigated for other

upper gastrointestinal disorders or symptoms. Thus, there is selection bias in these populations. Taking all types of gastric polyp together, their prevalence has been variously reported as 0.5 to 14%.[1]

Polyps in the stomach are histopathologically heterogeneous, and include hyperplastic polyps, fundic gland polyps, gastric adenomas, gastric neuroendocrine tumours (carcinoids) and inflammatory fibroid polyps. Fundic gland polyps are one of the most common types, with an estimated incidence of approximately 2 to 11%,[2-4] though this varies across different populations. Fundic gland polyps are more prevalent in Western countries with lower rates of *H. pylori* infection and higher rates of PPI therapy.[5]

Fundic gland polyps are also a heterogeneous group. Most appear to be sporadic and patients usually have fewer than ten in their stomach, though over 50 polyps have been observed occasionally.[6, 7] By contrast, much larger numbers are found in two familial cancer syndromes: familial adenomatous polyposis (FAP), caused by germline mutations in the *APC* gene, and a variant of FAP, gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS).[7-10] These syndromes sometimes feature hundreds or thousands of polyps, forming a carpet across the entire surface epithelium.[6]

An association between fundic gland polyps and PPI use has been suggested for many years. The initial observation linking PPI use with fundic gland polyps was reported by Graham in 1992; three patients developed fundic gland polyps following a year of omeprazole treatment.[11] Since then, a number of case reports, retrospective and prospective studies have further explored this connection, with varying results.[1-3, 11-17] Thus, whether PPIs increase the prevalence of fundic gland polyps, and the magnitude of the effect if they do, remains contentious.

This study aims to evaluate the available data on the suggested association with PPIs through a systematic review and meta-analysis.

Materials and Methods

Search Strategy

A systematic search and retrieval of records was performed by FM, in accordance with the Meta-analysis of Observational Studies and Epidemiology group (MOOSE) guidelines.[18] Major medical databases were searched from the earliest available records from Medline (PubMed), Medline (Ovid), Embase, Scopus, the Cochrane Library and ClinicalTrials.gov until March 2016. Abstracts from major meetings in gastroenterology were searched manually and assessed for relevance. These included Digestive Disease Week (2010-2015), the Annual Scientific Meeting of the American College of Gastroenterology (2010-15) and the United European Gastroenterology Week (2013-2015). The key search terms used were 'fundic gland polyps' AND 'proton pump inhibitors', and the latter Mesh term was searched using the 'explode' function of the electronic databases, to capture each of the specific types of PPI. Other text terms used to expand the search were 'fundic gland polyposis' OR 'gastric polyps' OR 'gastric polyposis' AND 'proton pump inhibitors [explode]'. Finally, manual searching of the bibliographies of relevant studies was performed.

Selection Criteria

Initial inclusion criteria were all randomised control trials (RCTs), case-control studies, cohort studies, case series and case reports that investigated a possible association between fundic gland polyps and PPIs. This was narrowed down to case-control studies (fundic gland polyp patients matched with controls), cohort studies and RCTs with data on co-occurrence of fundic gland polyps and PPIs. To be included in the meta-analysis, studies were required to have a group of patients exposed to PPIs and a control group of non-exposed subjects, both of whom had an upper gastrointestinal endoscopy performed and presence of fundic gland polyps recorded. The primary outcome was the odds ratio (OR) for the association between fundic gland polyps and PPI use. Further analyses were performed restricted to studies where the length of PPI use before endoscopy was at least 6 months or at least 12 months. Some studies only had data for PPI users with no control group, and others had data on the prevalence of PPI use in patients with fundic gland polyps but not in controls. These data were pooled into the secondary outcomes, pooled frequencies of PPI use in patients with polyps, frequency of polyps in patients taking PPIs.

Exclusion criteria included studies in non-humans, review articles without original data, studies published in a language other than English for which no English translation was available, studies which reported other changes in mucosal pathology but not fundic

gland polyps, studies in which subjects were on 'acid suppression therapy', not specifically stipulated as PPIs, and studies in which it was not possible to extract outcome data from published results. For the meta-analysis, case reports and small case series were excluded, however in the secondary analysis, small case series were included.

One investigator (FM) independently assessed potentially relevant papers in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram.[19]

Data Extraction

Full text articles remaining at the end of the data selection process were reviewed by FM and NY to identify study characteristics, (including whether cohort, case-control or RCT), sample population number, number of patients with and without fundic gland polyps who were PPI users and non-users respectively. In some studies that reported solely on patients with fundic gland polyps, the proportion taking PPIs was extracted for calculating the pooled frequency of PPI use in patients with these polyps. In one study,[20] only the OR, proportion with polyps taking PPI, and total numbers taking and not taking PPIs were reported, so the OR formula was used to calculate the number of polyps in the control group. In another study[3] data for number of PPI subjects with fundic gland polyps was split into several different groups according to time on PPI and presented only in a graph, so the raw data were extracted from the published plots. There were no occasions in which contacting the authors for further data was required.

Quality Assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the studies with control groups included in the meta-analysis.[21] NOS is a simple quality assessment tool for nonrandomised studies which uses a 'star system' to judge the selection of study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case control or cohort studies respectively. For the purposes of this meta-analysis, studies with a score of seven stars or more were considered 'high quality'. Both investigators (FM and NY) independently completed the NOS assessment, and the inter-investigator agreement was 92% (Cohen's kappa = 0.89).

Statistical Analysis

Outcomes for the primary analyses were reported as OR for the risk of fundic gland polyps in PPI use, with 95% confidence intervals (CI). All data were entered into the software package MIX 2.0 Pro to produce the meta-analysis and Forest plots.[22]Pooled ORs were calculated using the random effects model, which accounts for variation in true effect sizes between studies, and gives a more conservative pooled estimate. To assess the variance between studies, heterogeneity funnel plots were produced and the parameters Q, I^2, and tau^2 (with respective P-value and 95% confidence intervals) calculated.[22] The likelihood of publication bias was assessed by visually inspecting symmetry of funnel plots and calculating the regression coefficients by the arcsin-Thompson method as recommended by Rücker et al and Jin et al for observational studies with moderate to high heterogeneity.[23, 24]

Ethics Approval

Ethics approval was not required for this study since the analysed data had been published previously.

Results

Studies Retrieved

The initial search using electronic databases and manual searching retrieved 339 peer-reviewed articles and abstracts. After removing duplicates, 164 records remained. Preliminary screening of titles and abstracts resulted in seventy-four remaining articles, and a further thirty-eight review articles, case reports and studies not meeting the inclusion and exclusion criteria were rejected upon detailed evaluation. Of the thirty-six remaining records, sixteen were excluded due to lack of sufficient relevant data. The remaining twenty contained data relating to the prevalence of fundic gland polyps in PPI users or PPI use in subjects with fundic gland polyps. Figure 1 is a detailed flow diagram of the selection process described.

Study Characteristics

A summary of the study characteristics is provided in Table 1. A total of 40,218 subjects from twenty studies were included. Nine were cohort studies,[1-3, 15, 17, 20, 25-27] two were case-control studies,[28, 29] one was a randomised control trial,[30] and the remaining eight were case series,[31-38]. Eleven were retrospective,[3, 15, 17, 28, 29, 33, 35-38] and nine were

prospective.[1, 2, 20, 25, 27, 30-32, 34] Twelve studies contained data for the proportion of fundic gland polyps in PPI users compared with non-PPI users; these were included in the primary meta-analysis.[1-3, 15, 17, 20, 25-30] Eight studies lacked a control group but were used to calculate the pooled frequency of fundic gland polyps in PPI users or PPI use in fundic gland polyp subjects.[31-38]

All studies identified the presence of fundic gland polyps through upper gastrointestinal endoscopy and confirmed the diagnosis with biopsy and histological analysis. PPI use was ascertained from hospital or community medical records,[15, 17, 25, 31, 35-38] questionnaires [27] with verified data from medical records,[2, 3] interviews,[1] telephone interviews,[29, 33] and in some studies was not stipulated.[20, 26, 28, 32, 34] Not all studies reported indications for endoscopy, but for those that did the most common were gastro-oesophageal reflux disease, dysphagia, epigastric pain, dyspepsia and anemia.[3, 15, 20, 28, 30, 31, 35, 36]

Demographic data including age, sex and *Helicobacter pylori* infection status were assessed but were unable to be pooled due to the heterogeneity of their presentation. In most studies, the average age ranged from approximately 50-65 (except for Pashankar & Israel, who studied only children).[36] In twelve studies, there were more females than males. [1, 2, 17, 25, 27-29, 31-33, 35, 37] While there was considerable heterogeneity in the percentage of subjects infected with *H. pylori*, there were fewer fundic gland polyp subjects infected with *H. pylori* than non-fundic gland polyp subjects.

Pooled Effect Sizes

Twelve studies provided data on the co-prevalence of fundic gland polyps and PPIs where ORs could be calculated. In eight studies, the number of PPI users and controls (non-PPI users) diagnosed with fundic gland polyps was reported,[2, 3, 15, 17, 25-27, 30] and in another three studies, the number of subjects with and without fundic gland polyps taking PPIs was stated.[1, 28, 29] For the latter, it was possible to deduce the number of PPI users and controls with fundic gland polyps from the available data. In the Kroupa study,[20] the percentage of fundic gland polyps associated with PPI use was reported with an OR, enabling the number of FGPs in non-PPI users to be extracted. ORs for the development of fundic gland polyps while taking PPIs ranged from 0.3 to 12.0, though most did not reach statistical significance. When all twelve studies were pooled, the OR of developing fundic gland polyps while on PPIs compared to controls was 2.46 (Figure 2A (95% CI 1.42-4.27, p = 0.001)). Many of the studies also provided data on the

prevalence of fundic gland polyps after being on PPIs for various time intervals. Those which had data on fundic gland polyp prevalence after PPI use of at least 6 months [1-3, 26, 27, 29, 30] and at least 12 months [1-3, 26, 29, 30] were pooled into separate meta-analyses, shown in Figures 2B and 2C. The ORs for developing fundic gland polyps increased with time of PPI exposure, with the OR for patients exposed 12 months or longer approximately twice that from all studies (P<0.001). A sensitivity analysis was performed by pooling only the six top scoring studies using the Newcastle-Ottawa Scale (seven stars or above, see Table 1).[2, 3, 15, 25, 28, 30] The OR for these studies was 2.41 (95% CI 1.15-5.03, p = 0.019), not significantly different from the OR of 2.46 calculated using all twelve studies.

Six studies contained data on the prevalence of PPI use in subjects with fundic gland polyps, but lacked control groups.[31-33, 35, 37, 38] When pooled with three studies above that also had control data the prevalence of PPI use in fundic gland polyp subjects was 46.9% (Supplemental Table 1A, 95% CI 23.3 – 71.3%).[1, 28, 29] Conversely, the prevalence of fundic gland polyps in PPI users was pooled across fourteen studies and was calculated to be 15.1% (Supplemental Table 1B, 95% CI 8.0-23.9%).[1-3, 15, 17, 20, 25-30, 34, 36]

Evaluation of Heterogeneity and Publication Bias

There was significant heterogeneity between the twelve studies (Q = 153.9, p < 0.001, I^2 = 92.9% [95% CI 89.4-95.2%], tau^2 = 0.76 [95% CI 0.49-1.15]). In only those studies that provided data for PPI exposure 12 months or longer, heterogeneity was still evident (Q = 59.5, p<0.001; I^2 = 88.5% CI 88.5-95.5); tau^2 = 0.84 (CI 0.42-1.61). A funnel plot representation is provided in Figure 3 for the twelve RCT, cohort and case control studies included in the primary meta-analysis.

Examination of selectivity funnel plots for possible publication bias showed data points lying reasonably symmetrically within the p = 0.1 and 0.05 boundaries (data not shown); and regression curves constructed by the arcsin-Thompson method did not demonstrate a significant slope either when all studies were included (R^2 = 0.02, p = 0.65) or in the six with data for PPI exposure of ≥12 months (R^2 = 0.14, p = 0.47). Thus there was no strong evidence for publication bias.

Discussion

In the present study, data pooled from twelve studies demonstrated that PPI users are more than twice as likely to develop fundic gland polyps as non-PPI users. As further evidence for the association, the increased risk was four and five fold respectively when the meta-analysis was confined to studies with confirmed PPI duration of at least six and twelve months. It had previously been observed that at least twelve months of PPI usage is required to develop polyps.[2, 13, 16, 27, 40, 41] Ally et al. and Jalving et al. demonstrated that the prevalence of fundic gland polyps continues to increase with time of PPI usage, having provided data on PPI use for at least five years.[2, 3] It is important to note that the largest study included in this meta-analysis, by Vieth and Stolte, which showed no significant difference in fundic gland polyp prevalence between PPI users and controls, neglected to stratify the fundic gland polyp prevalence data by length of PPI use, and only required their subjects to have had four weeks of exposure to be included.[17]

The authors have recently become aware of a meta-analysis on this topic by Tran-Duy et al that is currently in press.[42] It is reassuring to see that the magnitude of effect of PPIs on the risk of fundic gland polyps found by Tran-Duy et al. (OR 2.45) was very similar to the results of the present meta-analysis with all studies included irrespective of PPI dose (OR 2.46). Tran-Duy et al. also showed a trend to a dose-response effect, although the duration of PPI use was stratified differently and the dose-response relationship they were able to demonstrate was less marked than in the present meta-analysis. Significantly, Tran-Duy et al. pooled seven observational studies and one RCT for their meta-analysis, while the present meta-analysis included a total of twelve studies. These extra studies contributed 31.9% of the total random effects weight in the present meta-analysis. Furthermore, the single RCT included by Tran-Duy et al. did not specify the type of gastric polyps.[43] The present study did include one RCT, by Fiocca et al.,[30] which specifically identified fundic gland polyps. For these reasons, the authors believe that the present meta-analysis makes a significant further contribution to this clinical question

Several measures of heterogeneity, including the Q statistic, tau^2 and I^2, were calculated for the different analyses performed in this study, and a high degree of heterogeneity was found between the twelve studies. There are several possible explanations for this.

Firstly, as discussed above, there was considerable difference in duration of PPI exposure reported by the various studies, and this is likely to be a major reason for the variance. The studies also varied in terms of the sample populations (different ethnicities, ages, proportions of males and females), reported prevalence of *Helicobacter pylori*, and the reasons for gastroscopy and thus inclusion in the study. There were methodological differences amongst studies; some were retrospective, others were prospective. One study in particular, by Fiocca et al.,[30] allocated a group to PPI treatment and another to a surgical treatment for gastroesophageal reflux disease, thus, this was a very different study design compared to the rest.

This meta-analysis is limited by the quality of the selected studies. Other than the RCT by Fiocca et al.,[30] all the studies pooled in this meta-analysis were cohort studies and case series, the majority of which were retrospective. All of the twelve studies were assessed for quality using the Newcastle-Ottawa Scale. Only six of the studies were awarded seven or more stars, thus regarded as high quality. However, when a meta-analysis was performed using just the data collected from these high-scoring studies, the calculated effect size was comparable to when all studies were included. Unlike Tran-Duy's report of a smaller number of pooled studies,[42] we did not demonstrate significant publication bias, as assessed by the arcsin-Thompson regression method. However testing for publication bias has low power when the number of studies in a meta-analysis is small.[44]

Some intrinsic limitations of individual studies were the reliability with which PPI usage was ascertained, the inability to confirm that subjects did not already have fundic gland polyps before PPI therapy was begun, the lack of comparability between cohorts for demographic factors such as age and sex, differences in *Helicobacter pylori* infection rate between cohorts and studies, and allowing sufficient follow-up time for fundic gland polyp development.

The mechanism by which PPIs may increase the prevalence of fundic gland polyps is uncertain. One suggestion is that fundic gland cysts are predisposed to by mucus-blocking of the fundic pits, as a result of the reduced flow of glandular secretions.[45] Fundic gland cysts have also been linked to PPI usage.[45] Synnerstad and Holm had demonstrated raised intraglandular pressure in rats treated with high doses of omeprazole.[46] It has been proposed that *H. pylori* infection has an inhibitory effect on fundic gland polyp development, and Cats et al. suggest that *H. pylori* protease degrades

the gastric mucus, thus facilitating glandular outflow and protecting against the retention and cystic dilation which results in fundic gland polyp development.[45] Fundic gland polyps have been observed to regress following acquisition of the bacterium.[2, 3, 17, 47]

In this meta-analysis, all the included studies reported lower rates of *H. pylori* infection in subjects with fundic gland polyps compared to controls, although some of them do report at least a small percentage of *H. pylori*–positive patients. One confounder may be that since infected patients are less likely to have reflux oesophagitis they are less likely to be treated with PPIs, though the difference in oesophagitis prevalence between H. pylori positive and negative patients (about 10%) is much smaller than the difference in polyp prevalence.[48]

This meta-analysis strongly suggests association between PPI use and fundic gland polyps, but does this amount to causation? Applying Bradford-Hill's classic criteria for causation in epidemiological studies supports the likelihood the association is causal: it has *strength* (the OR for studies with PPI duration ≥12 months is high); there is a *biological gradient* (increasing OR with increasing duration of PPI exposure); there is *consistency,* since most studies show at least a trend to a positive association; and the relationship is *plausible*, with the mechanism postulated above for glandular changes resulting from reduced glandular flow.[49] There have been reports of regression of fundic gland polyps following the cessation of PPI therapy.[50-53] One such case study comes from Kim et al. (2008); a patient with multiple fundic gland polyps that developed after commencing omeprazole demonstrated spontaneous resolution after its cessation.[53] This strengthens the suggestion of causality through the *biological gradient* criterion.

In recent years, concerns have been raised about other potential side effects of PPIs, including an increased risk of fractures,[54, 55] enteric infection,[56] vitamin B12 deficiency,[57] and community acquired pneumonia.[58,59] These reports come from epidemiological studies, where the associations may be confounded by factors such as obesity, smoking status, age, sex, gastroesophageal reflux disease and others.

Does the increased prevalence of fundic gland polyps in patients taking PPIs pose a significant hazard? Dysplastic changes in fundic gland polyps are estimated to occur in 1% of sporadic fundic gland polyps and 25% of FAP fundic gland polyps.[6] Gastric cancer risk in FAP is estimated to be 0.6%,[6] and some proportion of this may be attributable to fundic gland polyps. The occurrence of dysplastic fundic gland polyps or gastric

adenocarcinoma is part of the diagnostic criteria for GAPPS, but the risk of gastric cancer is unclear in these families.[7] Somatic mutations in the *E-cadherin* gene occur in 90% of sporadic fundic gland polyps, but not in the FAP or GAPPS-associated polyps, in which the pathway is disrupted by *APC* mutations.[7] Current evidence suggests that PPI-induced fundic gland polyps have no malignant potential,[2, 3] and there has been only a single case report of apparent high grade dysplasia in a non-syndromic case of the polyps.[60]

Conclusion

While this meta-analysis is limited by the quality of the pooled studies, it nevertheless provides strong evidence for an association between PPI usage and development of fundic gland polyps that is likely to be causal. In particular, increased duration of PPI use of at least six or at least twelve months is more closely linked to a higher risk of fundic gland polyp development. Although the evidence indicates that these polyps (as opposed to those in FAP or GAPPS syndromes) are a benign phenomenon, ongoing surveillance with respect to this question seems worthwhile.

List of Abbreviations

PPI – proton pump inhibitor

OR – odds ratio

RR – relative risk

CI – confidence interval

RCT – randomised control trial

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Felicity Martin (guarantor) takes responsibility for the integrity of this work as a whole, from inception to published article. All three authors contributed to the study and the manuscript, and have agreed on its content. FM performed the majority of data collection, extraction of poolable data and analysis and writing of the manuscript, NY contributed to study selection, extraction of poolable data, statistical analysis and writing, and GC-T was involved in the overall study planning and writing. All authors approved the final version of the manuscript.

Statement of Interests

The authors declare that they have no conflicts of interest (personal or financial).

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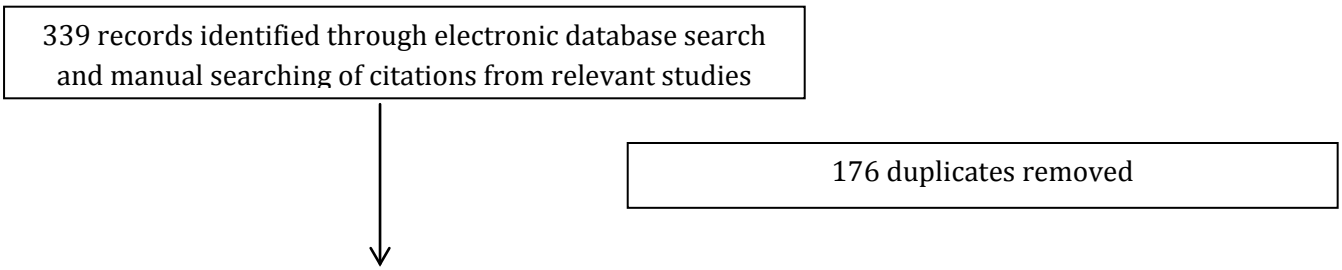
Legends for Figures

Figure 1. PRISMA 2009 Flow Diagram of selection process

Figure 2. Forest plots showing the OR for fundic gland polyp prevalence in PPI users compared to controls for any time period (2A), for at least 6 months (2B) and at least twelve months (2C), using a random-effects model and depicted on a logarithmic scale. The area of each box is proportional to the weighting of each study in the meta-analysis. The lateral points of the diamond provide the CI for the combined estimate.

Figure 3. Heterogeneity funnel plot for any PPI use. Effect size [$\log_e$(OR)] is measured on the x-axis, and within-study variance on the y-axis. Each study is represented by a single equally sized circle. Pseudo-confidence intervals are integrated into the plot.

Figure 1.



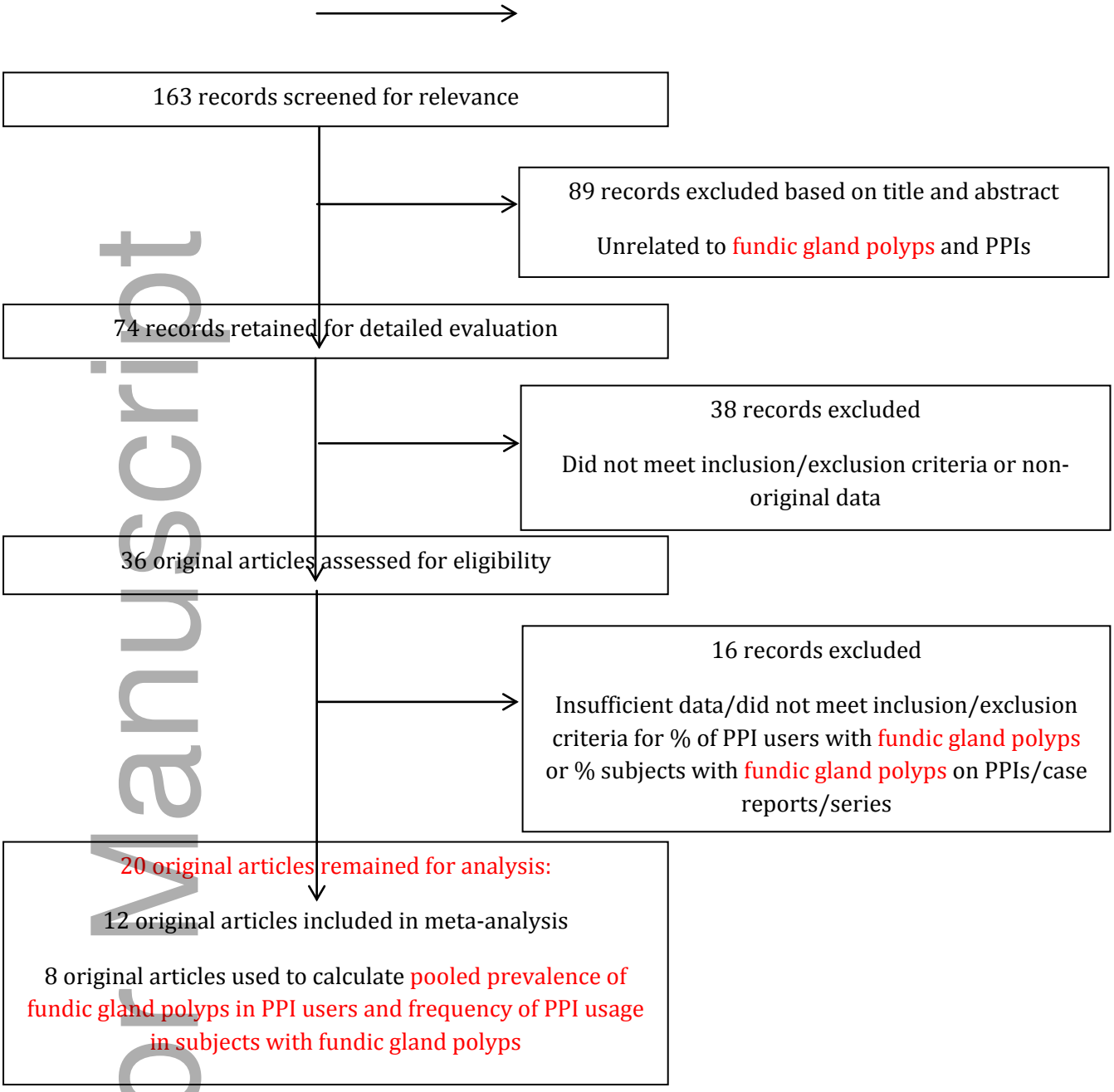


Figure 2.

Figure 2A, any PPI use

Author (year)	Sample size	Weight %	Measure (CI)
Choudhry (1998)	2303	7.81%	11.96 (4.41; 32.42)
Vieth (2001)	30347	10.35%	1.02 (0.84; 1.24)
Jalving (2006)	599	9.8%	2.32 (1.48; 3.65)
Ally (2009)	385	8.81%	1.85 (0.88; 3.89)
Hsu (2010)	259	9.6%	2.52 (1.51; 4.22)
Yoshida (2010)	1573	9.93%	1.11 (0.74; 1.66)
Zelter (2011)	1775	9.7%	9.51 (5.87; 15.4)
Fiocca (2012)	554	2.5%	5.45 (0.26; 114.12)
Cao (2014)	984	10.06%	0.75 (0.53; 1.07)
Huang (2014)	348	9.72%	6.74 (4.18; 10.86)
Kroupa (2014)	439	8.89%	2.6 (1.26; 5.34)
Camilo (2015)	105	2.82%	0.29 (0.02; 4.78)
Synthesis	**39671**	**100%**	**2.46 (1.42; 4.27)**

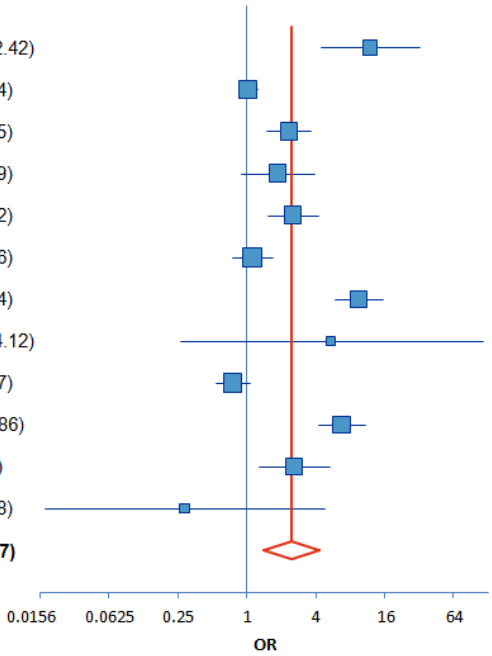
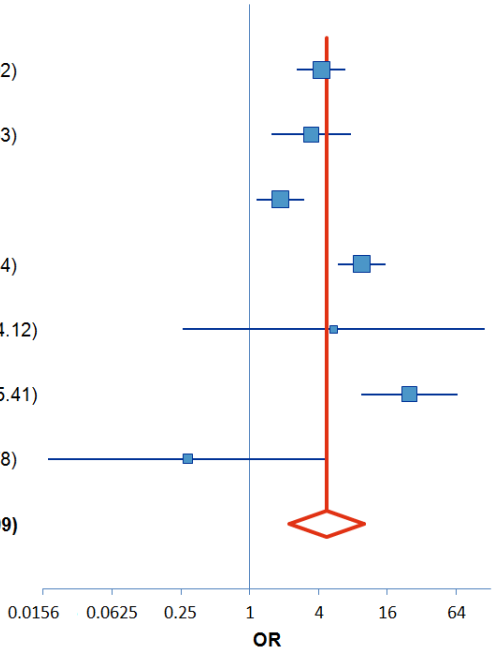


Figure 2B, ≥6 months PPI use

Author (year)	Sample size	Weight %	Measure (CI)
Jalving (2006)	437	19.13%	4.24 (2.59; 6.92)
Ally (2009)	238	16.91%	3.45 (1.56; 7.63)
Yoshida (2010)	1401	19.22%	1.86 (1.16; 3)
Zelter (2011)	1775	19.18%	9.51 (5.87; 15.4)
Fiocca (2012)	554	4.73%	5.45 (0.26; 114.12)
Huang (2014)	259	15.5%	24.91 (9.49; 65.41)
Camilo (2015)	105	5.33%	0.29 (0.02; 4.78)
Synthesis	**4769**	**100%**	**4.71 (2.22; 9.99)**



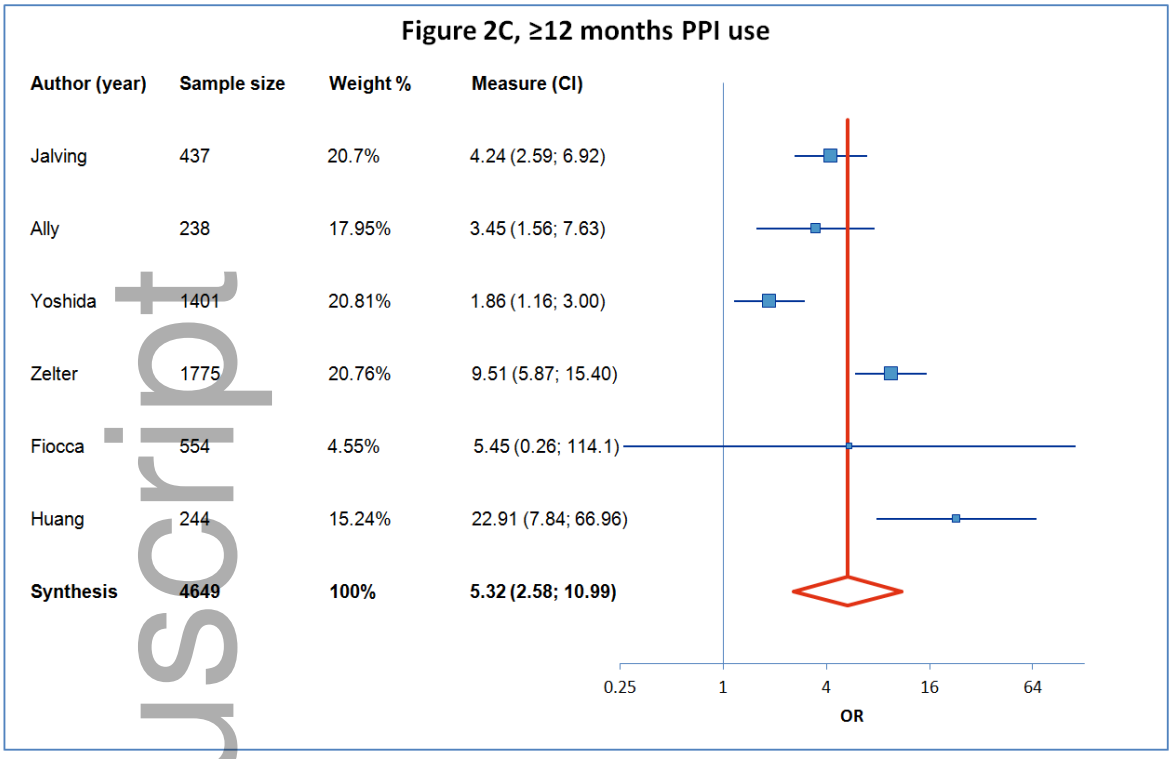


Figure 3.

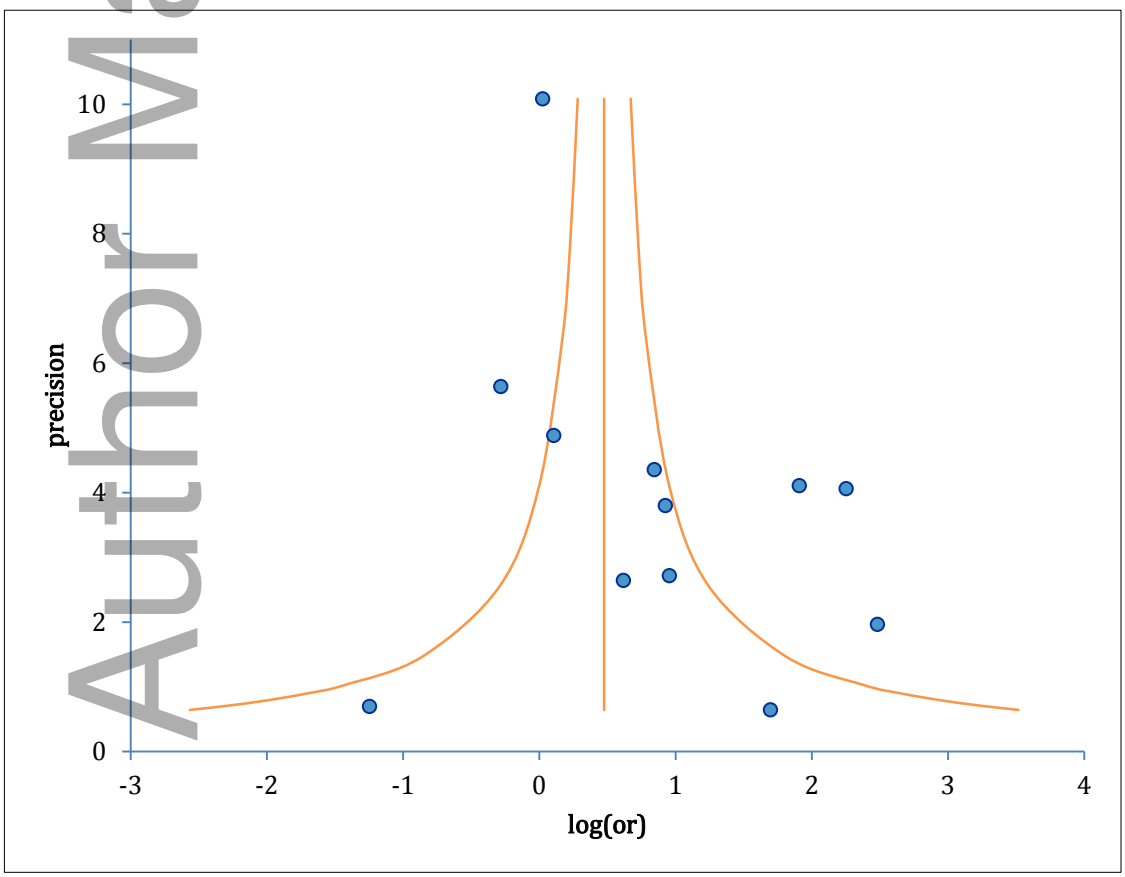


Table 1: Summary of study characteristics and quality regarding the association between PPIs and FGPs

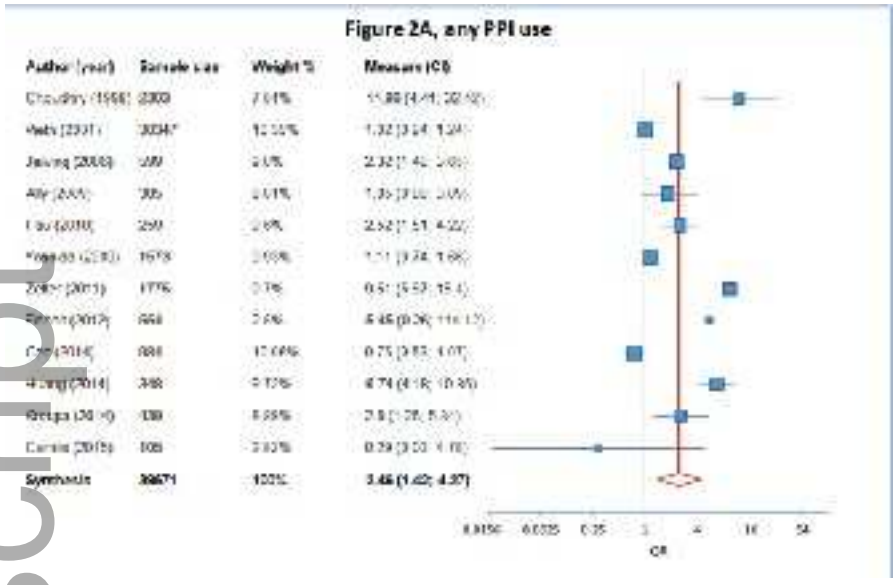
Authors	Year	Study Design[1]	N	Patients on PPIs		Patients not on PPIs		Duration of PPI use	Study Quality (Newcastle-Ottawa Scale)[2]
				FGPs	No FGPs	FGPs	No FGPs		
Dickey et al.	1996	Case series (P)	10	1	-	9	-	14 months	
Choudhry et al.	1998	Cohort study (R)	2,303	9	222	7	2065	*M* = 37.4 months [3-98 months]	7
Vieth & Stolte	2001	Cohort study (R)	30,347	116	2,135	1415	26,681	≥4 weeks	6
Declich et al.[3]	2005	Case series (P)	24	0	24	-	-	12 months	
Declich et al.[3]	2005	Case series (P)	63	1	-	62	-	12 months	
Pashankar & Israel	2002	Case series (R)	31	1	30	-	-	≥6 months	
Torbenson et al.	2002	Case series (R)	8	5	-	3	-	Available in 2 cases: 1 year and 7 years	
Jalving et al.	2006	Cohort study (P)	599	75	247	32	245	2 groups: <1 year or >1 year	7
Ally et al.	2009	Cohort study (R)	385	33	219	10	123	5 groups: <12 months, 13-24 months, 25-48 months, 49-60 months, >6 months	7

Samarasam et al.	2009	Case series (R)	109	69	-	40	-	>12 months	
Hongo & Fujimoto	2010	Case series (P)	191	26	165	-	-	104 weeks	
Hsu et al.	2010	Cohort study (P)	259	60	62	38	99	*M* = 21.89 months [1-97 months]	7
Yoshida et al.	2010	Cohort study (R)	1573	34	280	124	1,135	3 groups: <1 year, 1-3 years, ≥ 3 years	5
Garcia-Alonso et al.	2011	Case series (R)	19	11	-	8	-	>3 months	
Zelter et al.	2011	Cohort study (P)	1775	49	264	28	1,434	≥12 months	6
Fiocca et al.	2012	Randomised Control Trial	554	2	264	0	288	12 months	8
Cao et al.	2014	Case-control (R)	984	54	136	274	520	3 groups: 1-6 months, 6-12 months, >12 months	8
Huang et al.	2014	Case control (R)	348	109	38	60	141	<3months, 4-6months, 7-12months, >12months	5
Kroupa et al.	2014	Cohort study (P)	439	29	201	11	198	7 years	5
Camilo et al.	2015	Cohort study (P)	105	1	80	1	23	≥6 months	5.5
Levy &	2015	Case series (R)	92	49	-	13	-	Unknown	

[1] P = prospective, R = retrospective

[2] Rated only for those with control groups; number indicates number of stars awarded to study with a maximum of 9 stars possible

[3] Separated for the purposes of this table as two difference cohorts were described in the study



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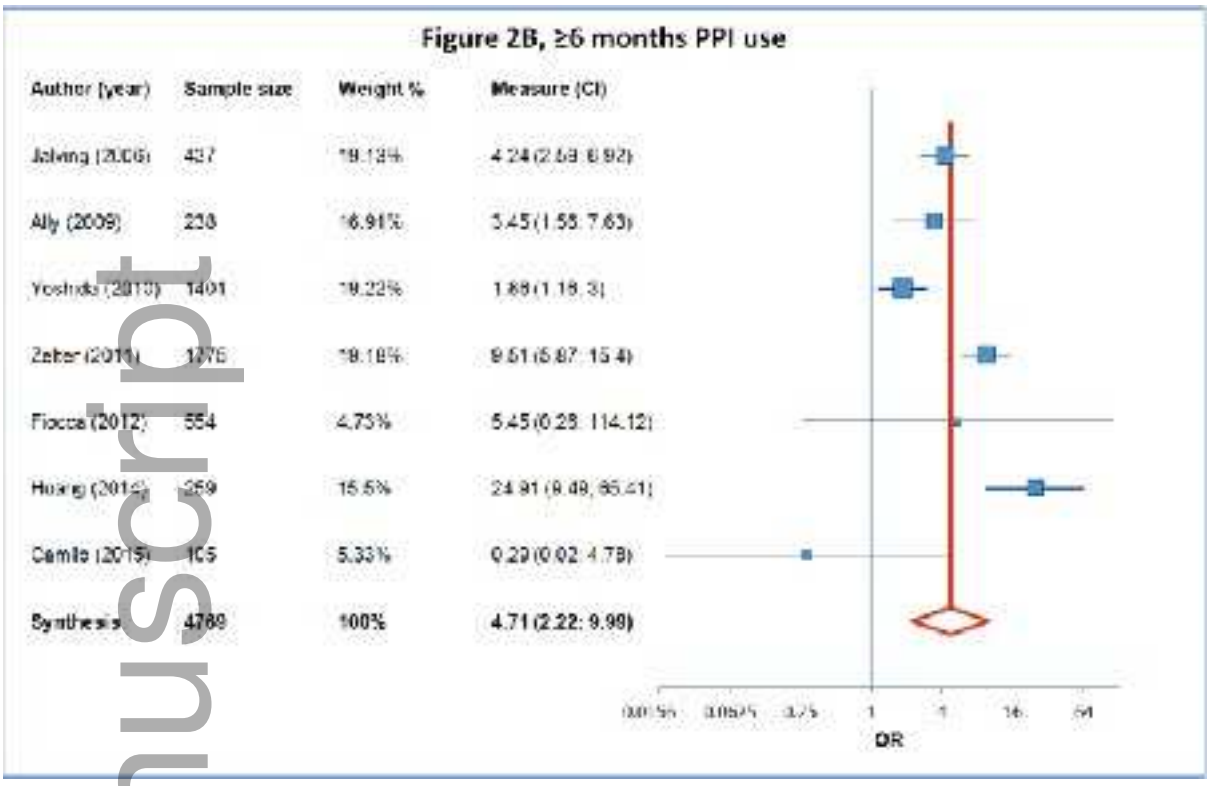

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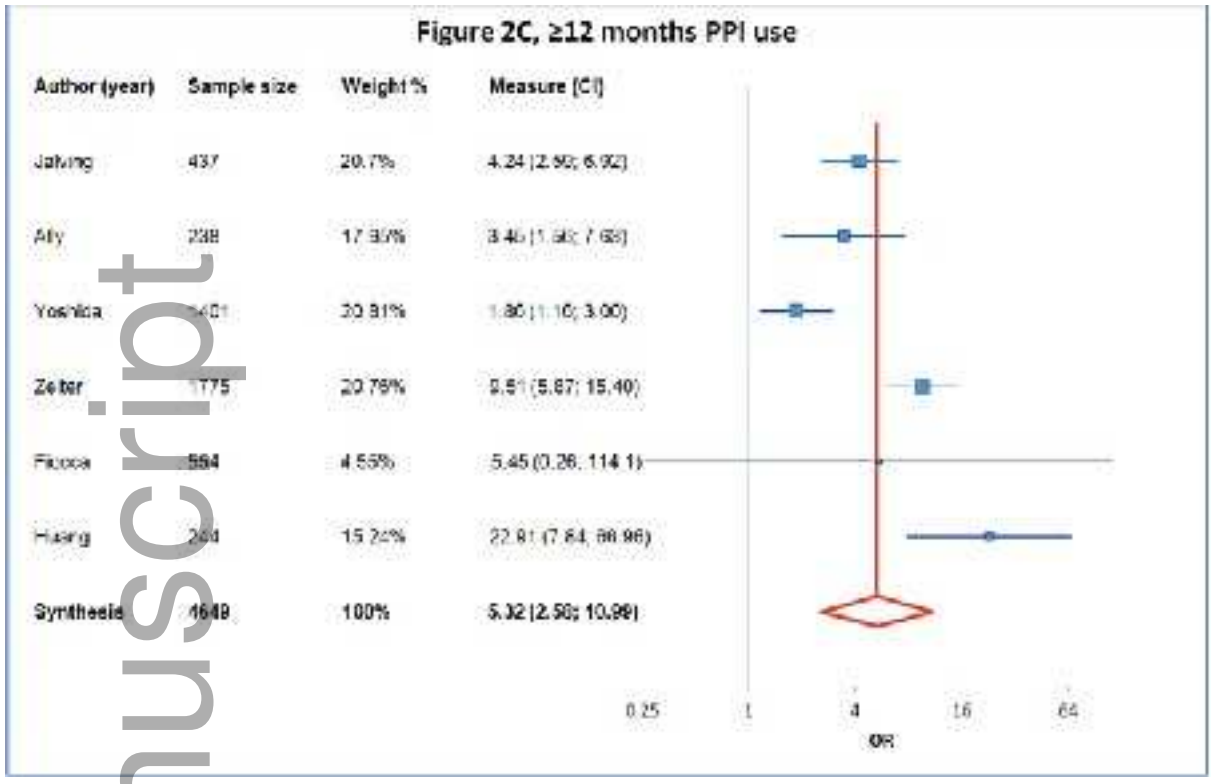

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