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Research Article

Long-Term Proton Pump Inhibitors (PPI) Therapy and Risk for Community-Acquired Pneumonia (CAP): A Systematic Review and Meta-Analysis.

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Abstract

Background: *Recent studies have suggested that the use of proton-pump inhibitors (PPIs) may increase the risk for community-acquired pneumonia (CAP).*

Objective: *This review aims to examine the effect of PPI therapy on CAP risk, with a special look at long- term PPI use.*

Methods: *A systematic literature search was conducted for articles published up to 1st October 2023. The databases used were PubMed, Scopus, ScienceDirect, and Google Scholar. STATA software version 15 was used for statistical analysis using a common-effect inverse-variance model and a p-value of .05 as the significance threshold.*

Results: *The initial search identified 760 articles. After a study selection process, 15 studies were included in the review and 9 studies in the meta-analysis. This paper included 108, 176 CAP cases and 1,248,785 healthy controls. The adjusted effect sizes for current PPI use across included studies ranged from 1.02 to 3.3, with most of them between 1.02 and 1.5. The meta-analysis performed in this review also found an increased risk for CAP among current PPI users, with an adjusted odds ratio (AOR) of 1.13 (95% CI, 1.09 - 1.18, I2 = 88.8%, p<0.001). These results show that PPI use increases the risk of CAP incidence. Additionally, study findings showed a general trend where the risk of community- acquired pneumonia decreased with increasing duration of PPI use. Short-duration PPI use (<1 year) had higher odds for CAP risk compared to long-term PPI use (>1 year).*

Conclusion: *Proton-pump inhibitor therapy is associated with an increased risk for CAP. The strength of this association is also found to decrease with increasing duration of PPI use. This means that long- term use of PPI is associated with a relatively lower risk of CAP.*

Keywords: *Long-term, Proton Pump Inhibitors (PPI), Community Acquired Pneumonia (CAP), Adverse effects.*

Introduction

Proton pump inhibitors (PPIs) were first used in clinical practice in 1988 and have since been the standard for management of a variety of acid-related gastrointestinal illnesses, including gastro-esophageal reflux disease (GERD), [1, 2, 3] peptic ulcers [4, 5] and non-ulcer dyspepsia. [6, 7] This wide application is due to an accepted safety profile, since they are generally well tolerated by patients, and serious side effects are rarely reported. However, a growing number of publications have linked long-term use of PPIs to adverse effects such as hip fractures, [8] clostridium difficile infection, [9, 10, 11] drug-drug interactions, e.g. clopidogrel [12, 13] and community-acquired respiratory tract infection. [14, 15, 16, 17]

Community-acquired respiratory tract infections are among the most prevalent infectious ailments globally, and they significantly contribute to both mortality and morbidity. A study conducted in the United States in 2008 revealed that, when adjusted for age, the mortality rate attributable to influenza and pneumonia was 20.3 per 100,000 individuals. [18] As of November 2022, the annual incidence of CAP in the United States was 24.8 cases per 10,000 adults with higher rates as age increased. [19] According to Niederman et al. [20] the global mortality for hospitalized CAP averages 12% across regions, but increases in specific populations such as those with bactermia and those from nursing homes. In Regunath and Oba, [19] the mortality rate for those admitted to the intensive care unit due to CAP was as high as 23%. Additionally, Womack and Kropa [21] reported a 30-day mortality for 6% of those hospitalized with CAP.

The pathogens causing CAP are classified as either typical agents such as Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, or as atypical agents such as Legionella, Mycoplasma, Chlamydia pneumoniae, and Chlamydia psittaci. [19] When using sputum culture for CAP etiological diagnosis, the predominant pathogen detected was Streptococcus pneumoniae or pneumococcus, accounting for 9-20% of all CAP cases. [22, 23] Conversely, in cases where serological testing is conducted, Mycoplasma pneumoniae emerges as the most prevalent organism, contributing to 13-37% of the total CAP cases. [22, 23, 24] Additionally, Chlamydia pneumoniae has been reported in about 17% of outpatients diagnosed with CAP. [24] Legionella spp. have also been observed, with rates ranging from 0.7% to 13% across various patient cohorts. [25]

The reported risk factors for the occurrence of CAP are age > 60 years with alcoholism, asthma, heart and lung diseases, immunosuppressive therapy, smoking, low body mass index (BMI), diabetics and history of respiratory infection and pneumonia. [26, 27, 28, 29] Recently, several studies have reported an observed correlation between the use of acid-suppressing medications like PPIs and an increased risk for community-

acquired pneumonia (CAP). The exact mechanism by which acid-suppressive medications increase the susceptibility to community-acquired pneumonia (CAP) remains to be fully explained. However, it is postulated that changes in gastric pH, resulting from these medications, cause modifications in the normal microbiota of the gastrointestinal tract and oropharyngeal regions. This potentially leads to diminished pathogen elimination or enhanced pathogen colonization. [29] Specifically, the escalation of gastric pH induced by acid-suppressive agents stimulates the proliferation of microorganisms within the oral and oropharyngeal cavities. [30, 31] Given that gastric acid plays a pivotal role in protecting against infections, the mitigation of its acidic environment presents a plausible mechanism to account for the heightened risk of CAP associated with proton pump inhibitors (PPIs). [32, 33]

This systematic review aims to examine the risk for community-acquired pneumonia caused by PPI use, with a special look at the long-term use of PPIs.

Methods

This systematic review is reported following guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. [34]

Information Sources and Study Selection

A systematic literature search was conducted for articles published up to 1st October 2023. The index databases used were PubMed, Scopus, ScienceDirect, and Google Scholar. Topic keywords were used to generate search strings. The identified studies were then subjected to a study selection process.

Table 1: Search strings

Databases	Search strings
PubMed/ Scopus/ Google Scholar	(“proton pump inhibitor” OR PPI OR “acid-suppressive” OR “acid suppressant” OR “gastric acid inhibitor” OR “gastric acid suppressor”) AND (“community-acquired pneumonia” OR CAP OR “community pneumonia” OR “outpatient pneumonia”)
ScienceDirect	(“proton pump inhibitor” OR PPI OR “acid-suppressive” OR “acid suppressant” OR “gastric acid inhibitor”) AND (“community-acquired pneumonia” OR CAP OR “community pneumonia” OR “outpatient pneumonia”)

The search string for ScienceDirect was shorted because the database only accepts search strings with a maximum of 8 Boolean operators. The search in ScienceDirect was limited to the Title, abstract, and keywords, to limit the number of irrelevant studies during searching.

Inclusion and exclusion criteria

For articles to be considered eligible for inclusion, they had to be original research articles and written in the English language. The study population had to be >18 years of age. This review included both observational studies that evaluated PPI use and CAP incidence in human subjects.

Exclusion criteria were non-original research articles like systematic reviews, meta-analyses, editorials, article comments, and literature reviews. Case reports were also excluded. Studies with patients <18 years old, critically ill patients, or Helicobacter pylori treatment were excluded.

Review of methodological quality

The case-control studies were appraised using the Joanna Briggs Institute (JBI) critical appraisal checklist for case-control studies. Both cohort and longitudinal studies were appraised using the JBI critical appraisal checklist for cohort studies, due to their methodologic similarity. [35]

Data Extraction

Each article included in the review was summarized in a table for study characteristics. The extracted attributes include the author's name, publication year, study design, study region (country), number of participants, age, sex, study duration, and the factors confounded during the calculation of the effect size. There was also a separate table where the reported effect sizes were summarized according to the duration of PPI use.

Statistical Analysis

The statistical analysis was done using the STATA software where the reported effect sizes across studies were pooled to give an overall effect size estimate. This approach was borrowed from Lambert et al. [33]

The analysis used the common-effect inverse-variance model. The I2 statistic was used to determine heterogeneity and a p-value<0.05 was held as the significance threshold.

Results

Search Results

The initial search identified 760 articles from databases. 479 articles from Scopus, 56 from ScienceDirect, 125 from PubMed, and 100 from Google Scholar. 26 duplicates were removed. During the title and abstract screening, 698 articles were excluded following the eligibility criteria, and the remaining 36 articles were subjected to a full-text review. 21 of these articles were excluded because they did not fully satisfy the inclusion criteria. 15 final studies were included in the systematic review and 9 in the meta-analysis. The reasons for exclusion are shown in Figure 1. PRISMA flowchart was produced using PRISMA 2020-compliant flow diagrams. [36]

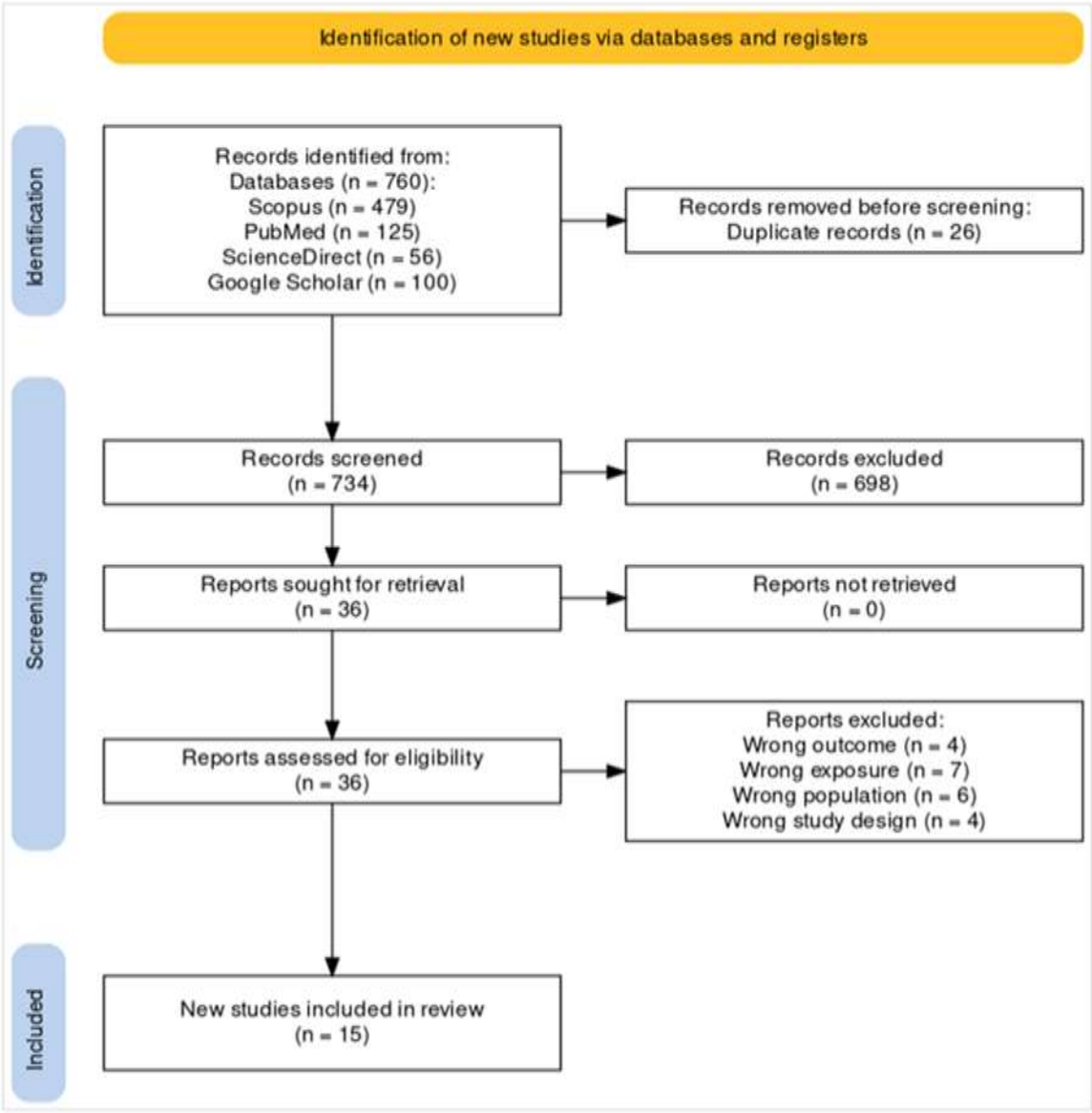

Figure 1: PRISMA flowchart showing the study selection process

Results of quality appraisal

3 case-control studies scored 'fair' and 7 scored 'good' on overall quality. This is shown in Table 5 in the appendix. 2 of the cohort studies scored 'fair' and 2 scored 'good' on overall quality. The longitudinal study scored 'good' on overall quality. This is shown in Table 6 in the appendix.

Results of data extraction

Table 2: Study Descriptor table

Study	Study design	Study Region	Number of participants	Participants' age andsex proportion	Study duration	Adjustments for OR calculation
Myles et al. [16]	CCS	United Kingdom	3709 cases and 22 174 controls	Age > 40 years, 46% Male	2001-2002	Ischemic heart disease, smoking status
Dublin etal. [37]	CCS	UnitedStates	1125 cases and 2235 controls	Median age was 77 yrs, IQR was 71–82yrs, Age range was 65–94 yrs, 50.8% Male	2000–2003	Age, asthma, smoking status
Evers et al. [38]	CCS	Denmark	618 cases and 3082 controls	46% Male	1996-2017	Antibiotic use, immunosuppressive medication
García Rodríguezet al. [39]	CCS	United Kingdom	7297 cases and 9993 controls	Aged 20–79 yrs, 52% Male	2000-2005	Age, sex, smoking, presence of peptic ulcer, use of oral steroids
Gau et al. [40]	CCS	UnitedStates	194 cases and 952 controls	Aged ≥ 65 yrs, Meanage of 80 yrs, 34% Males	2004-2006	Age, sex, smoking status, history of CHF,COPD, use of antibiotics, NSAID
Gulmez[41]	CCS	Denmark	7,642 cases and 34,176 controls	52.8% Men	2000-2004	Age, sex, NSAID, COPD
Hermos etal. [42]	CCS	UnitedStates	1,544 cases and 15,440 controls	Mean age of 65.8 ±12.2 yrs, 97% Male	1998-2007	Age, sex, COPD
Laheij [43]	CCS	Netherlands	5551 cases and 359,132 controls	NR	1995-2002	Age, sex, any ongoing therapy, COPD, use of antibiotics
Meijvis etal. [44]	CCS	Netherlands	430 cases and 1720 controls	Mean age was 62±18 yrs, 59% Male	2004-2006, 2007-2010	Use of NSAID, antidiabetics, COPD, asthma
Sarkar et al. [45]	CCS	United Kingdom	80,066 case and 799 881 controls	Aged ≥18 yrs, 50% Men	1987-2002	Smoking status, COPD, CHF, alcoholism
Filion et al. [46]	CS	Canada,UK, & USA	96,870 exposed (PPI users) and 4,141,634 unexposed	Aged > 40 yrs	1997-2010	Age, sex, asthma, COPD
Rougheadet al. [47]	CS	Australia	185533 PPI users	Aged ≥ 65 yrs, Meanage of 79.4±5.2 yrs,58% Men	2002-2006	Age, sex, number of occupational therapy visits
Othman etal. [48]	CS-SCCS	United Kingdom	160 000 PPI users and 160 000 non-PPIusers	Aged ≥18 yrs, mean age of 56±16 yrs , 45% Men	1990-2013	Smoking status, alcohol use, immunosuppression
Ramsay etal. [49]	CS-SCCS	Australia	105467 PPI users	Aged ≥ 65 yrs, Median age of 83yrs (IQR, 80–86), 51.5% Male	2007-2011	Age, sex, number of occupational therapy visits
Zirk-Sadowskiet al. [50]	LS	United Kingdom	75050 exposed (PPI users) and 75050 non-exposed	Aged ≥ 60 yrs, mean age of 71±7.3 yrs, 42% Men	NR	Age, sex, number of hospital visits, number of hospitalizations

yrs=years, CCS-case-control studies, CS-cohort study, SCCS-self-controlled case series, LS- longitudinal study, COPD- chronic obstructive pulmonary disease, CHF- congestive heart failure, NSAID- Non - steroidal anti-inflammatory drugs, CHF-congestive heart failure; All the case-control studies were nested; The cases in the CCS meant they were diagnosed with community-acquired pneumonia (CAP).

Characteristics of included studies: A summary

This paper included 15 studies, 10 nested case-control studies, 4 cohort studies, with 2 of them including self-controlled case series, and 1 longitudinal study. The mean age of inclusion across the studies varied, with most of them including participants aged ≥ 60 years.

In the review, as seen in Table 2, only the case-control studies reported participants as CAP cases versus healthy controls. In total, this review included 108, 176 cases and 1,248,785 healthy controls in the case-controlled studies. The participants in the cohort and longitudinal studies were reported as PPI-exposed versus non-exposed controls. In regard to this, this review included 622,920 PPI-exposed participants and 4,376,684 non-exposed controls, among the cohort and longitudinal studies.

Results of included studies: A summary

From nested case-control studies

In Dublin et al., [37] the prevalence of PPI use was 12% for CAP cases and 7% for controls. Analysis showed that the odds of CAP incidence was OR=1.13 (95%CI 0.88-1.44) for current PPI use compared to non-users. In Evers et al., [38] the AOR was 2.21 (95% CI, 1.66–2.94) for CAP in current PPI users compared with non-users. García Rodríguez et al., [39] used a relative risk analysis and reported CAP risk of RR (Relative risk) = 1.16 (95% CI, 1.03–1.31) for current PPI users. The adjusted odds ratio (AOR) of PPI use for CAP was 1.18 [95% CI = 0.80 - 1.74] in Gau et al. [40] Gulmez [41] reported an AOR of 1.5 (95% CI, 1.3-1.7), associating the current use of PPIs with CAP. In Hermos et al.,[42] current PPI use was associated with CAP with an AOR = 1.29 (95%, 1.15–1.45). In Laheij [43] the adjusted relative risk for CAP among current PPI users was ARR= 1.89 (95% CI, 1.36-2.62) compared to past users (people who had used PPIs before the study period and stopped during the study period). From the analysis in this study, the adjusted attributable risk percentage for PPI use was 42%. This means that PPI use was responsible for 42% of CAP cases or 1.05 CAP per 100 person-years. Considering that the study period was 0.42 years, this meant that 1 case of pneumonia per 226 patients (exposed and unexposed) was attributable to PPIs. Current PPI use in Meijvis et al., [44] was associated with

an AOR=1.6 (95% CI 1.2–2.2) for CAP incidence. Myles et al., [16] associated current PPI use with an increased risk of pneumonia (adjusted OR=1.55, 95% CI 1.38–1.77). Sarkar et al., [45] was the only case-control study that found no association between current PPI use and CAP incidence. The AOR for CAP incidence was 1.02 (95% CI, 0.97 to 1.08).

From cohort studies

Using a cohort study design, Filion et al. [46] and Roughead et al. [47] had their participants either as PPI-exposed or PPI-non-exposed. The risk for hospitalized CAP in Filion et al. [46] was AOR=1.05 (95% CI, 0.89 to 1.25). Roughead et al. [47] found that there was an increased risk of hospitalization for CAP for those exposed to PPIs compared with the unexposed group. The reported Rate Ratio (RR) was 1.16 (95% CI, 1.11–1.22).

From cohort studies including a self-controlled case series analysis

Othman et al. [48] and Ramsay et al. [49] used the same study methodology. Participants were analyzed using a cohort study design and a self-controlled case series design. When using the cohort study design, the incidence of CAP among the PPI users was compared to non-PPI users. When using the self-controlled case series, only the group of PPI users was used to perform analysis. The analysis would compare the incidence rate of CAP during the exposure period to the incidence rate during the baseline period (no-PPI use).

By using a cohort study design, the adjusted Cox regression in Othman et al. [48] showed an increased risk of CAP at Hazard Ratio (HR) =1.67 (95% CI, 1.55 to 1.79) for PPI users compared to non-users. Ramsay et al. [49] also showed an increased risk for CAP hospitalization due to PPI use, with the highest risk seen during the first 7 days of treatment. The Adjusted rate ratio (ARR) for CAP in 0-7 days of PPI use was 3.24 (95%CI, 2.50 – 4.19).

The self-controlled case-series analysis by Ramsay et al., [49] showed that the risk for CAP in the first 7 days of PPI therapy was Adjusted rate ratio (ARR) = 3.07 (95%CI, 2.69 – 3.50). From prior event rate ratio analysis by Othman et al., [48] the rate of pneumonia for the exposed patients was similar before a PPI prescription (62.1 per 1000 person-year) to the rate after a PPI prescription (61.4 per 1000 person-year). This would translate to an incidence rate ratio of 1.19 (95 CI, 1.14 to 1.25) in the 30 days after a PPI prescription, with a higher rate ratio of 1.92 (95 CI, 1.84 to 2.00) for the 30 days before a PPI prescription.

From a longitudinal study

Zirk-Sadowski et al. [50] was the only study that explicitly looked at long-term PPI use. In the study, the second year of PPI therapy was associated with an increased risk of incident pneumonia with an adjusted hazard ratio (AHR) = 1.82, (95% CI, 1.27–2.54).

Table 3: Summary of CAP risk due to PPI use

Study	Current PPI use
Myles et al. [16]	AOR=1.55 (95% CI, 1.38–1.77)
Dublin et al. [37]	AOR=1.32(95% CI 1.17-1.49)
Evers et al. [38]	AOR=2.21 (95% CI 1.66–2.94)
García Rodríguez et al. [39]	RR = 1.16 (95% CI 1.03–1.31)
Gau et al. [40]	AOR=1.18 (95% CI, 0.80 - 1.74)
Gulmez [41]	AOR=1.5 (95% CI, 1.3-1.7)
Hermos et al. [42]	AOR=1.29 (95% CI, 1.15–1.45)
Laheij [43]	RR=1.89 (95% CI, 1.36-2.62)
Meijvis et al. [44]	AOR = 1.6 (95% CI, 1.2–2.2).
Sarkar et al. [45]	AOR = 1.02 (95% CI, 0.97 - 1.08)
Filion et al. [46]	AOR=1.05 (95% CI, 0.89 - 1.25)
Roughead et al. [47]	Rate Ratio [RR] = 1.16 (95% CI, 1.11–1.22)
Othman et al. [48]	HR=1.67 (95% CI, 1.55 - 1.79)
Ramsay et al. [49]	RR=3.24, (95% CI, 2.50 - 4.19)

OR=Odds Ratio, AOR=Adjusted Odds Ratio, RR=Risk Ratio, HR=Hazard Ratio

From table 3 above, it can be seen that current PPI use has a positive correlation with CAP incidence. However, it is also clear that the adjusted correlation is not strong since the value of the AOR across studies mostly ranges between 1.02 and 1.5.

Different PPI durations

In García Rodríguez et al., [39] where the relative risk (RR) of CAP for current PPI use was = 1.16, only the first 12 months of use showed an increased risk. This meant that long-term PPI use was not associated with CAP risk. Using a timing analysis, Evers et al. [38] divided the PPI users into current, recent past, and distant past users. The study reported that there was a higher percentage of CAP cases identified as current users. In Gulmez, [41] recent initiation of treatment using PPIs (0-7 days before the study index date) had a strong association with CAP with OR = 5.0 (95% CI, 2.1-11.7). This risk seemed to decrease in situations where treatment was started more than 84 days before the study index, OR =1.3 (95% CI, 1.2-1.4). In Hermos et al.

[42] those with an increasing duration of PPI use demonstrated decreasing risk. Those with a 1-15 days duration of PPI use had AOR=1.25 (95%CI, 0.91–1.71), and those with 46-90 days had AOR of 0.88 (95%CI, 0.71–1.09), similar to those with 91–180 days duration of PPI use. Analysis in Meijvis et al., [44] showed that patients with a PPI prescription ≤15 days before the index date had an AOR of 3.1 (95% CI 1.1–8.8). The AOR was 3.3 (95% CI 0.91-11.6) for patients with a PPI prescription initiated 16–29 days before the index date. Use of PPIs <6 months but >3 months before the index date was significantly associated with a risk for CAP of AOR=2.4 (95% CI, 1.1–5.0). Myles et al. [16] found PPI users of ≤30 days had an AOR of 1.55 (1.36–1.77), those with usage at 31-90 days had an AOR of 1.69 (1.42–2.03), and those with use at > 90 days had an AOR at 1.17 (1.04–1.31). In Sarkar et al., [45] there was a strong increase in risk for CAP associated with PPI use started within the previous 2 days (AOR = 6.53 (CI, 3.95 to 10.80)), within 7 days (AOR = 3.79 (CI, 2.66 to 5.42)), and 14 days (adjusted OR, 3.21 [CI, 2.46 to 4.18]. The study also found no statistically significant association with longer-term PPI therapy. In Zirk-Sadowski et al., [50] the second year of PPI therapy was associated with an increased risk of incident pneumonia with an adjusted hazard ratio (AHR)=1.82, (95% CI, 1.27–2.54).

The summary of how CAP risk varies with the duration of PPI use is shown in table 4 below. It is evident that the risk for CAP due to PPI use decreases as the duration of PPI use increases. In the table, the highest risk of CAP at an adjusted odds ratio was 6.53 (95% CI, 3.95 to 10.80) for < 2 days of use, [45] this was followed by OR =5.0 (95% CI, 2.1-11.7) for 7 days of PPI use.

Table 4: Risk for CAP for different durations of PPI use

Study	Duration of use						
	<7days	<15days	<31days	<90days	91-180days	< 1year	> 1year
Myles et al. [16]				AOR=1.69			
				(95% CI, 1.42–2.03)			
García Rodríguez et al. [39]			RR = 1.21			RR = 1.40	RR = 1.05
			(95% CI, 0.90-1.63)			(95% CI, 1.14-1.71)	(95% CI, 0.90-1.22)
Gulmez [41]	OR =5.0			OR=1.3			
	(95% CI, 2.1-11.7)			(95% CI, 1.2-1.4)			
Hermos et al. [42]		AOR=1.25		AOR=0.74; 45 days	AOR=0.88		
		(CI, 0.91–1.71)		(CI, 0.56-0.96)	(CI, 0.72–1.09)		
				AOR=0.88; 46-90 days			
				(CI, 0.71–1.09)			
Meijvis et al. [44]		AOR = 3.1	AOR = 3.3				
		(95% CI, 1.1–8.8)	(95% CI, 0.91–11.6)				
Sarkar et al. [45]	AOR = 6.53; 2 days	AOR= 3.21					
	(95% CI, 3.95-10.8)	(95% CI, 2.46-4.18)					
	AOR = 3.79; 7 days						
	(95% CI, 2.66-5.4)						
Filion et al. [46]						OR=1.08	
						(95% CI, 0.88-1.32)	
Othman et al. [48]			RR=1.19			RR=1.92	
			(95% CI, 1.14-1.25)			(95% CI, 1.84 - 2.00)	
Ramsay et al. [49]	RR=3.24		RR=2.02	RR=1.55; >30 days			
	(95% CI, 2.5-4.19)		(95% CI, 1.68 – 2.42)	(95% CI, 1.44-1.67)			
Zirk-Sadowski et al. [50]							HR=1.82
							(95% CI, 1.27–2.54)

OR=Odds Ratio, AOR=Adjusted Odds Ratio, RR=Risk Ratio, HR=Hazard Ratio

Meta-analysis

The meta-analysis in this paper pooled data from 9 studies, using the common-effect inverse- variance model. The adjusted odds ratios across studies were pooled together to give an overall estimate of the effect size as Odds ratio. This was the similar approach used by Lambert et al., [33] who carried out a meta-analysis on the same topic. The analysis showed an increased risk of CAP due to current PPI use, with a pooled Odds Ratio of 1.13 (95% CI, 1.09 - 1.18). The I^2 statistic for this measure was 88.8% ($p<0.001$), indicating significant heterogeneity across studies.

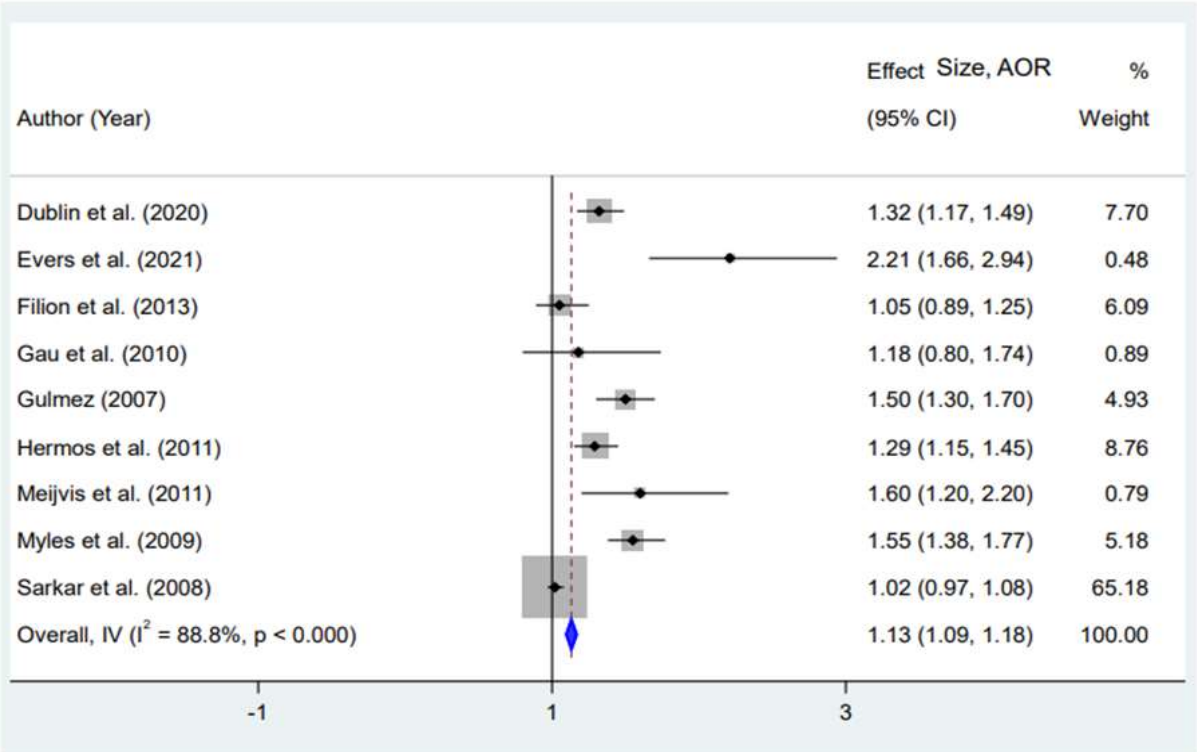

Figure 2: STATA forest plot

The meta-analysis for long-term PPI use could not be done due to a low number of studies as shown in Table 3. Only García Rodríguez et al. [39] and Zirk-Sadowski et al. [50] reported the risk for CAP development for PPI longer than 1 year.

Discussion

The results of this systematic review reveal a positive relationship between proton pump inhibitor (PPI) use and the incidence of Community-Acquired Pneumonia (CAP). Current PPI use shows a positive effect on CAP incidence. However, it is noteworthy that the strength of this association varies across different studies, with adjusted odds ratios (AOR), spanning a considerable range from 1.02 to 3.3. [41, 45]. Notably, several studies report an AOR greater than 1, indicating an increased risk of CAP in current PPI users. [16, 38, 42] However, these values are not consistently high, and they tend to hover around 1.02 to 1.5 in the majority of studies. [37, 39, 40, 43, 44, 50] In the meta-analysis, the risk of developing CAP due to current PPI use was AOR=1.13 (95% CI, 1.09 - 1.18). This also shows a positive but not a strong effect. This effect size is almost

similar to that obtained by Lambert et al. [33] The study reported an odds ratio of 1.49 (95% CI, 1.16–1.92) for CAP risk. However, an analysis by a different paper, Nguyễn et al., [51] found a very strong association of AOR=1.86 (95% CI, 1.30–2.66). Unlike this paper, Nguyễn et al. [51] only included nested case-control studies, and conjoined the use of H2-receptor antagonist (H2RA) with that of PPIs, and analysed it as a single exposure. This may have led the study to include more CAP cases and hence a relatively higher odds ratio as a result. The authors also noted the effect of confounders on the high OR. The authors stated that if further confounders had been identified and adjusted for, then the estimated OR would have been close to 1, [51] similar to what we found in this review.

Analysis of the effect of duration of PPI use shows that the relationship between PPI use and CAP incidence lies in the timing and duration of PPI therapy. Across the studies, it is evident that as the duration of PPI use increases the risk of CAP decreases. Several studies show that short-term PPI use, especially within the first few days or weeks, is associated with a higher risk of CAP. [45] For instance, PPI use initiated within the previous 2 days was linked to a significantly higher CAP risk (AOR = 6.53), which decreased over time [41, 42, 44, 45]. Conversely, long-term PPI use, especially beyond the first year, may not exhibit a significantly increased CAP risk. [39, 50]. The study by Zirk-Sadowski et al. [50] is a notable outlier in this review, as it explicitly focused on long-term PPI use. This study reported that the second year of PPI use was associated with an increased risk of incident pneumonia. The adjusted hazard ratio (AHR) of 1.82 indicates a significant long-term effect. This finding shows that though diminished, prolonged use of PPIs can impact CAP risk. This relationship between PPI use duration and CAP risk has been reported in the literature before. In Lambert et al., [33] PPI use for less than 1 month was associated with the highest risk of CAP, (OR = 2.10; 95% CI 1.39-3.16), this decreased to OR=1.51 (95% CI, 0.92-2.49) for 1-6 months and OR=1.37 (95% CI 0.85-2.20) for duration > 6months. Similarly, in Nguyễn et al. [51] the OR for 1-6 months of use was 2.05 (1.22–3.45) while that for > 6 months of use was 1.91 (1.22–3.00).

The reason for CAP risk being higher for short-duration PPI use compared to long-term use may be due to that, CAP diagnosis mostly occurs in medical care settings where PPI is commonly prescribed. [42] In Hermos et al. [42] the cases of CAP occurring before (n = 1235) and after (n = 1544) PPI initiation, showed a time-dependent distribution of CAP cases. Among the 330 CAP cases that occurred within 90 days before PPI initiation, half occurred within 13 days. Also, in the analysis by Othman et al. [48] the study results showed a greater increase in CAP in the year before than the year after the PPI prescription. The rate of pneumonia for the exposed patients was similar before a PPI prescription (62.1 per 1000 person-year) to the rate after a PPI prescription (61.4 per 1000 person-year). This would translate to an incidence rate ratio of 1.19 (95 CI, 1.14

to 1.25) in the 30 days after a PPI prescription, with a higher rate ratio of 1.92 (95CI, 1.84 to 2.00) for the 30 days before a PPI prescription. [48] Despite this data, neither Hermos et al. [42] nor Othman et al. [48] disagreed that CAP risk reduced with increasing duration of PPI use.

Study limitation

This review only included observational studies that relied on retrospective databases. Due to this, a higher OR would have been more fitting to prove an association. The adjustment for confounding factors among the studies may not be adequate as there could be other unknown confounders.

Conclusion

This review examined the effect of PPI therapy on CAP risk, with a special look at long-term PPI use. This review found that among the included studies, the adjusted effect sizes ranged from 1.02 to 3.3 with most of them around 1.02 to 1.5. Considering that the included studies were observational and using retrospective data, it can be concluded that these values are enough to show a positive association but not enough to ascertain it. This paper also looked at how the duration of PPI use affected the risk for CAP incidence. The findings show a general trend where the risk of community-acquired pneumonia decreases with increasing duration of PPI use.

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