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Outpatient Proton Pump Inhibitor Therapy and Risk of Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis

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Background

- Community-acquired pneumonia (CAP) is a common cause of morbidity, mortality and healthcare spending
- Proton pump inhibitors (PPIs) are commonly prescribed, often without an appropriate indication
- PPI exposure is associated with *Clostridium difficile* and other enteric infections
- PPI exposure may increase CAP risk

Methods

- Systematic searches performed on February 13, 2013:
  - MEDLINE (via PubMed)
  - EMBASE
  - CINAHL
  - Cochrane Central Register of Controlled Trials
  - Scopus
  - Web of Science
- Handsearching and citation searching
- Inclusion criteria:
  - Case-control, cohort, or randomized study design
  - Participants ≥ 18 years old
  - Outpatient PPI exposed and unexposed groups
  - CAP outcome assessed

Figure 1. Study Selection (PRISMA Flowchart)

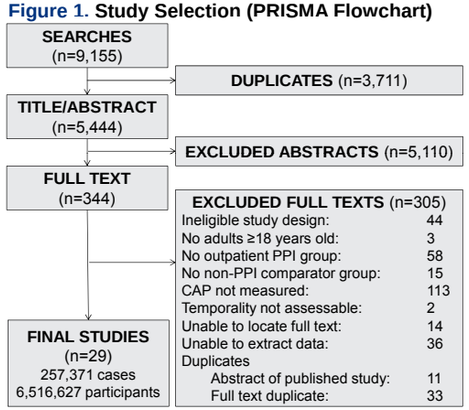

Table 1. Study Characteristics

Author, Year Design	Location Conduct Years	Source of Cases	# Cases / # Participants
Almirall, 2008 Case-Control	Spain 1999-2000	Patients >14 years old at 64 primary care centers	1,336 / 2,662
Dublin, 2010 Case-Control	WA, USA 2000-2003	Adults 65-94 years old in integrated healthcare delivery system	1,125 / 3,360
Ernst, 2012 Case-Control	UK 1997-2009	Anti-parkinsonian drug users aged 40-89 in General Practice Research Database	1,835 / 17,923
Filion, 2013 Cohort	Canada, UK, USA 1997-2010	New NSAID users ≥40 years old in eight research databases	5,135 / 4,238,504
Gau, 2010 Case-Control	OH, USA 2004, 2006	Rural community hospital admissions ≥65 years old	194 / 1,146
Gulmez, 2007 Case-Control	Denmark 2000-2004	Government Patient Registries	7,642 / 41,818
Hennessy, 2007 Case-Control	UK 1987-2002	Adults ≥65 years old in the General Practice Research Database	12,044 / 60,220
Hermos, 2012 Case-Control	USA 1996-2007	New England Veterans Healthcare System	1,544 / 16,984
Jena, 2012 Cohort	USA 1997-2007	Adults ≥30 years old in six employer-based insurance plans	16,827 / 54,490
Laheij, 2003 Cohort	Netherlands 2002	Outpatient endoscopy service and surrounding community	6 / 405
Laheij, 2004 Cohort	Netherlands 1995-2002	Integrated Primary Care Information (IPCI) project	475 / 5,165
Liu, 2012 Case-Crossover	Taiwan 1998-2007	Adults with history of stroke and pneumonia hospitalization	13,832 / 13,832
Long, 2013 Case-Control	USA 1997-2009	IBD patients <64 years old in the Life Link Health Plan Claims Database	4,856 / 23,784
Mastronarde, 2009 RCT	USA 2004-2008	Adults with poorly controlled asthma enrolled in ALA ACRC	1 / 402
Meijvis, 2011 Case-Control	Netherlands 2004-2010	Two teaching hospitals	430 / 2,150
Muellerova, 2012 Case-Control	UK 1996-2005	COPD patients ≥ 45 years old in General Practice Research Database	1,469 / 8,814
Myles, 2009 Case-Control	UK 2001-2002	Patients >40 years old in The Health Improvement Network (THIN)	3,709 / 25,883
Nielsen, 2012 Case-Control	Denmark 1997-2009	Patients ≥15 years old in the Danish National Registry of Patients	70,914 / 780,054
Pasina, 2011 Cohort	Italy 2008	Patients ≥65 years old admitted at 38 internal medicine wards	28 / 1,332
Quagliarello, 2005 Cohort	CT, USA 2001-2003	Nursing home residents >65 years old	112 / 613
Ramsay, 2013 Cohort	Australia 2007-2011	Adults ≥ 65 years old, eligible for DVA services	6,775 / 105,467
Rodriguez, 2009 Case-Control	UK 2000-2005	Patients 20-79 years old in The Health Improvement Network (THIN)	7,297 / 17,920
Roughead, 2009 Cohort	Australia 2002-2006	Patients ≥65 years old with full Veterans' Affairs benefits	13,876 / 185,533
Sarkar, 2008 Case-Control	UK 1987-2002	Patients ≥18 years old in General Practice Research Database	80,066 / 879,947
Scheiman, 2011 RCT	Global 2007-2008	Aspirin users ≥18 years old with history or risk of ulcer at 240 centers	9 / 2,426
Sugano, 2011 RCT	Japan 2007-2008	Long-term low-dose aspirin users with ulcer history in multicenter trial	1 / 461
Sugano, 2012 RCT	Japan 2007-2009	Long-term NSAID users with ulcer history in multicenter trial	6 / 366
van de Garde, 2006 Case-Control (*ERS*)	Netherlands 1995-2000	Adults >18 years old in the PHARMO record linkage system	1,108 / 4,925
van de Garde, 2006 Case-Control (*Thorax*)	UK 1987-2001	Diabetic patients ≥ 18 years old in General Practice Research Database	4,719 / 20,041

Figure 2. Forest Plot of Effect Estimates for Risk of CAP

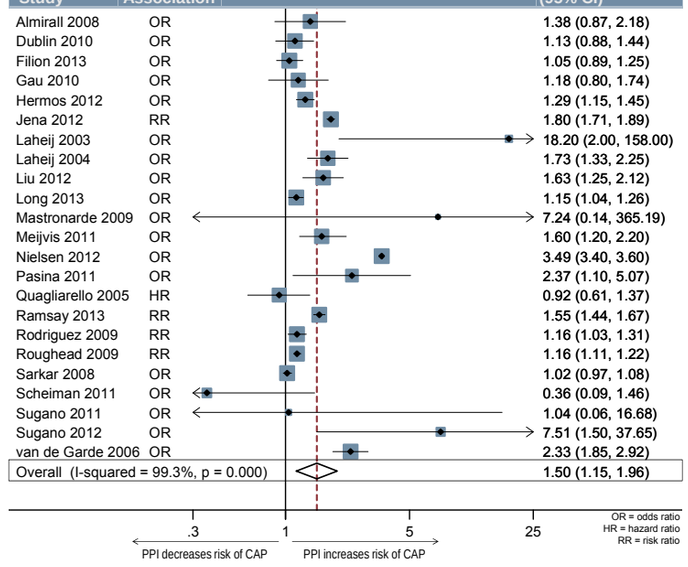

Table 2. Sensitivity Analyses

Analysis	Pooled Estimate (95% CI)	I^2 (p-value for heterogeneity)	# of Studies
PPI only	1.49 (1.13-1.96)	88.4% (<0.001)	21
Strict CAP definition	1.32 (1.08-1.60)	52.5% (0.062)	6
Strict Risk of Bias	1.24 (1.07-1.44)	96.7% (<0.001)	11

Table 3. Subgroup Analyses

Subgroup		Pooled Estimate (95% CI)	I^2 (p-value for heterogeneity)	# of Studies
PPI Dose	High (>1 DDD)	1.33 (1.05-1.69)	34.0 % (0.168)	7
	Low (≤1 DDD)	1.31 (1.04-1.66)	71.4% (0.001)	8
PPI Duration	<1 month	2.10 (1.39-3.16)	72.5% (0.003)	6
	1-6 months	1.51 (0.92-2.49)	89.2% (<0.001)	5
	>6 months	1.37 (0.85-2.20)	74.1% (0.028)	5
Age	<65 years	1.23 (0.99-1.53)	48.3% (0.085)	6
	>65 years	1.24 (1.06-1.46)	82.8% (<0.001)	10

DDD = defined daily dose

Table 4. Secondary Analyses

Exposure/ Outcome	Pooled Estimate (95% CI)	I^2 (p-value for heterogeneity)	# of Studies
H2RA Exposure	1.00 (0.90-1.12)	33.7% (0.159)	8
CAP Hospitalization	1.65 (1.11-2.45)	99.4% (<0.001)	14

H2RA = H2 receptor antagonist

Conclusions

- Outpatient PPI use is associated with increased CAP risk
- CAP risk is highest shortly after PPI initiation
- CAP risk does not vary with PPI dose
- CAP risk is not elevated with H2RA exposure

Implications

- Providers should consider potential harm due to CAP risk when deciding to initiate or continue PPI therapy
- Further research is needed to investigate mechanisms underlying the association between PPI use and CAP risk

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