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Helicobacter pylori increases the risk of low-dose aspirin ulcers: a meta-analysis

Abstract

Background and Aim: Owing to wide-spread use, low-dose aspirin (LDA) produces a substantial amount of peptic ulcer disease. Current guidelines are ambivalent about the need for *Helicobacter pylori* eradication to protect against LDA ulcers. This study aimed to determine, through meta-analysis, if (and by how much) infection alters the baseline risk of peptic ulcers during LDA therapy.

Methods: Literature screening was performed in MEDLINE and EMBASE from inception to May 2018. Original studies reporting prevalence or incidence of uncomplicated ulcers in LDA users were included. Ulcer endpoints needed to be specified separately, according to *Helicobacter pylori* infection status. Meta-analysis was performed in MIX 2.0 Pro.

Results: Ten cross-sectional studies and seven randomized controlled trials were included (n = 5964). The pooled odds ratios (OR) with 95% confidence intervals (CI) for the risk of LDA ulcers in *Helicobacter pylori*-positive vs. -negative individuals were 1.68 (95%CI 1.40-2.02) and 1.65 (95%CI 1.29-2.08) under fixed- and random-effects models, respectively. Heterogeneity among studies was minimal (I^2 = 26.9%). After adjusting for the protective effects of antisecretory drugs, the OR increased to 1.94 (95%CI 1.54-2.46).

Conclusion: This analysis suggests *Helicobacter pylori* increases the risk of LDA ulcers by almost 70% in a population where some were taking proton pump inhibitors and/or other acid suppressants. Without antisecretory drugs, the risk almost doubles. Clinically, these findings may support the use of a test-and-treat approach to *Helicobacter pylori* in LDA users, particularly those at higher risk of developing for peptic ulcers.

Keywords: Aspirin; *Helicobacter pylori*; Peptic Ulcer

1.0 Introduction

Aspirin, at doses less than 325 mg per day (low-dose aspirin, LDA), is widely used for the primary and secondary prevention of cardio- and cerebro-vascular disease. Recent guidelines recommending LDA for colorectal cancer prophylaxis[1,2] are likely to further increase its use. However, LDA therapy is associated with several adverse events, particularly peptic ulcer disease (PUD) and its complications.

Used chronically, LDA is associated with a 10% point-prevalence of endoscopic ulcers and a 2-4-fold increased risk of peptic ulcer bleeding.[3,4] Whether infection with *Helicobacter pylori* (*H. pylori*) alters this risk is unclear. Historically, both agents were considered independent risk factors for peptic ulcers. However, examination of their known gastrotoxic mechanisms reveals points of both synergy and antagonism. The complexity of this interaction is evident in their divergent effect on cyclooxygenase (COX) enzymes – important mediators of gastroduodenal mucosal defense. While aspirin inhibits mucosal COX activity,[5,6] *H. pylori* infection invokes COX-II upregulation and inflammatory damage.[7,8] Given this apparent antagonism, the net result at the gastroduodenal mucosa is difficult to predict. Moreover, the literature addressing this association is largely indirect and limited by statistically underpowered studies, with small sample size.

A recent meta-analysis found *H. pylori* to enhance the risk of peptic ulcer *bleeding* in LDA users.[9] However, its effect on the baseline risk of PUD in this population has not yet been established. In alignment with this, current guidelines are ambivalent about the need for *H. pylori* testing and eradication in LDA users to protect against PUD.[4,10]

The present study systematically identified publications reporting PUD prevalence or incidence in LDA users of known *H. pylori* status. The aim was to subject them to a meta-analysis to clarify the nature of this relationship and guide clinical care in this commonly encountered situation.

2.0 Methods

2.1 Search Strategy

An exploded literature search using the Medical Subject Headings (MeSH) *'peptic ulcer', 'low-dose aspirin'* and *'Helicobacter pylori'* was initially performed in MEDLINE (Ovid) on March 20, 2018.

Articles were screened for title, abstract and full text (as required). The Yale MeSH Analyser[11] was used to identify commonalities across MeSH and keywords from ten relevant publications, sampled for this purpose. Ubiquitous terms included *'Helicobacter pylori'*, *'aspirin'* and *'non-steroidal anti-inflammatory drugs'*. A comprehensive search was then conducted using this standardized set of terms, applied as MeSH and text-words in MEDLINE and EMBASE. Literature screening was performed up until May 28, 2018. Search results were limited to human studies, published in English. The detailed search strategy applied in MEDLINE has been provided in the Appendix (Figure S1). Title, abstract and full text (as required) were screened to identify studies that met selection criteria. References of selected papers were further scanned. The comprehensive literature search was performed independently by two authors (GS and SG). Discrepancies were discussed to achieve resolution.

2.2 Study selection

Studies of interventional or observational design were included if they reported endoscopic PUD incidence or prevalence separately for *H. pylori* positive and negative LDA users. Studies were excluded if they did not report original data, pertain to adult participants (≥18 years) or have an available online full text.

2.3 Primary outcome measure

The primary outcome measure was the number of LDA users, of established *H. pylori* status, with and without PUD.

2.4 Data Extraction

Primary outcome data were extracted independently by two authors (GS and SG). Further information was collected by a single author (GS) and included: bibliographic details, study country of origin, study design, methods of *H. pylori* testing, methods of PUD diagnosis and population demographics (mean age/age range, mean LDA dose/dose range, mean duration of LDA use, and the proportion of active tobacco smokers, nonsteroidal anti-inflammatory drug [NSAID] users, antisecretory drug users and subjects with a history of PUD).

2.5 Quality Assessment

All studies were assessed using the Newcastle-Ottawa Scale (NOS).[12] Cross-sectional studies were assessed using adapted NOS case-control criteria. Randomized-controlled trials (RCTs) that did not directly address the primary aim of this analysis were assessed using adapted NOS cohort study criteria to evaluate the comparability of *H. pylori* positive and negative cohorts within each trial.

The NOS employs a three-component system to evaluate the selection criteria, demographical comparability and methods of exposure or outcome ascertainment, of relevant study groups. Overall quality is appraised on a nine-point scale.

Scores were averaged from the independent assessments of two authors (GS and SG). Studies scoring ≥7 were considered higher quality. To test for inter-rater reliability, a Pearson's correlation coefficient (r) was calculated, as well as a Cohen's Kappa coefficient for the percentage of higher-quality studies according to each author.

2.6 Statistical Analysis

Statistical analysis was performed using MIX 2.0 Pro software.[13]

Primary outcome data were pooled through meta-analysis to generate a summary odds ratio (OR) with 95% confidence intervals (CI) for the risk of PUD in *H. pylori* positive compared to *H. pylori* negative LDA users. Fixed- and random-effects models were both explored.

Heterogeneity was assessed using Cochran's Q test as well as calculating the proportion of inter-study variability due to true heterogeneity as opposed to chance (I^2). At I^2 = 25%, 50% and 75%, heterogeneity is considered low, moderate and high, respectively.[14]

A heterogeneity funnel plot and Egger's regression test of plot asymmetry[15] were used to evaluate the possibility of publication bias.

Three sensitivity analyses were performed, to adjust for the impact of study quality, antisecretory drug use (proton-pump inhibitors [PPIs] and histamine-2 receptor antagonists) and concomitant non-aspirin NSAID use.

A further sensitivity analysis was performed to assess the impact of *H. pylori* on LDA ulcer risk in patients receiving PPIs.

2.7 Reporting

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.[16]

3.0 Results

Of 392 articles retrieved in an initial exploded search, ten[3,17-25] were applied to the Yale MeSH analyzer to identify ubiquitous search terms for the comprehensive literature screen.

Excluding duplicates, 3796 publications were retrieved using the comprehensive search strategy. Title and abstract screening identified 95 articles for full text review. Of these, seventeen[3,17-32] (seven RCTs and ten cross-sectional studies, n = 5964) met the criteria for inclusion in the meta-analysis. A PRISMA flow diagram of this screening process is provided in Figure 1.

3.1 Study Characteristics

Key study characteristics are summarized in Table 1 and 2.

Five RCTs,[19-21,26,27] exploring antisecretory drug efficacy for the prevention of LDA-induced PUD, included extractable data on the impact of *H. pylori*. Placebo or active controls were employed in all studies. Two further RCTs[17,18] more directly addressed the impact of *H. pylori* on PUD risk in LDA users. Baseline endoscopy screening, to exclude active PUD, was implemented in all but one study.[17] Study durations ranged from 45 days to 24 months, while LDA dose ranged from 75-300 mg daily.

Seven cross-sectional studies[22,24,25,28,29,31,32] included patients with cardiovascular disease on long-term LDA therapy (≥1 month). A further study[3] included any patient administered long-term LDA (≥28 days). Two final studies enrolled individuals on long-term LDA (≥1 month), who were undergoing endoscopy for investigation of primarily gastrointestinal symptoms.[23,30] Mean LDA dose ranged from 100-160 mg daily in five cross-sectional studies[3,24,28,29,31] and was not reported in the remainder.

3.2 Quality Assessment

Eleven studies[17-22,24-26,29,32] were judged to be higher quality (NOS score ≥ 7). There was good agreement between authors: r = 0.956, p < 0.0001, Cohen's kappa (for the proportion of higher quality studies) was 1.00. NOS assessments for each study are provided in Table S1 and S2.

3.3 Pooled Effect

The summary OR for risk of PUD in *H. pylori* positive compared to negative LDA-users was 1.68 (95%CI 1.40-2.02) and 1.65 (95%CI 1.29-2.08), under the fixed- and random-effects models, respectively. A forest plot of the fixed-effect analysis is presented in Figure 2. There was minimal evidence of heterogeneity (Q = 21.9, P = 0.15 [both models]; I^2 = 26.9 [both models]).

3.4 Sensitivity Analyses | (Table 3)

Eleven higher quality studies[17-22,24-26,29,32] (n = 4683) were included in an initial sensitivity analysis. While the pooled effect size (fixed-effect) was slightly lower (OR 1.42, 95%CI 1.13-1.78), heterogeneity was again minimal (Q = 10.49, p = 0.40; I^2 = 4.67%).

A second analysis included 13 studies (or subgroups within studies; n = 2702) that prohibited antisecretory drug use[3,17-21,26,27,29,30] or demonstrated statistically comparable antisecretory drug use across *H. pylori* positive and negative groups.[23,25,28] The pooled effect (fixed-effect) and heterogeneity were again similar to the complete analysis, however the effect size was larger (OR 1.94, 95%CI 1.54-2.46; Q = 16.63, p = 0.16; I^2 = 27.83). Complementing this, data were available from four studies (n=1007) where *all* patients were receiving PPIs.[21,26-28] In those, the pooled effect size was no longer significantly different from unity (OR 1.20, 95%CI 0.48-2.96), though the statistical power was fairly low.

A final sensitivity analysis included 12 studies (n = 3658) in which concomitant non-aspirin NSAID use was an exclusion criterion.[3,17-26,29] While the pooled effect size was similar to the complete analysis, moderate heterogeneity was detected (OR 1.58. 95%CI 1.25-2.01; Q = 20.77, p = 0.04; I^2 = 47.03%).

3.5 Publication Bias

A heterogeneity funnel plot had acceptable symmetry on subjective evaluation (Figure 3). Egger's regression test of plot asymmetry further demonstrated the y-intercept did not deviate significantly from zero (95%CI = -1.29 to +1.66), indicating publication bias against negative studies was unlikely.

4.0 Discussion

This study is the first meta-analysis to address the impact of *H. pylori* on the baseline risk of PUD in individuals on long-term LDA therapy. Of seventeen evaluable studies, fifteen trended towards a positive association between *H. pylori* and LDA ulcers. However, only four had sufficient power to demonstrate statistical significance in their own right. Through pooling data from almost 6000 patients, *H. pylori* was seen to increase the risk of uncomplicated PUD while on LDA by approximately 70%. The likely validity of this observation is reinforced by significant effect sizes persisting in three sensitivity analyses, after adjusting for the impact of study quality, antisecretory use and concomitant non-aspirin NSAID use. Notably, the summary effect was largest among studies with absent or negligible antisecretory use. Conversely, the sensitivity analysis using four studies with data on patients taking *only* PPIs showed a similar ulcer prevalence in infected and non-infected groups. As proton-pump inhibitors are known to suppress *H. pylori* growth,[33] these findings support *H. pylori* as an augmenter of LDA ulceration.

More direct evidence for the proposition that *H. pylori* increases ulcer risk in LDA-treated patients would likely come from an RCT in which infected patients were randomized to receive eradication therapy or not. The study by Giral et al. did just that.[18] While statistical power was low (with a sample size of 40), no patients in the eradicated group had developed an ulcer by the 4-month endoscopy, compared with three among the untreated controls (p=0.057, Fisher's test).

Two frequently cited consensus guidelines are ambivalent about the need for *H. pylori* testing and eradication to protect against LDA ulcers.[4,10] While, Bhatt et al. support a test and treat approach if there is a history of peptic ulcer bleeding, Chey et al. more recently suggested this strategy 'could be considered', although the quality of evidence was recognised as only moderate. The present analysis adds some weight to the argument for a test and treat approach to *H. pylori* in patients on long-term LDA, and provides a measure of the level of increased risk of PUD these patients experience.

Extrapolating data from the seven RCTs[17-21,26,27] analyzed in this study, gives a wide annual incidence of 12-80% for the development of peptic ulcers while on LDA. Omitting one study,[20] this range becomes 12-40%. If a conservative estimate of a 25% annual incidence is applied to the current finding of roughly a 2-fold increased risk of LDA ulcers with *H. pylori* infection (in individuals not using antisecretories), the number needed to treat (NNT) to prevent one asymptomatic ulcer per year is about ten.

Of course the significance of LDA-induced PUD lies largely in its complications, such as hemorrhage, which has an annual risk nearer to 1%.[9] Thus, the NNT to prevent one LDA ulcer bleed annually by *H. pylori* eradication will be at least an order of magnitude higher than our estimate for endoscopic ulcers.

The economic practicalities of a test-and-treat approach must also be accounted for, especially since eradication therapy fails in approximately 20% of patients after one course of antibiotics.[10] Thus, whether such management is appropriate will vary on a case-by-case basis. Importantly, this study provides a tangible level of risk for clinicians and patients to weigh against the time and cost constraints of *H. pylori* testing and eradication. This approach is most likely to be cost-effective in LDA users who already have a higher baseline risk of PUD (the elderly, active smokers, those concomitantly using other NSAIDs and those with a history of PUD)[34] and particularly individuals who have had a previous ulcer bleed.[35]

Strengths and Limitations

This analysis was limited by the methodology of the included studies. Most were of cross-sectional design, while the remainder were RCTs treated as cohort studies, as none directly address the primary aim. Ten studies[20,22-26,28-31] were not conducted at a population level and may have also introduced participation bias. Selection bias, for individuals with active PUD, could further not be ruled out of three studies.[17,23,30] Despite these limitations, the results of a sensitivity analysis limited to only higher quality studies did not differ greatly from the complete analysis.

Some potential confounding factors could not be reconciled in this analysis. Older age, tobacco smoking and past PUD are known risk factors for the development of gastroduodenal ulcers.[34] However, except for two publications,[18,23,25,29] age and smoker status were not described separately for *H. pylori* positive and negative groups. Further, past PUD was an exclusion criterion in four studies,[17,18,21,28] an inclusion

criterion in two studies[26,27] and either not accounted for or not matched to infection status in the remainder.

A strength of this study was the substantial number of publications that were retrieved for pooling; most of which were considered higher quality and none of which were grey literature. In part this was due to a comprehensive search strategy that did not initially exclude studies based on outcome measures. Literature screening, data extraction and quality assessments were further performed rigorously by two authors. A thorough approach was also applied to data analysis through exploring both fixed- and random-effects models. Despite differences in study methodology and population demographics, heterogeneity was found to be almost negligible, as was the likelihood of publication bias.

5.0 Conclusion

This meta-analysis indicates that *H. pylori* infection increases the risk of gastroduodenal ulcers during LDA therapy by approximately 70%. In the absence of antisecretory drugs, the risk is almost double. These findings provide a quantification of the added ulcer risk attributed to *H. pylori*, which clinicians and patients can consider when commencing LDA therapy. It is likely *H. pylori* testing and eradication would be most beneficial in LDA users already at higher risk of PUD and its complications. Future research should aim to address this inference by stratifying subjects according to baseline PUD risk level.

6.0 References

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7.0 Tables

Table 1: *Characteristics of included randomised controlled trials*

Author [ref] Country Year	Design			Sample Size (n) [a]	Mean Age ± SD (years)	Active Smokers (%)	History of PUD (%)	*H. pylori* testing	Endoscopic ulcer cut-off point = mucosal defect diameter (mm)	Hp+ LDA+ #PUD/n	Hp- LDA+ #PUD/n	Mean NOS Score [b]
	Subjects	Treatment	Length									
Feldman[17] USA 2001	Healthy volunteers	LDA (81 or 325 mg/d) or placebo	45d	Hp+ (22) Hp- (24)	40±2	NS	0	Serology + Histology + RUT	≥5	2/22	0/24	7
Giral[18] Turkey 2004	Individuals with CVD or CAD starting LDA(300 mg/d)	*H. pylori* eradication or placebo	4m	Hp+ (16) Hp-/er (24)	Hp+ (58±11) Hp- (51±10) Hp-er (54±9) [c]	Hp+ (12.5) Hp- (0) [c]	NS	Histology + RUT	≥5	3/16	0/24	9
Iwakiri[26] Japan 2014	Outpatients on chronic LDA therapy (81 or 100 mg/d) with a history of healed PUD	Rabeprazole (10mg/d)	24w	Hp+ (66) Hp- (85)	69.7±9.6	17.2	100	Serology + Eradication History	≥3	2/66	0/85	7.75
		Rabeprazole (5mg/d)		Hp+ (68) Hp- (82)	69.2±9	15.3				1/68	3/82	
		Teprenone (50mg TDS)		Hp+ (75) Hp- (76)	69.3±7.9	14.6				20/75	12/76	

Scheiman[19] Canada 2011	LDA-users with moderate ulcer risk [d]	Esomeprazole (20 or 40mg/d)	26w	NS [e]	NA	NA	NA	UBT	≥3	NA	NA	8
		Placebo		Hp+ (171) Hp- (574)	67.4 (SD NS)	9.1	27.6			10/171	39/574	
Sugano[27] Japan 2011	Chronic LDA-users (81-324mg/d) with a history of healed PUD	Lansoprazole (15mg/d)	12m treatment + 12m follow-up	Hp+ (128) Hp- (85)	69.3±8.6	23	100	NS	≥3	3/128	3/85	6
		Gefarnate (50mg BD)		Hp+ (122) Hp- (105)	68.7±8.8	22.6				38/122	15/105	
Taha[20] UK 2009	Outpatients using LDA with a history of CVD, CbVD or diabetes	Famotidine (20mg BD)	12w	Hp+ (58) Hp- (146)	63 (SD NS)	20.6	52.9	RUT	≥3	0/58	8/146	8
		Placebo		Hp+ (71) Hp- (129)	63 (SD NS)	25.5	47			16/71	22/129	
Yeomans[21] Int. 2008	LDA-users	Esomeprazole (20mg/d)	6m	Hp+ (112) Hp- (360)	69.5±6.6	NS	NS	UBT	≥3	3/112	5/360	8
		Placebo		Hp+ (112) Hp- (368)	69.1±6.5	NS				8/112	18/368	

SD = standard deviation; PUD = peptic ulcer disease; Hp+ = *H. pylori*-positive; Hp- = *H. pylori*-negative; LDA+ = LDA users; NOS = Newcastle-Ottawa Scale; LDA = low-dose aspirin (75-325mg daily); d = days; NS = not stated; RUT = rapid urease test; CVD = cardiovascular disease; CAD = coronary artery disease; m = months; Hp-er = *H. pylori* eradicated; TDS = three times daily; w = weeks; NA = not applicable; UBT = urea breath test; BD = twice daily; CbVD = cerebrovascular disease; Int. = international.

[a] Sample size of LDA-users according to *H. pylori* status
[b] Averaged from the independent assessments of two authors
[c] Statistical tests were not performed to detect differences in patient demographics across *H. pylori* positive and negative groups
[d] Moderate risk was defined as having a history of uncomplicated PUD and aged ≥65y or aged ≥60y with one of: stable coronary artery disease; complaints of upper gastrointestinal symptoms, which, as judged by an investigator, required endoscopy and resulted in the finding of ≥5 gastric and/or duodenal erosions at baseline endoscopy; LDA-naïve (LDA therapy initiated within one month of randomization)
[e] Data for ulcer incidence according to *H. pylori* status was not available for esomeprazole arms

Table 2: *Characteristics of included cross-sectional (prevalence) studies*

Author [ref] Country Year	Inclusion Criteria	Sample Size (n) [a]	Mean±SD Age (years)	Anti-secretory use (%)	Active Smokers (%)	History of PUD (%)	*H. pylori* testing	Endoscopic ulcer cut-off point = mucosal defect diameter (mm)	Hp+ LDA+ #PUD/n	Hp- LDA+ #PUD/n	Mean NOS Score [b]
Fukuda[28] Japan 2012	Consecutive outpatients with CVD on LDA (≤100mg/d) for ≥8w	Hp+ (45) Hp- (58)	68.3 (SD NS)	PPI or H2RA (69.2) [c]	58.3	32	Serology	≥3	1/45	0/58	6
Fukuzawa[25] Japan 2012	Consecutive outpatients with CVD on LDA for ≥3m	Hp+ (39) Hp- (52)	67.1±8.9	NS	NS	NS	UBT	≥5	8/39	9/52	7
Iijima[29] Japan 2012	Consecutive outpatients with CVD and/or CbVD on LDA (100mg/d) for ≥1m without a history of *H. pylori* eradication	Hp+ (55) Hp- (38)	Hp+ (73.5) Hp- (67.9) [‡]	-	Hp+ (32.7) Hp- (34.2) [†]	NS	Serology + Eradication History	≥5	8/55	5/38	7

Kawai[22] Japan 2010	Consecutive outpatients with CVD on LDA for ≥3m	Hp+ (55) Hp- (46)	67.2±8.3	PPI or H2RA (24.8)	PUD+ (12.5) PUD- (9.4) †	5.9	UBT	>3	7/55	9/46	8
Negovan[30] Romania 2016	Consecutive outpatients on LDA- (75-125mg/d) for ≥1m undergoing endoscopy for digestive symptoms or symptomatic anemia or screening before cardiac surgery [d]	Hp+ (63) Hp- (96)	NS [e]	-	PUD+ (13.2) PUD- (8.1) †	PUD+ (61.9) PUD- (39.8) ‡	Histology	>5	25/63	26/96	6
Pilotto[23] Italy 2004	Consecutive 65+ yo, LDA-users (75-300mg/d) for ≥3m, with GI symptoms, undergoing endoscopy	Hp+ (112) Hp- (133)	Hp+ (79.7±7.5) Hp- (79.7±7.5) †	PPI Hp+ (15.2) Hp- (24) †	NS	NS	Histology + RUT	NS	41/112	21/133	6
Shiotani[24] Japan 2009	CVD patients on LDA (100mg/d) undergoing recommended upper GI endoscopy for PUD and gastric cancer screening	Hp+ (167) Hp- (138)	71 (SD NS)	PPI or H2RA (67.9)	PUD+ (10.4) PUD- (15.8) †	PUD+ (10.9) PUD- (21.1) †	Serology + Eradication History	>5	22/167	16/138	7.75
Tamura[31] Japan 2011	Outpatient or hospitalized CVD patients on LDA for ≥3m from three centres	Hp+ (68) Hp- (82)	71.6 (SD NS)	PPI or H2RA (72)	10.7	30	UAA + Eradication History	≥3	3/68	3/82	6

Uemura[32] Japan 2014	CVD patients on LDA (75-330mg/d) for ≥1m, from 63 institutions	Hp+ (700) Hp- (754)	68.1±9.5	PPI or H2RA (34.7)	PUD+ (20.2) PUD- (9.7) ‡	PUD+ (27.7) PUD- (21.6) †	Serology + Eradication History	≥5	59/700	35/754	7.5
Yeomans[3] Int. 2005	LDA-users for ≥28d from five centers [f]	Hp+ (65) Hp- (119)	49.9±2.1 – 67.6±2 [g]	-	4.3 – 11.1 [g]	2.6-21.2 [g]	Histology or RUT	≥3	14/65	6/119	6.5

SD = standard deviation; PUD = peptic ulcer disease; Hp+ = *H. pylori*-positive; Hp- = *H. pylori*-negative; LDA+ = LDA users; NOS = Newcastle-Ottawa Scale; LDA = low-dose aspirin (75-325mg daily); CVD = cardiovascular disease; w = weeks; NS = not stated; PPI = proton-pump inhibitor; H2RA = histamine-2 receptor antagonist; m = month; UBT = urea breath test; CbVD = cerebrovascular disease; yo = year old; RUT = rapid urase test; UAA = urine antigen assay

† Difference between groups was not statistically significant
‡ Difference between groups was statistically significant

[a] Sample size of LDA-users according to *H. pylori* status
[b] Averaged from the independent assessments of two authors
[c] 41 subjects did not use antisecretory drugs
[d] 60.4% of subjects had upper GI symptoms prior to endoscopy, including 46 patients who described ≥1 episode of upper-abdominal, ulcer-like pain
[e] Approximately 39% of subjects in *H. pylori*-positive and -negative groups were aged over 70 years
[f] Edmonton, Melbourne, Sydney, Nottingham and Zaragoza
[g] Tabulated range represents the upper and lower limit across five collection centers

Table 3: *Sensitivity analyses (fixed-effect model)*

Inclusion Criteria	Number of studies	Number of subjects	Pooled OR	95%CI	Cochran's Q (heterogeneity)	I^2
Higher quality (mean NOS score [a] ≥ 7)	11	4683	1.42	1.13, 1.78	P = 0.40	4.67%
Comparable [b] antisecretory drug use across *H. pylori* positive and negative groups	13	2702	1.94	1.54, 2.46	P = 0.16	27.83%
All patients taking a PPI	4	1007	1.20	0.48, 2.96	P=0.62	0%
No concomitant non-aspirin NSAID use	12	3658	1.58	1.25, 2.01	P = 0.04	47.03%

OR = odds ratio; 95% CI = 95 percent confidence intervals; I^2 = proportion of true inter-study variability; NOS = Newcastle-Ottawa Scale; *H. pylori* = *Helicobacter pylori*; PPI = Proton pump inhibitor; NSAID = non-steroidal anti-inflammatory drug

[a] Averaged from the independent assessments of two authors
[b] No significant statistical difference between the proportion of antisecretory drug users in *H pylori* positive and negative groups

8.0 Figure Legends

Figure 1: *PRISMA flow diagram of study selection process*. Full texts of 95 publications were assessed for eligibility. Seventeen studies met all inclusion/exclusion criteria and were pooled for meta-analysis.

Figure 2: *Forest plot reporting odds ratios (OR) with 95% confidence intervals (CI) for LDA-induced PUD in H. pylori positive compared to negative individuals (fixed-effect model).* OR with 95%CI is represented by the orange diamond. The size of each square is proportional to the individual contribution (weight) of each study to the pooled effect.

Figure 3: *Funnel plot of 17 studies included in a meta-analysis (fixed-effect model).* Within study variance is measured on the y-axis, while effect size is measured on the x-axis. The pooled effect (odds ratio) is represented by the vertical orange line. Curved orange lines represent pseudo-confidence intervals. An Egger's regression test of funnel plot asymmetry was non-significant (95%CI for the y-intercept = -1.29 to +1.66).

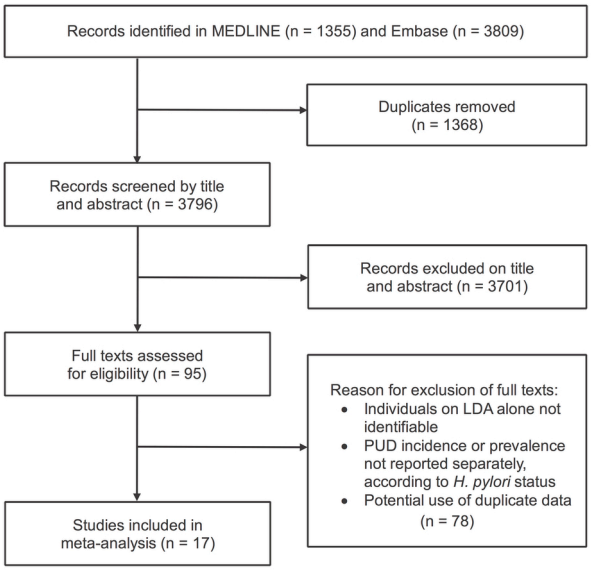

Figure 1

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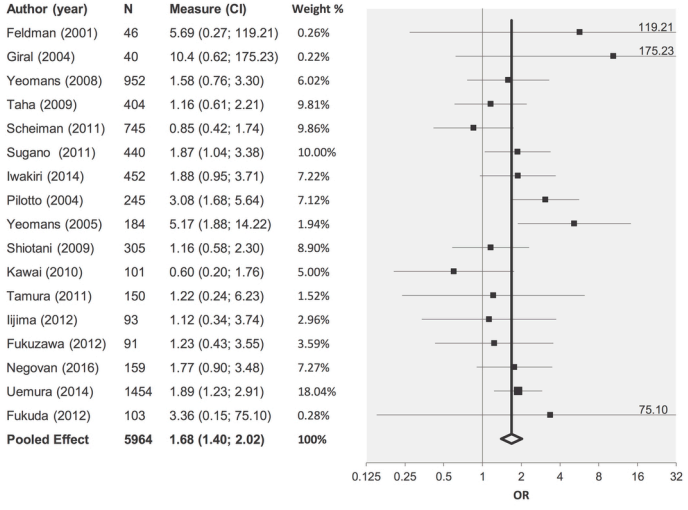

Figure 2

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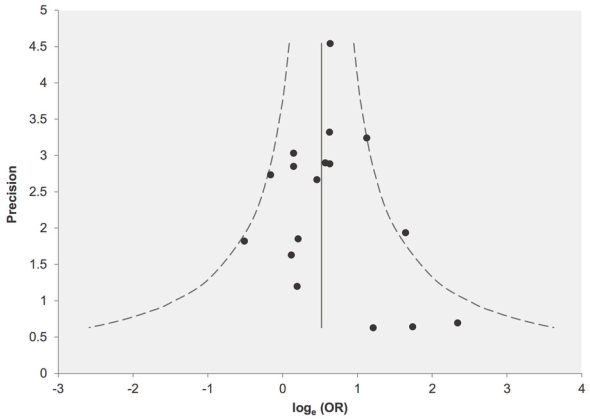

Figure 3

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