

Effects of *Helicobacter pylori* and Nonsteroidal Anti-Inflammatory Drugs on Peptic Ulcer Disease: A Systematic Review

GEORGE V. PAPATHEODORIDIS,* STAVROS SOUGIOULTZIS,† and
ATHANASIOS J. ARCHIMANDRITIS*

*Second Department of Internal Medicine, Medical School of Athens University, Hippokraton General Hospital, and †Department of Pathophysiology, Gastroenterology Section, Medical School of Athens University, Laikon General Hospital, Athens, Greece

Background & Aims: The aim was to systematically review the interactions between *Helicobacter pylori* (HP) infection and NSAID use on the risk of uncomplicated or bleeding peptic ulcer. **Methods:** All relevant full articles published in MEDLINE from January 1989–June 2004 were included. Sensitivity analyses for type of controls or use of aspirin or non-aspirin NSAIDs were performed. **Results:** In 21 studies involving 10,146 patients, uncomplicated peptic ulcer was more common in HP-positive than HP-negative patients (pooled odds ratio [OR], 2.17) or in HP-positive than HP-negative NSAID users (OR, 1.81). In 6 age-matched controlled studies, ulcer was more common in HP-positive than HP-negative patients (OR, 4.03), irrespective of NSAID use, and in NSAID users than non-users (OR, 3.10), irrespective of HP status; the risk of ulcer was 17.54-fold higher in HP-positive NSAID users than HP-negative non-users. The use of aspirin or non-aspirin NSAIDs did not affect the results. Ulcer bleeding was evaluated in 17 studies involving 4084 patients. NSAID use was more frequent in bleeding patients than control subjects (OR, 5.13), irrespective of HP status and type of controls. In contrast, HP infection in bleeding patients compared with control subjects was less frequent in the 8 studies with ulcer cases as control subjects (OR, 0.40) and more frequent in the 9 studies with uninvestigated subjects as controls (OR, 2.56). In the latter studies, presence compared with the absence of both HP and NSAIDs increased the risk of bleeding 20.83-fold. **Conclusion:** HP infection and NSAID use represent independent and synergistic risk factors for uncomplicated and bleeding peptic ulcer.

Aspirin and non-aspirin NSAIDs are widely used agents,^{1,2} although their consumption is often associated with the development of serious gastrointestinal complications, with the most common being acute bleeding from peptic ulcers.^{3,4} Both uncomplicated and complicated peptic ulcers mostly develop in NSAID users with certain risk factors, such as older age, history of peptic ulcer with or without complications, recent dyspepsia, or use of antico-

agulants.² However, none of these factors can be modified or removed to reduce the risk of NSAID gastrotoxicity.

Helicobacter pylori (HP) infection is also a documented risk factor for peptic ulcer disease.⁵ Because HP infects almost 50% of the population worldwide and is more prevalent in older individuals,⁶ the establishment of a synergistic or additive effect of HP infection and NSAID use in peptic ulcer development would be of great clinical importance, because eradication of the bacterium would likely reduce the risk of upper gastrointestinal complications in infected NSAID users. Although the presence of 2 factors that might damage the gastric mucosa, such as HP and NSAIDs, would be reasonably considered to increase the risk of peptic ulcer, data from several, mainly epidemiologic studies appeared to be controversial and did not always confirm such an assumption.⁷ In a systematic review published in 2002, the combined analysis of the data available up to October 2000 showed that HP infection and NSAID use act synergistically for the development of peptic ulcer and ulcer bleeding.⁸ However, several relevant studies have been published after 2000, and the interactions between HP infection and NSAID use in several patient subgroups have not been entirely clarified.⁶ Thus, the aim of our systematic review was to evaluate in detail the relations between HP infection and use of NSAIDs on the risk of developing uncomplicated or bleeding peptic ulcer.

Methods

Data Identification

We searched the MEDLINE/PUBMED database from January 1989–June 2004 to identify all medical literature included under the search text terms *aspirin* or *NSAID* and *pylori* and *ulcer* or *bleeding* or *complication*. We also performed a

Abbreviations used in this paper: CI, confidence interval; HP, *Helicobacter pylori*; OR, odds ratio.

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1542-3565/06/\$32.00

PII: 10.1053/S1542-3565(05)01042-6

full manual search of all review articles and of the retrieved original studies.

Inclusion Criteria

Studies published as full articles were included in our systematic review if they met all the following criteria: (1) to be observational studies (case-control, cross-sectional, or cohort) or randomized trials; (2) to investigate endoscopically the presence or absence of uncomplicated or bleeding peptic ulcer; (3) to include adults (>16 years old) taking NSAIDs and, in case of ulcer bleeding, include both patients with bleeding and nonbleeding control subjects; (4) to provide data on the prevalence of HP infection and NSAID use; and (5) to exclude patients with recent (within the last 4 weeks) antibiotic use or anti-ulcer drugs or a history of gastric surgery as well as patients with non-ulcer gastrointestinal bleeding (unless they provided data for ulcer and non-ulcer bleeding separately).

Data Extraction

Data were extracted independently from each study (by G.V.P. and S.S.) by using a predefined form, and disagreement was resolved by consensus.

Events for Analysis

The events selected for analysis were (1) endoscopically documented, uncomplicated peptic ulcer with a diameter ≥ 3 mm and (2) acute bleeding from peptic ulcer documented by endoscopy.

Statistical Analysis

The pooled odds ratio (OR) and 95% confidence interval (CI) were calculated from the raw study data by using the Mantel-Haenszel (fixed effect model) or the DerSimonian and Laird method (random effect model). The χ^2 test was used to assess heterogeneity, which was considered to be present if *P* value was less than .05. In the absence of statistically significant heterogeneity, pooled OR and 95% CI by the fixed effect model are given in the results, whereas in the case of significant heterogeneity, pooled OR and 95% CI by the random effect model are given. In the presence of significant statistical heterogeneity, we searched for the sources of any possible clinically important (methodologic or biologic) heterogeneity. Agreement in the selection of studies between the 2 reviewers was evaluated by the κ coefficient.

Because of the lack of statistical power for heterogeneity testing for both the detection and extent of clinically significant heterogeneity, we performed separate sensitivity analyses according to the following parameters. First, because two thirds of the studies selected for the evaluation of uncomplicated peptic ulcer included control subjects (non-users of NSAIDs) unmatched for age, which influences both the prevalence of HP infection⁵ and the risk of NSAID-induced peptic ulcer,⁹ we performed separate analyses for the effect of HP infection on the risk of uncomplicated peptic ulcer according to the study design (age-matched or unmatched controls).

Second, because almost half of the studies selected for evaluation of peptic ulcer bleeding included cases with uncomplicated ulcers as nonbleeding controls and the prevalence of HP infection is expected to be rather high in such patients,⁵ separate analyses for ulcer bleeding were performed for studies including patients with uncomplicated ulcers and for studies including endoscopically uninvestigated subjects as nonbleeding controls. These analyses are only provided in the Results.

Third, all analyses for uncomplicated peptic ulcer were performed separately for aspirin or non-aspirin NSAID users, because it is still controversial whether these 2 types of agents have the same ulcerogenic potential.⁶ Such a sensitivity analysis was not performed for ulcer bleeding because of limited available data.¹⁰⁻¹³

Results

Descriptive Assessment

There were 626 citations generated by the literature searches. Of those, 37 were found to meet our inclusion criteria. In particular, the presence of uncomplicated ulcer was reported in 21 studies¹⁴⁻³⁴ and of ulcer bleeding in 17 studies^{10-13,26,35-46}; one study evaluated patients with both uncomplicated and bleeding ulcers.²⁶ Initial agreement between the reviewers for the selection of relevant articles was high ($\kappa = 0.94$).

Uncomplicated Peptic Ulcer

In the 21 studies that evaluated the presence of uncomplicated ulcer, raw data on the HP status were provided for 10,146 cases, 3938 users and 6208 non-users of NSAIDs.¹⁴⁻³⁴ The main characteristics of these studies are shown in Table 1 of Appendix.

The overall pooled prevalence of ulcer was significantly higher in HP-positive (40%, 2468/6214) than HP-negative (29%, 1126/3932) subjects, irrespective of NSAID use (heterogeneity, *P* < .001; pooled OR, 2.17; 95% CI, 1.69-2.79; *P* < .001). In particular among NSAID users, the pooled prevalence of ulcer was significantly higher in HP-positive than HP-negative cases (47% vs 39%; heterogeneity, *P* < .001; pooled OR, 1.81; 95% CI, 1.40-2.36; *P* < .001) (Figure 1A; Table 2 of Appendix).¹⁴⁻³⁴ Similarly, the pooled prevalence of ulcer was significantly higher in HP-positive than HP-negative NSAID non-users (36% vs 19%; heterogeneity, *P* < .001; pooled OR, 6.02; 95% CI, 2.72-13.33; *P* < .001) in the 9 studies providing raw data for both users and non-users of NSAIDs (Figure 1B; Table 2 of Appendix).^{15,16,19,20,22,27,28,30,32}

In the latter 9 studies,^{15,16,19,20,22,27,28,30,32} the prevalence of ulcer was not significantly different between users (31%, 431/1331) and non-users of NSAIDs (30%, 1891/6208) (heterogeneity, *P* < .001;

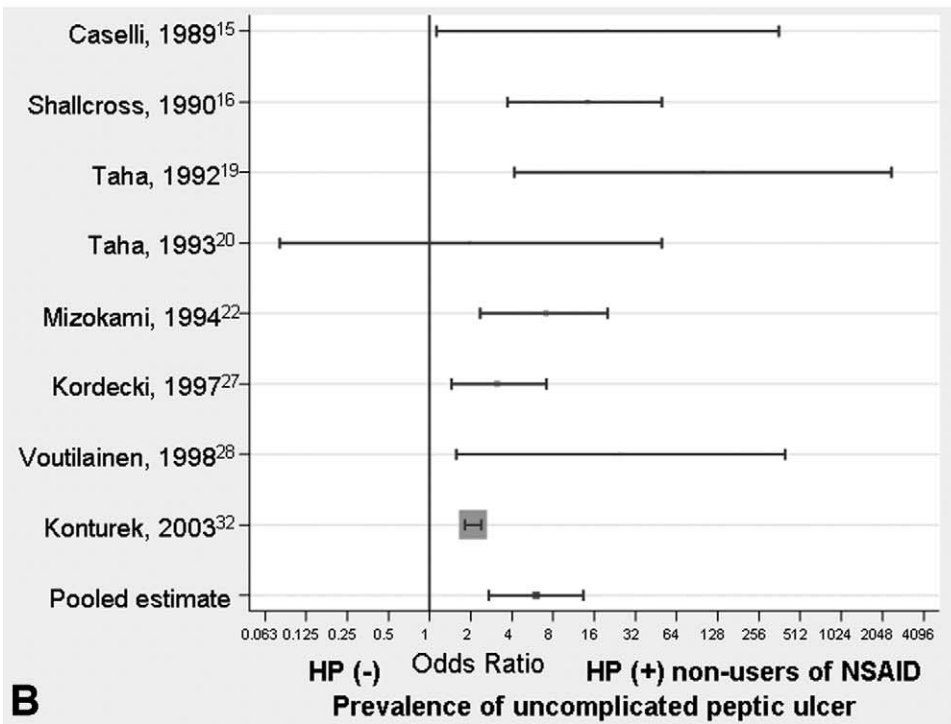
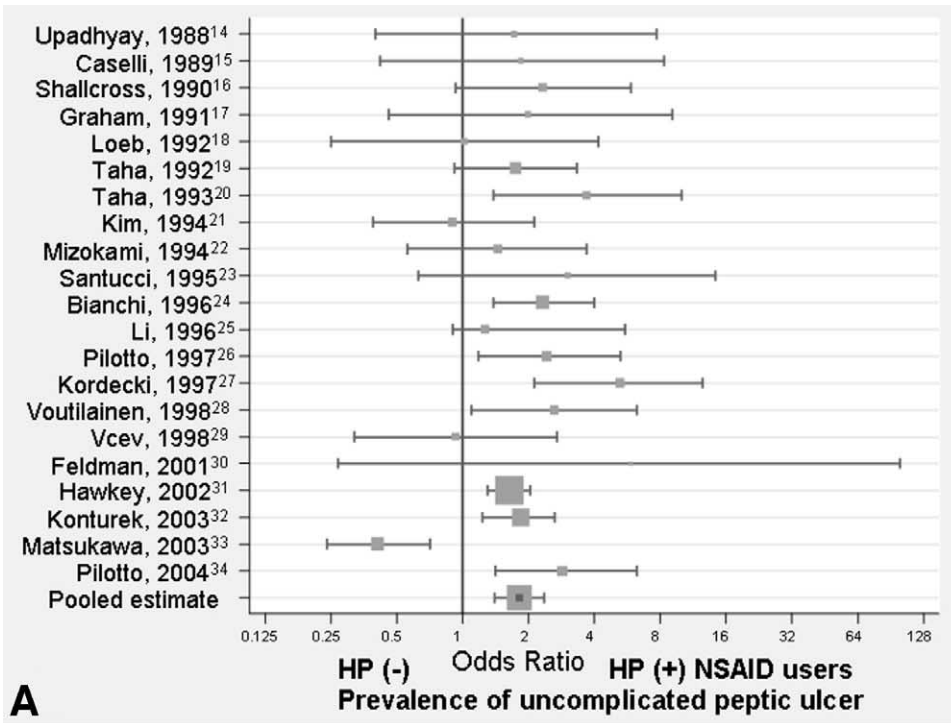


Figure 1. Risk of uncomplicated peptic ulcer in users (A)¹⁴⁻³⁴ or non-users (B)^{15,16,19,20,22,27,28,30,32} of NSAIDs in relation to the presence of HP infection. Plot standard graphic representation of ORs (logarithmic scale) and 95% CIs; area of symbol inverse proportional to estimate's variance. For both (A) and (B), significant heterogeneity ($P < .001$) and pooled estimate by random effect model ($P < .001$).

pooled OR, 1.87; 95% CI, 0.97–3.58; $P = .06$). However, the effect of NSAID use was found to be significantly affected by the HP status. In particular, the pooled prevalence of ulcer did not significantly differ between HP-positive users and HP-positive non-users of NSAIDs (38% vs 36%; heterogeneity, $P < .001$; pooled OR, 1.47; 95% CI, 0.78–2.75; $P =$

.24), but it was significantly higher in HP-negative users than HP-negative non-users of NSAIDs (26% vs 19%; heterogeneity, $P < .001$; pooled OR, 5.00; 95% CI, 1.71–14.71; $P = .003$) (Figure 2A and B; Table 3 of Appendix). The pooled prevalence of ulcer was also significantly higher in HP-positive NSAID users than HP-negative NSAID non-users (38% vs 19%; heter-

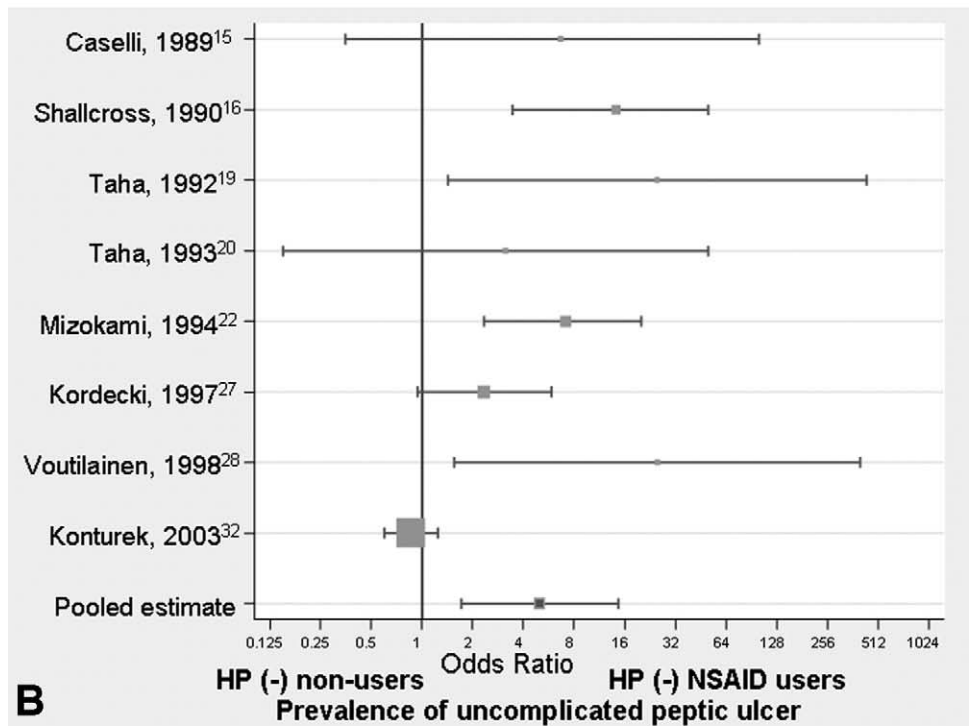
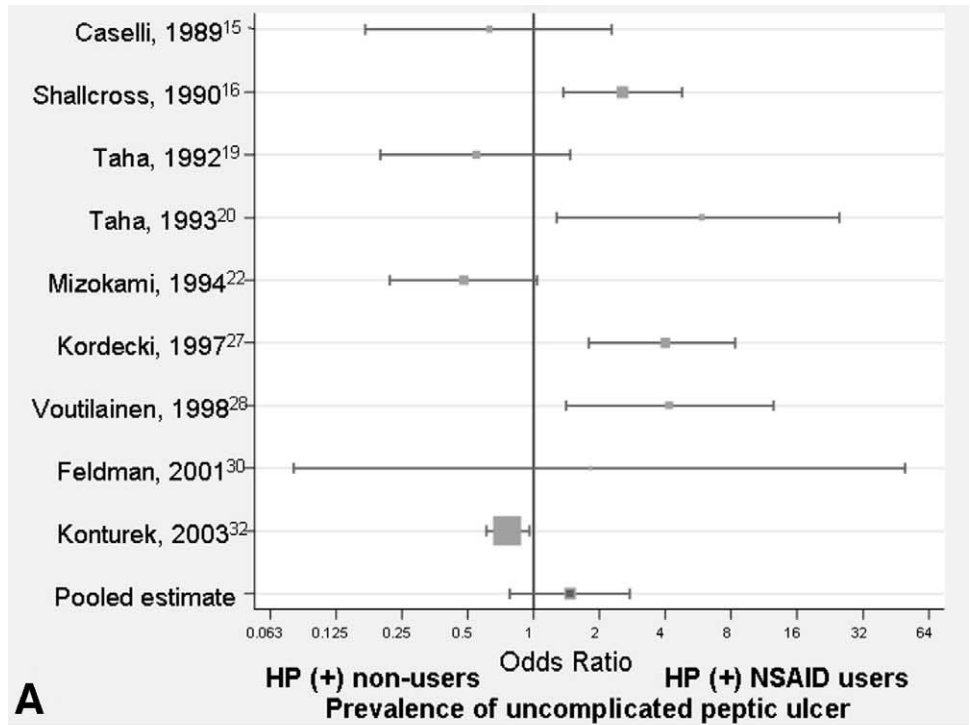


Figure 2. Risk of uncomplicated peptic ulcer in HP-positive (A) or HP-negative (B) subjects in relation to the use of NSAIDs.^{15,16,19,20,22,27,28,30,32} Plot standard graphic representation of ORs (logarithmic scale) and 95% CIs; area of symbol inverse proportional to estimate's variance. For both (A) and (B), significant heterogeneity ($P < .001$) and pooled estimate by random effect model ($P = .06$ for [A] and $P = .003$ for [B]).

ogeneity, $P < .001$; pooled OR, 9.80; 95% CI, 3.11–30.30; $P < .001$).

The pooled results of the subgroup analyses for the effect of HP infection and/or NSAID use on the risk of uncomplicated ulcer in 6 of the 7 age-matched controlled studies^{15,20,23,27,28,30} and in the remaining 14 unmatched studies^{14,16–19,21,22,24–26,29,31,32,34} are shown

in Table 1. One age-matched controlled study was excluded from this analysis, because it was the only one including exclusively patients with gastric ulcers in the group of NSAID non-users.³³ The pooled prevalence of HP infection was significantly higher in patients with ulcers than control subjects, irrespective of NSAID use in the analyses of both types of studies, whereas the NSAID

Table 1. Pooled Effects of HP Infection and/or Use of NSAIDs on the Risk of Uncomplicated Peptic Ulcer in Age-Matched Controlled or Unmatched Studies

	Age-matched controlled studies		Unmatched studies	
	OR (95% CI) Peptic ulcers/total (%)	References	OR (95% CI) Peptic ulcers/total (%)	References
HP effect	4.05 (2.80–5.88) ^{a,b}	15,20,23,27,28,30	2.06 (1.87–2.28) ^{a,b}	14,16–19,21,22,24–26,29,31,32,34
HP-positive cases	138/366 (38)		2275/5714 (40)	
HP-negative cases	58/423 (14)		1013/3422 (30)	
HP effect in NSAID users	3.60 (2.23–5.78) ^{a,b}	15,20,23,27,28,30	1.78 (1.53–2.08) ^{a,b}	14,16–19,21,22,24–26,29,31,32,34
HP-positive users	97/202 (48)		801/1681 (48)	
HP-negative users	43/229 (19)		625/1605 (41)	
HP effect in NSAID non-users	5.03 (2.53–10.00) ^{a,b}	15,20,23,27,28,30	7.41 (2.01–27.78) ^{c,d}	16,19,22,32
HP-positive non-users	41/164 (25)		1474/4033 (37)	
HP-negative non-users	15/194 (8)		361/1817 (20)	
NSAID effect	2.99 (1.26–7.09) ^{d,e}	15,20,27,28,30	1.22 (0.59–2.53) ^d	16,19,22,32
NSAID users	129/393 (33)		284/938 (30)	
Non-users of NSAID	56/358 (16)		1835/5850 (31)	
NSAID effect in HP-positive subjects	3.03 (1.82–5.03) ^{a,b}	15,20,27,28,30	0.88 (0.45–1.74) ^d	16,19,22,32
HP-positive NSAID users	88/178 (49)		187/550 (34)	
HP-positive non-users of NSAID	41/164 (25)		1474/4033 (37)	
NSAID effect in HP-negative subjects	3.86 (1.79–8.33) ^{b,f}	15,20,27,28,30	5.59 (0.95–33.33) ^{d,g}	16,19,22,32
HP-negative NSAID users	31/188 (16)		126/423 (30)	
HP-negative non-users of NSAID	15/194 (8)		361/1817 (20)	
NSAID plus HP effect	15.38 (7.69–31.25) ^{a,b}	15,20,27,28,30	7.30 (1.44–37.04) ^{d,e}	16,19,22,32
HP-positive NSAID users	88/178 (49)		187/550 (34)	
HP-negative non-users of NSAID	15/194 (8)		361/1817 (20)	

^a*P* < .001.^bNonsignificant heterogeneity.^c*P* = .003.^dSignificant heterogeneity.^e*P* = .015.^f*P* = .001.^g*P* = .057.

use was significantly associated with the presence of peptic ulcer only in the analyses of age-matched controlled studies but not of unmatched studies (Table 1). The risks of ulcer in relation to the presence of HP infection or NSAID use in the age-matched controlled studies appear in Figures 3 and 4.

The effect of HP infection and/or NSAID use on the risk of gastric or duodenal ulcer was also evaluated. In the 5 age-matched controlled studies, which provided data on the site of peptic ulcer,^{15,20,23,28,30} presence of HP infection significantly increased the risk of both duodenal and gastric ulcers, irrespective of NSAID use, but its effect was stronger on the risk of duodenal ulcer (pooled OR, 5.05; 95% CI, 2.32–10.99; *P* < .001) than that of gastric ulcer (pooled OR, 1.74; 95% CI, 1.06–3.16; *P* = .03). In the same studies,^{15,20,23,28,30} NSAID use was found to significantly increase the risk of gastric

ulcer (pooled OR, 7.87; 95% CI, 3.28–18.87; *P* < .001) but not the risk of duodenal ulcer, irrespective of presence of HP infection (Table 2).

The effect of HP infection and/or NSAID use on the risk of ulcer was also evaluated separately in 4 studies with subjects taking aspirin alone^{27,30,33,34} and in 13 studies with subjects taking non-aspirin NSAIDs alone^{14,16,17,19–24,28,29,31,33} (Table 3). The overall effect of HP infection or the effect of HP infection in NSAID users did not differ significantly between these 2 subgroups of studies. The effect of aspirin could be evaluated in 2 of the 4 studies^{27,30} and the effect of non-aspirin NSAIDs in 5 of the 13 studies.^{16,19,20,22,28} In HP-positive subjects, the risk of ulcer was found to increase 3.8-fold by aspirin use (*P* < .001) and only 1.6-fold by non-aspirin NSAID use without reaching statistical significance (*P* = .32). In contrast, in HP-negative subjects,

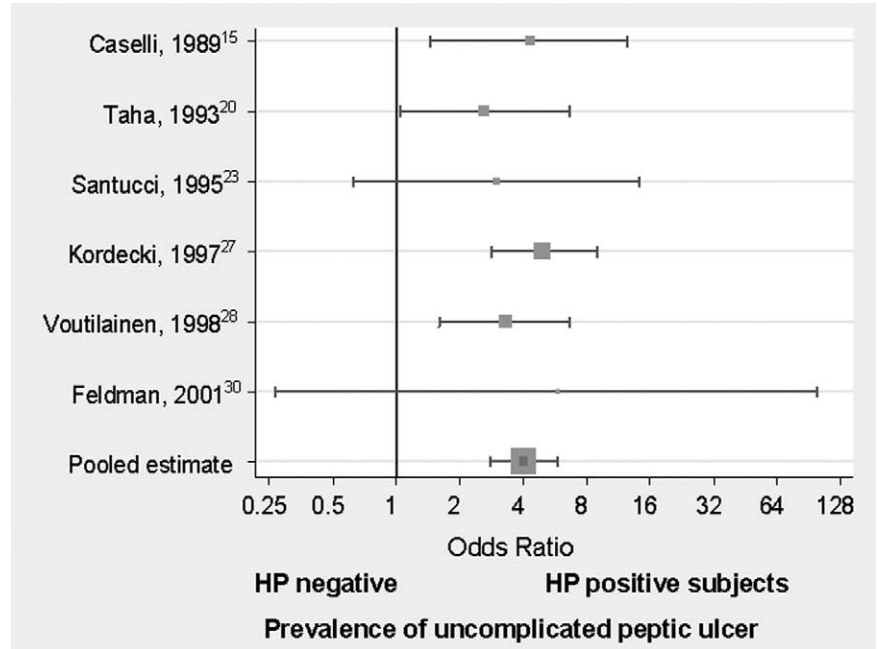


Figure 3. Risk of uncomplicated peptic ulcer in relation to the presence of HP infection in 6 age-matched controlled studies.^{15,20,23,27,28,30} Plot standard graphic representation of ORs (logarithmic scale) and 95% CIs; area of symbol inverse proportional to estimate's variance. Nonsignificant heterogeneity ($P = .88$). Pooled estimate by fixed effect model ($P < .001$).

the risk of ulcer was found to increase 2.5-fold by aspirin use ($P = .068$) and 10-fold by non-aspirin NSAID use ($P < .001$) (Table 3).

Peptic Ulcer Bleeding

In the 17 studies that evaluated the development of ulcer bleeding, raw data on HP status were provided for 4084 cases, 1588 patients with ulcer bleeding and 2496 nonbleeding control subjects.^{10-13,26,35-46} The main characteristics of these studies are shown in Table 4 of Appendix.

In the 9 studies with uninvestigated subjects as non-bleeding controls,^{10-13,36,38-41} HP infection was detected significantly more frequently in patients with ulcer bleeding (76%, 798/1055) than in control subjects (56%, 587/1043) (heterogeneity, $P = .52$; OR, 2.56; 95% CI, 2.11-3.11; $P < .001$) (Figure 5). In these studies, a similar effect of HP infection was observed in both users (397/532 or 75% vs 252/438 or 56%; heterogeneity, $P = .15$; OR, 2.35; 95% CI, 1.75-3.14; $P < .001$) and non-users of NSAIDs (174/209 or 83% vs

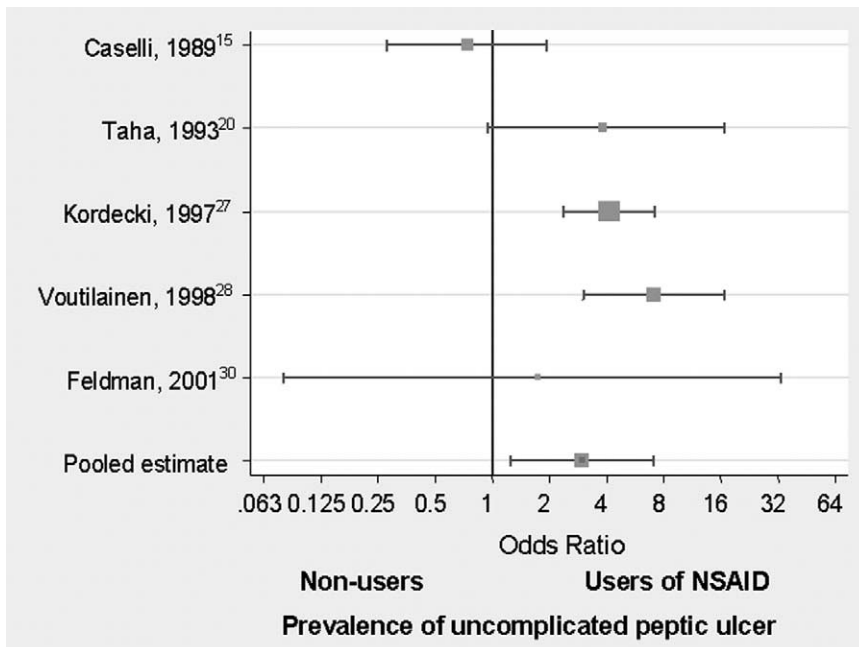


Figure 4. Risk of uncomplicated peptic ulcer in relation to the use of NSAIDs in 5 age-matched controlled studies.^{15,20,27,28,30} Plot standard graphic representation of ORs (logarithmic scale) and 95% CIs; area of symbol inverse proportional to estimate's variance. Significant heterogeneity ($P = .02$). Pooled estimate by random effect model ($P = .01$).

Table 2. Pooled Effects of HP Infection and/or Use of NSAIDs on the Risk of Uncomplicated Gastric or Duodenal Ulcer in Age-Matched Controlled Studies

	OR (95% CI)		OR (95% CI)	
	Gastric ulcers/total (%)	References	Duodenal ulcers/ total (%)	References
HP effect	1.74 (1.06–3.16) ^{a,b}	15,20,23,28,30	5.05 (2.32–10.99) ^{b,c}	15,20,23,28,30
HP-positive cases	34/250 (14)		33/250 (13)	
HP-negative cases	27/313 (9)		8/313 (3)	
HP effect in NSAID users	1.84 (1.00–3.38) ^{b,d}	15,20,23,28,30	3.34 (1.42–7.87) ^{b,c}	15,20,23,28,30
HP-positive users	29/137 (21)		19/137 (14)	
HP-negative users	27/198 (14)		8/198 (4)	
HP effect in NSAID non-users	7.35 (0.88–62.50) ^{b,f}	15,20,28,30	9.43 (1.70–52.63) ^{b,c}	15,20,28,30
HP-positive non-users	5/113 (4)		14/113 (12)	
HP-negative non-users	0/115		0/115	
NSAID effect	7.87 (3.28–18.87) ^{c,g}	15,20,28,30	0.97 (0.29–3.27) ^{b,h}	15,20,28,30
NSAID users	51/297 (17)		21/297 (7)	
Non-users of NSAID	5/228 (2)		14/228 (6)	
NSAID effect in HP-positive subjects	4.88 (1.82–12.99) ^{b,e}	15,20,28,30	0.96 (0.39–2.34) ^{b,h}	15,20,28,30
HP-positive NSAID users	26/113 (23)		13/113 (12)	
HP-positive non-users of NSAID	5/113 (4)		14/113 (12)	
NSAID effect in HP-negative subjects	8.20 (3.37–20.00) ^{b,e}	15,20,28,30	3.69 (0.45–30.30) ^{b,h}	15,20,28,30
HP-negative NSAID users	25/184 (14)		8/184 (4)	
HP-negative non-users of NSAID	0/115		0/115	
NSAID plus HP effect	12.66 (3.11–50.00) ^{b,c}	15,20,28,30	7.94 (1.41–45.45) ^{a,b}	15,20,28,30
HP-positive NSAID users	26/113 (23)		13/113 (12)	
HP-negative non-users of NSAID	0/115		0/115	

^a*P* = .03.^bNonsignificant heterogeneity.^c*P* < .001.^d*P* = .049.^e*P* = .005.^f*P* = .07.^gSignificant heterogeneity.^h*P* > .20.

202/343 or 59%; heterogeneity, *P* = .60; OR, 4.03; 95% CI, 2.59–6.29; *P* < .001) (Figure 6A and B; Table 5 of Appendix).

On the contrary, in the 8 studies with cases with endoscopically documented peptic ulcers as nonbleeding controls,^{26,35,37,42–46} HP infection was detected significantly less frequently in patients with ulcer bleeding (74%, 368/494) than in control subjects (92%, 1249/1363) (heterogeneity, *P* = .001; OR, 0.40; 95% CI, 0.23–0.68; *P* = .001). In these studies, the difference in the pooled prevalence of HP infection between patients with ulcer bleeding and control subjects maintained statistical significance in non-users (166/201 or 83% vs 1016/1070 or 95%; heterogeneity, *P* = .04; OR, 0.44; 95% CI, 0.20–0.66; *P* = .001) but not in users of NSAIDs (202/293 or 69% vs 233/295 or 79%; heterogeneity, *P* < .001; OR, 0.65; 95% CI, 0.23–1.84; *P* = .42) (Table 6 of Appendix).

The overall effect of NSAID use could be evaluated in 12 studies,^{10,11,35–37,39,40,42–46} because 4 studies did not include NSAID non-users,^{12,13,26,41} and 1 study did

not include NSAID users among the control subjects.³⁸ NSAID use significantly increased the risk of ulcer bleeding in both studies with uninvestigated subjects (heterogeneity, *P* = .16; pooled OR, 4.85; 95% CI, 3.77–6.25; *P* < .001)^{10,11,36,39,40} (Figure 7) and studies with cases with ulcers as controls (heterogeneity, *P* = .04; pooled OR, 5.59; 95% CI, 4.29–7.30; *P* < .001).^{35,37,42–46}

The effect of NSAID use in relation to the HP status could be evaluated in 9^{11,35,37,40,42–46} of the latter 12 studies, because the HP status was not provided separately for patients and/or control subjects in 3 of them.^{10,36,39} In the 2 of these 9 studies with uninvestigated subjects as nonbleeding controls,^{11,40} NSAID use was reported significantly more frequently by bleeding patients than control subjects in both HP-positive patients (171/312 or 55% vs 46/232 or 20%; heterogeneity, *P* = .08; pooled OR, 5.21; 95% CI, 3.48–7.75; *P* < .001) and HP-negative patients (51/76 or 67% vs 29/156 or 19%; heterogeneity, *P* = .51; pooled OR, 11.49; 95% CI, 5.78–22.73; *P* < .001) (Table 7 of Appendix).

Table 3. Pooled Effects of HP Infection and/or Use of NSAIDs on the Risk of Peptic Ulcer in Users of Aspirin or Non-Aspirin NSAID Alone

	Aspirin users			Non-aspirin NSAID users		
	Peptic ulcers/ total (%)	OR (95% CI)	References	Peptic ulcers/ total (%)	OR (95% CI)	References
Total HP effect		1.81 (0.28–8.62) ^a	27,30,33,34		2.06 (1.52–2.80) ^{a,b}	14,16,17,19– 24,28,29,31,33
HP-positive	120/288 (42)			756/1580 (48)		
HP-negative	55/236 (23)			621/1630 (38)		
HP effect in users		1.83 (0.35–9.61) ^a	27,30,33,34		1.68 (1.42–1.99) ^{b,c}	14,16,17,19– 24,28,29,31,33
HP-positive users	98/230 (43)			658/1251 (53)		
HP-negative users	40/149 (27)			615/1374 (45)		
HP effect in non-users		3.25 (1.49–7.04) ^{c,d}	27,30		10.53 (4.95–22.73) ^{a,b}	16,19,20,22,28
HP-positive non-users	22/58 (38)			185/515 (36)		
HP-negative non-users	15/87 (17)			104/585 (18)		
NSAID effect		3.98 (2.36–6.71) ^{b,c}	27,30		2.31 (0.97–5.49) ^{a,e}	16,19,20,22,28
Users	62/142 (44)			185/515 (36)		
Non-users	37/145 (26)			104/585 (18)		
NSAID effect in HP-positive subjects		3.82 (1.49–8.00) ^{b,c}	27,30		1.63 (0.62–4.31) ^a	16,19,20,22,28
HP-positive users	51/87 (59)			100/223 (45)		
HP-positive non-users	22/58 (38)			98/329 (30)		
NSAID effect in HP-negative subjects		2.48 (0.93–6.54) ^{c,f}	27,30		10.10 (4.59–22.22) ^{b,c}	16,19,20,22,28
HP-negative users	11/55 (20)			104/300 (35)		
HP-negative non-users	15/87 (17)			6/256 (2)		
NSAID plus HP effect		9.35 (4.90–17.86) ^{b,c}	27,30		18.52 (4.52–76.92) ^{a,b}	16,19,20,22,28
HP-positive users	51/87 (59)			100/223 (45)		
HP-negative non-users	15/87 (17)			6/256 (2)		

^aSignificant heterogeneity.^b $P < .001$.^cNon significant heterogeneity.^d $P = .003$.^e $P = .057$.^f $P = .068$.

Similarly, in the 7 studies with ulcer cases as nonbleeding controls,^{35,37,42–46} NSAID use was also reported more frequently by bleeding patients than control subjects in HP-positive patients (184/380 or 48% vs 191/1292 or 15%; heterogeneity, $P = .012$; pooled OR, 5.43; 95% CI, 3.88–7.63; $P < .001$) and HP-negative patients (68/103 or 66% vs 31/83 or 37%; heterogeneity, $P = .014$; pooled OR, 3.51; 95% CI, 0.85–14.49, $P = .082$), although the difference did not reach statistical significance in the latter cases (Table 8 of Appendix).

In the comparison between subjects with or without both HP infection and NSAID use, presence of both factors was detected significantly more frequently in patients with ulcer bleeding than in nonbleeding control subjects, but such an effect was greater in the studies with uninvestigated subjects (87% or 171/196 vs 27% or 46/173, respectively; heterogeneity, $P = .02$; pooled OR, 20.83; 95% CI, 7.94–55.55; $P < .001$)^{11,40} compared with the studies with ulcer cases as controls (83% or 175/210 vs 78% or 186/238, respectively; heterogeneity, $P = .15$; pooled OR, 1.91; 95% CI, 1.10–3.31; $P = .02$).^{35,37,42,44–46}

Discussion

The overall results of our systematic review suggest that HP infection and NSAID use have at least additive effect on the risk of developing uncomplicated peptic ulcer. The effect of each factor might be seen more clearly when it acts alone. In our study, the risk of ulcer was found to increase 6-fold by HP infection in non-users and 5-fold by NSAID use in HP-negative subjects, whereas it increased 10-fold by the simultaneous presence compared with the absence of both factors. It should be noted that there was significant heterogeneity in all analyses for the risk of ulcer, which is probably related to variations in the inclusion and exclusion criteria as well as the design and differences among the study populations.

The background prevalence of HP infection might be an important factor in interpreting the findings of studies evaluating its effect on the risk of peptic ulcer, but such data are not available for most studies. Because both the prevalence of HP infection and the risk of NSAID-induced peptic ulcer are age-dependent,^{5,9} the analyses of

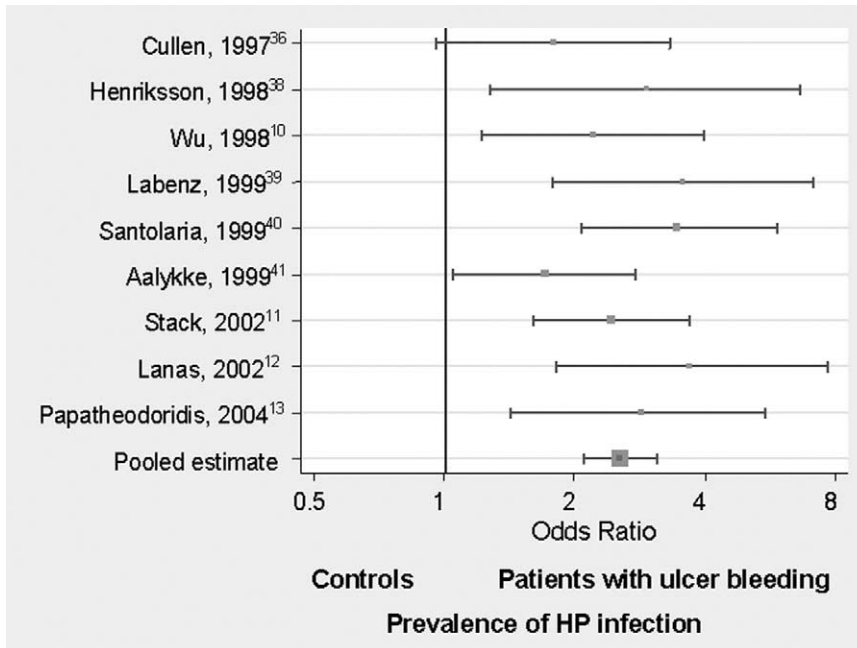


Figure 5. Effect of HP infection on the risk of peptic ulcer bleeding in 9 studies with uninvestigated subjects as controls.^{10-13,36,38-41} Plot standard graphic representation of ORs (logarithmic scale) and 95% CIs; area of symbol inverse proportional to estimate's variance. Nonsignificant heterogeneity ($P = .52$). Pooled estimate by fixed effect model ($P < .001$).

data of age-matched controlled studies are expected to provide more meaningful results. In fact, except for the overall NSAID effect, there was no significant heterogeneity in any other analysis of the age-matched controlled studies, in which the risk of ulcer increased 3.5-fold to 5-fold by HP infection irrespective of NSAID use, 3- to 4-fold by NSAID use irrespective of HP infection, and 15-fold by presence compared with absence of both factors (Table 1, Figure 3).

In contrast, there was significant heterogeneity in almost all analyses of the unmatched studies, which tended to underestimate the effects of HP infection and particularly of NSAID use. In the latter studies, the risk of ulcer was found to increase 2-fold by HP infection and not to be affected by NSAID use. It should be noted that the absence of NSAID effect was mostly due to the findings of a recent, large ($n = 5967$) Polish study,³² in which ulcers were detected in 22% of HP-negative subjects not taking NSAIDs (20% of all ulcers), and there was a negative interaction between HP infection and NSAID use on the development of duodenal ulcers (the majority of ulcers in this study). Whether the development of ulcers in HP-negative subjects not taking NSAIDs is an isolated phenomenon in certain populations or whether it is increasing in recent years as suggested by Konturek et al³² cannot be easily answered. A similar proportion of ulcers in HP-negative non-users of NSAIDs was also reported in an older, small Polish study,²⁷ which did not strongly influence the results of our meta-analysis. Nevertheless, the prevalence of ulcers unrelated to HP and NSAIDs has been found recently to

increase in some reports (without exceeding 10%)⁴⁷ but not in others.⁴⁸ It should be noted that the relative proportion of non-HP, non-NSAID ulcers is expected to increase following the progressively decreasing prevalence of HP infection, whereas underreporting of NSAID use and false-positive endoscopic findings should also be taken into account.

Whether aspirin and non-aspirin NSAIDs are associated with a similar risk of ulcer and particularly whether they have similar interactions with HP infection are not clear. It has been suggested that the damaging effect of aspirin on the gastric mucosa might be less potent than the effect of non-aspirin NSAIDs,⁴⁹ but even low doses of aspirin, such as 75 mg per day, have been shown to increase the risk of gastroduodenal ulcerations.^{50,51} According to our meta-analysis, HP infection had a similar effect on the risk of ulcer (increase of 1.7- to 1.8-fold) in users of aspirin and non-aspirin NSAIDs. On the other hand, the use of aspirin compared with the use of non-aspirin NSAIDs was associated with a greater increase of the risk of ulcer in HP-positive subjects (3.8-fold vs 1.6-fold) and a lower increase of the risk of ulcer in HP-negative subjects (2.5-fold vs 10-fold) (Table 2). Such findings might have been influenced by the heterogeneity among studies, whereas their validity for aspirin users might be limited by the small sample size. However, they might also suggest that the ulcerogenic activity of aspirin, which is lower than that of non-aspirin NSAIDs in the absence of HP (prevalence of ulcers: 20% in HP-negative aspirin users and 35% in HP-negative non-aspirin NSAID users), is greatly increased in the

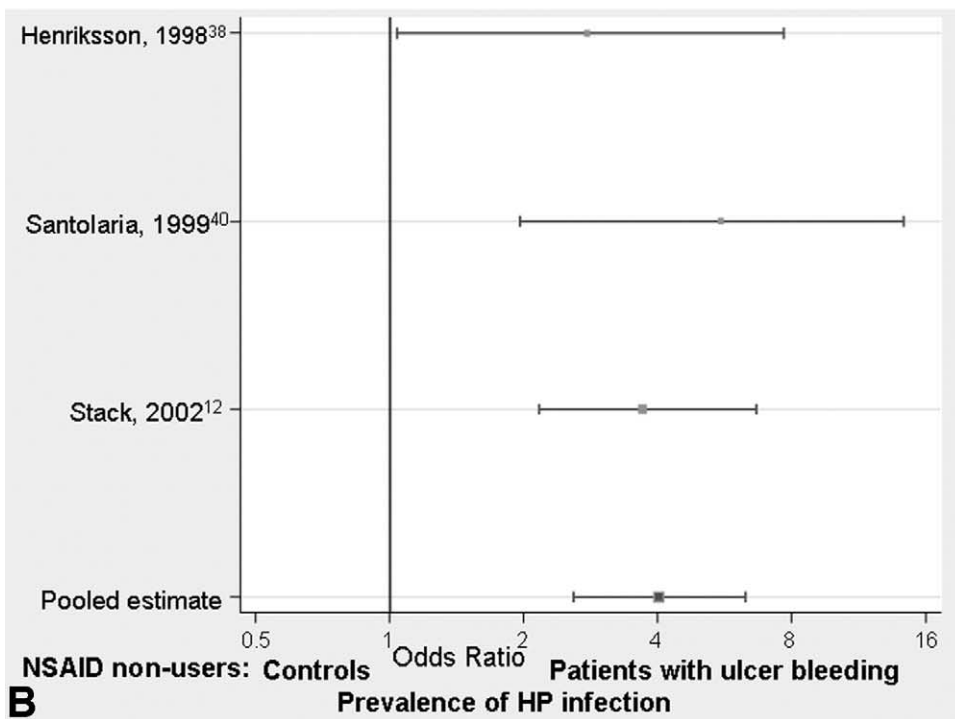
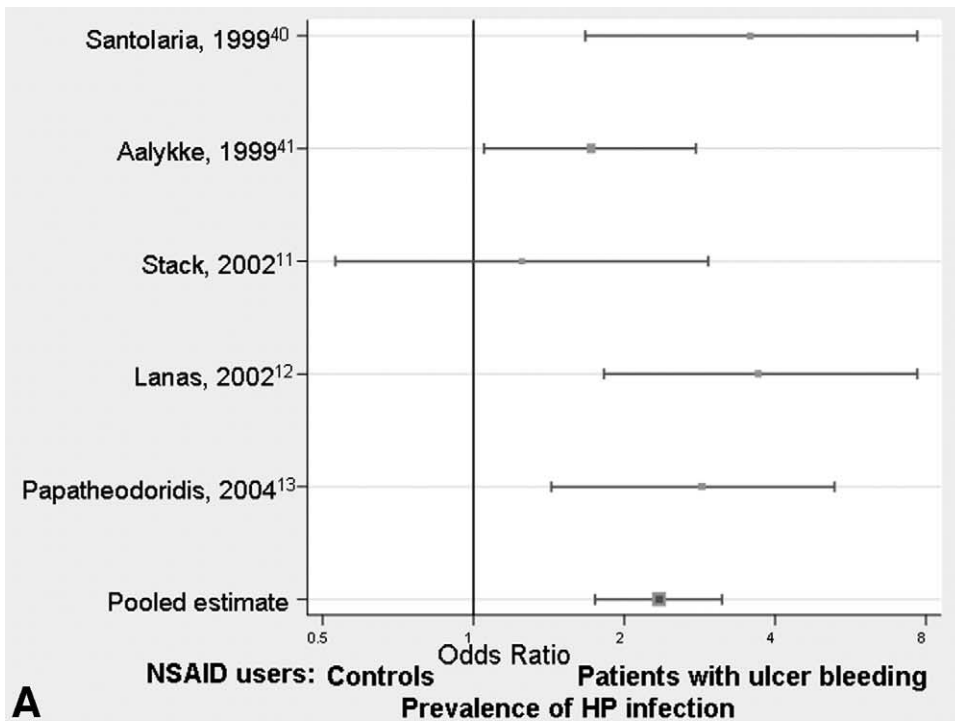


Figure 6. Effect of HP infection on the risk of peptic ulcer bleeding in users (A) or non-users (B) of NSAIDs in 9 studies with uninvestigated subjects as nonbleeding controls.^{10-13,36,38-41} Plot standard graphic representation of ORs (logarithmic scale) and 95% CIs; area of symbol inverse proportional to estimate's variance. For both (A) and (B), nonsignificant heterogeneity ($P = .15$ for [A] and $P = .60$ for [B]) and pooled estimate by fixed effect model ($P < .001$).

presence of HP infection (prevalence of ulcers: 59% in HP-positive aspirin users and 45% in HP-positive non-aspirin NSAID users). This is compatible with the results of a randomized therapeutic trial in HP-positive NSAID users with recent ulcer bleeding, according to which HP eradication was associated with significant reduction of the risk of rebleeding similar to that

achieved by long-term omeprazole therapy only in aspirin but not in non-aspirin NSAID users.⁵²

The majority of ulcers in NSAID users are completely asymptomatic because they are incidentally found at endoscopy in more than 20% of cases, whereas ulcer complications develop in only 2%–5% of them.^{4,53-57} Thus, the evaluation of the effects of NSAIDs on the risk

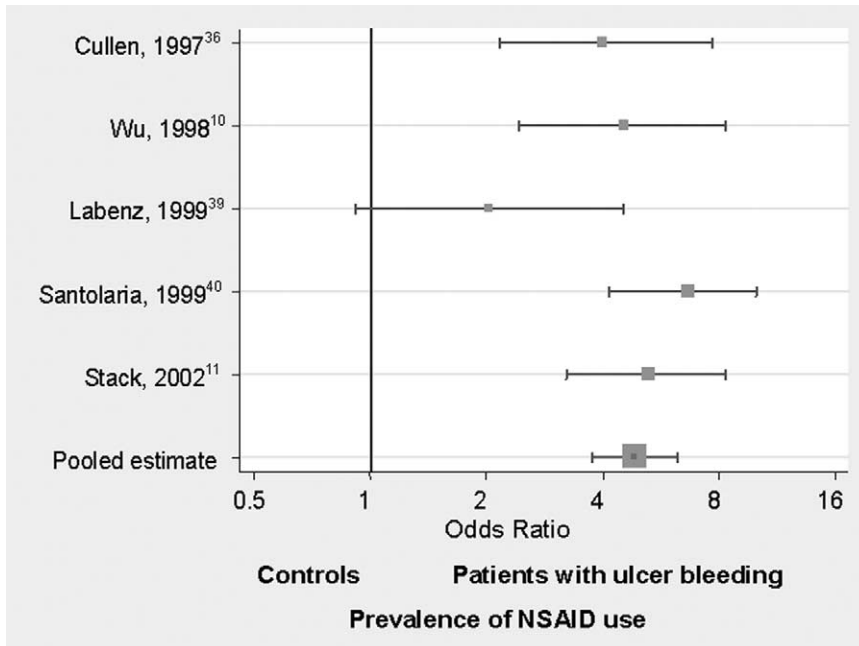


Figure 7. Effect of NSAID use on the risk of peptic ulcer bleeding in 5 studies with uninvestigated subjects as controls.^{10,11,36,39,40} Plot standard graphic representation of ORs (logarithmic scale) and 95% CIs. Nonsignificant heterogeneity ($P = .16$); area of symbol inverse proportional to estimate's variance. Pooled estimate by fixed effect model ($P < .001$).

of ulcer complication is more important for clinical practice. To define better the roles of HP and NSAIDs on the risk of ulcer bleeding, we performed subanalyses according to the nonbleeding control group. Specifically, we detected 2 main types of studies, those that included patients with ulcers and those that included endoscopically uninvestigated subjects as controls. In studies with ulcer patients as control subjects, HP infection was more common in nonbleeding controls than in bleeding patients (the difference reached statistical significance in the total analysis and in the analysis of NSAID non-users). We speculate that this is probably related to the strong association between uncomplicated ulcer and HP infection, particularly in patients with chronic dyspeptic symptoms undergoing endoscopy.⁵

The risk of ulcer bleeding might be more meaningful to be evaluated in studies with uninvestigated subjects as controls to avoid the strong association between HP infection and peptic ulcer. All these studies included age-matched nonbleeding control subjects.^{10-13,36,38-41} The results of these analyses suggest that HP infection and NSAID use have a synergistic effect on the risk of ulcer bleeding. In particular, HP infection was more common (OR, 4.0) in bleeding patients than in control subjects not taking NSAIDs, and NSAID use was more common (OR, 11.5) in HP-negative bleeding patients than in control subjects, whereas the presence compared with the absence of both factors significantly increased the risk of bleeding (OR, 20.8).

In conclusion, HP infection and NSAID use represent independent, synergistic risk factors for uncomplicated

and complicated peptic ulcers. Thus, HP eradication will have a beneficial effect in NSAID users. However, whether HP testing and subsequent HP eradication must be recommended to all NSAID users cannot be answered directly by such data, and this question should be examined by prospective randomized controlled trials of HP eradication in several subgroups of NSAID users. In current clinical practice, taking into consideration that guidelines are usually influenced by cost-benefit analysis data, HP testing and eradication should probably be individualized,^{6,7,58} taking into account the presence of other risk factors such as history of complicated or uncomplicated peptic ulcer, old age, recent-onset dyspepsia, treatment with anticoagulants,^{2,9,59-61} and the duration⁵⁹⁻⁶⁴ and perhaps the type (aspirin or non-aspirin) of NSAID use.⁵²

Appendix: Supplementary Data

To access the supplementary materials accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org.

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- Address requests for reprints to: George V. Papatheodoridis, MD, Assistant Professor in Medicine & Gastroenterology, 2nd Department of Internal Medicine, Medical School of Athens University, Hippokraton General Hospital of Athens, 114 Vas Sophias Avenue, 115 27 Athens, Greece. e-mail: gepapath@med.uoa.gr; fax: +30-210-7706871.**
- The authors thank Nikos Pantazis, biostatistician, for statistical advice.