Association between aspirin and upper gastrointestinal complications: Systematic review of epidemiologic studies

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Aims Because of the widespread use of aspirin for prevention of cardiovascular diseases, side-effects associated with thromboprophylactic doses are of interest. This study summarizes the relative risk (RR) for serious upper gastrointestinal complications (UGIC) associated with aspirin exposure in general and with specific aspirin doses and formulations in particular.

Methods After a systematic review, 17 original epidemiologic studies published between 1990 and 2001 were selected according to predefined criteria. Heterogeneity of effects was explored. Pooled estimates were calculated according to different study characteristics and patterns of aspirin use.

Results The overall relative risk of UGIC associated with aspirin use was 2.2 (95% confidence interval (CI): 2.1, 2.4) for cohort studies and nested case-control studies and 3.1 (95% CI: 2.8, 3.3) for non-nested case-control studies. Original studies found a dose–response relationship between UGIC and aspirin, although the risk was still elevated for doses lower or up to 300 mg day^{-1}. The summary RR was 2.6 (95% CI: 2.3, 2.9) for plain, 5.3 (95% CI: 3.0, 9.2) for buffered, and 2.4 (95% CI: 1.9, 2.9) for enteric-coated aspirin formulations.

Conclusions Aspirin was associated with UGIC even when used at low doses or in buffered or enteric-coated formulations. The latter findings may be partially explained by channeling of susceptible patients to these formulations.

Keywords: aspirin, complications, epidemiology, meta-analysis

Introduction

Safety data from randomized, controlled, trials showed that aspirin use increases about two-fold the risk of severe gastrointestinal events and suggested a lower, but persistent, risk associated with low doses [1–5]. Based on the general population, early observational studies have reported risks of upper gastrointestinal complications (UGIC) from 1 to 10 times higher among aspirin users, with an estimated pooled relative risk between 2 and 3 [6, 8], Nonetheless, the fact that aspirin is widely available over-the-counter without prescription complicates the assessment of its effects in observational studies.

During the last years, aspirin has been increasingly used in a long-term fashion for primary and secondary prevention of cardiovascular diseases. Since the dose required for thromboprophylaxis ($\leq$300 mg day^{-1}) is lower than that needed for analgesic or anti-inflammatory indications [2], the assessment of side-effects associated with low doses is particularly important. Moreover, to diminish gastric damage, enteric-coated and buffered aspirin formulations have been suggested as alternatives to plain aspirin. Endoscopic studies showed a reduction in gastric and duodenal injury with the use of enteric-coated aspirin, but not with buffering [9–12]; whether these preparations are associated with lower risks of UGIC than plain aspirin outside an experimental setting is still unclear.

Our objective was to systematically review the literature on serious gastrointestinal complications associated with aspirin use and to evaluate the influence of dose and formulation of aspirin as well as the effect of study design. Since studies published before 1990 were included in previous reviews [6–8], this paper summarizes the main results from observational epidemiologic studies published from 1990 to 2001.

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Methods

To be considered, a publication had to meet predefined inclusion criteria: Articles had to be case-control or cohort studies on aspirin use and UGIC (defined as bleeding, perforation, or other serious upper gastrointestinal event resulting in hospitalization or visit to specialist), and the articles had to provide valid relative risk estimates or enough data for us to estimate a relative risk comparing aspirin users with nonusers.

We conducted a MEDLINE search from 1990 to February 2001 searching for the terms: 'anti-inflammatory nonsteroidal agents' (both overall and aspirin), 'adverse effects', and 'toxicity' combined with 'peptic ulcer', 'stomach ulcer', 'duodenal ulcer', or 'gastrointestinal diseases' (including haemorrhage and perforation). The search was restricted to human studies on adults.

We identified 2477 entries and examined their abstracts. Studies on any nonsteroidal anti-inflammatory drug were considered in this first screening to avoid missing those in which aspirin was one among other drugs. When the abstract had no clear reason for exclusion, the full article was obtained. We also examined the references of previous reviews. Inclusion criteria were applied independently by two of us and decisions regarding inclusion of studies were reached by consensus. When two articles reported results from the same study population, the most recent version was chosen. However, if the earliest version provided additional subanalyses, they were considered.

A total of 46 original research articles were examined, but 20 of them did not provide specific data on aspirin [13–32]. Among the remaining 26 studies, four were rejected for the following reasons: inappropriate reference group for this particular analysis [33], the outcome was identification of gastrointestinal bleeding with endoscopy rather than the presence of serious gastrointestinal complications [34], the outcome combined upper and lower gastrointestinal bleeding [35], or methodological concerns regarding both the design (i.e. patients with ulcer history excluded only from cases) and the analysis (i.e. unclear interpretation of discordant pairs for McNemar's test) [36]. From the 22 published epidemiologic studies fulfilling all the inclusion criteria, one reported the same results in a different language [37, 38], three reported results from the same study population as more recently published articles [39–41], and one presented additional analyses from a sample that overlapped with a previous article [42]. Hence, the final number of analysed studies was 17 [38, 43–58].

A standardized data extraction form was designed to collect information on study methodology and objective quality-related characteristics. The list of characteristics was based on literature about the methods of epidemiologic studies in general and on previous meta-analyses on anti-inflammatory drugs and UGIC [6, 7, 59]. Data from articles was abstracted in duplicate and entered into a database.

To determine whether it was appropriate to pool the individual results into one common summary measure, the heterogeneity in effects between studies was analysed using the DerSimonian & Laird's test statistic for heterogeneity (Q) [60]. We calculated a summary relative risk (RR) and 95% confidence interval (CI), weighting study estimates by the inverse of the variance and estimating linear predictors for the log effect measure [61, 62]. In addition to these fixed effects estimates, we also calculated the corresponding random effects models. The odds ratio from case-control studies was assumed to provide a valid estimate of the relative risk [63]. We explored potential publication bias qualitatively using a 'funnel plot' [64].

Results

The relative risks of UGIC associated with aspirin use reported in the original studies are shown in Table 1 and Figure 1. The pooled RR was 2.6 (95 CI: 2.4, 2.7). However, the individual RR estimates were heterogeneous ($P<0.01$) and varied from 1.4 to 11.2. We explored sources of variability among results and estimated specific RRs.

Methodological factors

The main study characteristics are summarized in Table 2. Among the 16 studies considered, three were cohorts and 14 were case-control studies. Nonetheless, three case-control studies were nested in a well-defined cohort [54, 55, 58]. Ten case-control studies used matched designs. The nested case-control studies obtained their control subjects from registries; the other case-control studies ascertained controls from hospitals ($n=7$), communities ($n=1$), or both ($n=3$). Study years ranged from 1982 to 1998. Three studies restricted their sample to elderly populations. Seven studies used computerized records as the source of exposure and outcome information (all cohort and nested case-control studies and one hospital-based case-control study); the rest were based on interviews. Nine studies specifically excluded oesophageal lesions and only considered lesions located in the stomach or duodenum. Studies often had the following exclusion criteria: cancer ($n=10$), oesophageal varices ($n=10$), Mallory-Weiss disease ($n=10$), alcoholism ($n=7$), chronic liver disease ($n=7$) or/and coagulopathies ($n=6$). Aspirin exposure was defined as use during the last week in nine studies, use in the last month in three studies, and use reaching the index date or prescriptions that would cover the index date in the other

Table 1 Pooled and individual relative risk (RR) and 95% confidence intervals (CIs) of UGIC associated with aspirin use. Studies published from 1990 to 2001.

Study	*Cases* (n)	*Controls* (n)	*RR*⋆	*95% CI*
Laporte *et al.* [43]	875	2682	7.2	5.4, 9.6
Holvoet *et al.* [44]	161	161	2.2	1.3, 4.0
Nobili *et al.* [38]	441	1323	11.2	7.8, 16.9
Keating J, [45]†	77	77	2.6	1.0, 7.3
Henry *et al.* [46]	644	1268	2.4	1.9, 3.0
Savage *et al.* [47]†	494	972	2.1	1.5, 3.0
Weil *et al.* [48]	1121	2115	3.0	2.5, 3.7
Hallas *et al.* [49]	183	NA	1.9	1.2, 2.9
Kelly *et al.* [51]†	550	1202	2.4	2.0, 3.0
Matikainen *et al.* [50]†	48	156	1.5	0.6, 3.4
Pérez Gutthann *et al.* [54]	1377	10 000	1.4	1.0, 1.8
McMahon *et al.* [52]	172	NA	2.3	1.4, 3.8
Wilcox *et al.* [53]	461	1895	3.0	2.4, 3.7
García Rodríguez *et al.* [55]	1505	20 000	2.3	1.7, 3.2
Lanas *et al.* [56]	1122	2231	2.4	1.8, 3.3
Sorensen *et al.* [57]	804	NA	2.6	2.2, 2.9
De Abajo *et al.* [58]	2105	11 500	2.0	1.7, 2.3
Pooled RR: Fixed effects			2.6	2.4, 2.7
Random effects			2.7	2.2, 3.2
P value test for heterogeneity: <0.001				

⋆Relative risk estimate and 95% CIs provided in the publication.
n: number of cases or controls. NA: not applicable, cohort study.
†Estimated from raw data provided in the publication.

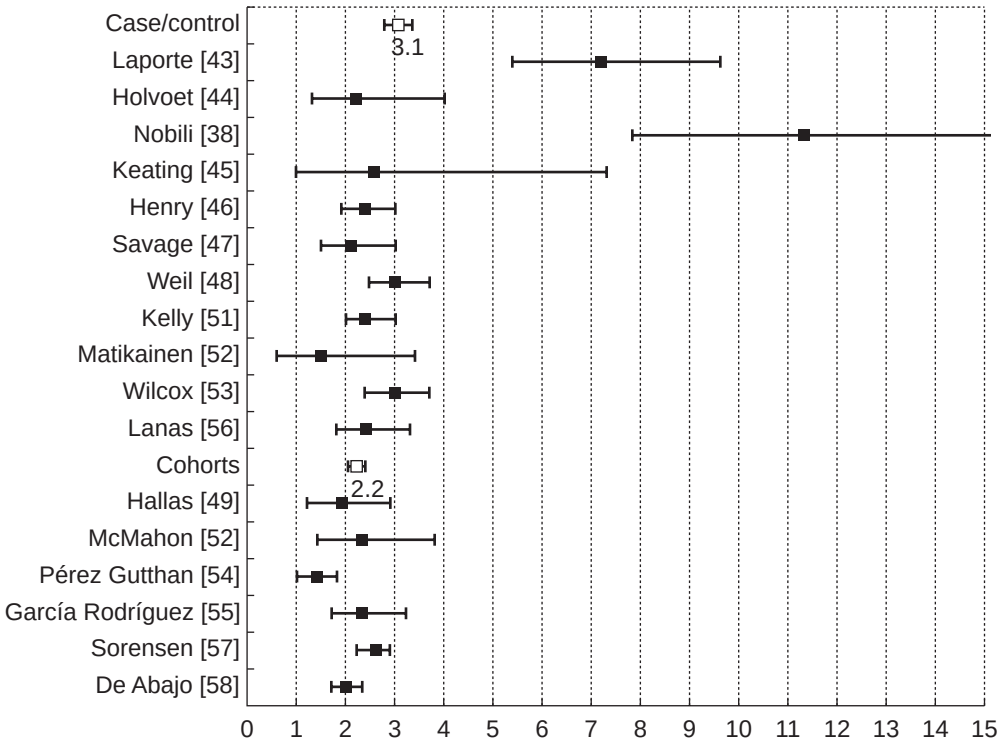

Figure 1 Relative risks and 95% confidence interval reported in original publications on aspirin use and UGIC during 1990–2001, stratified by study design.

Table 2 Description of studies on UGIC and aspirin use published from 1990 to 2001.

Study	*Design*	*Period*	*Location*	*Exposure assessment*	*Exposure window*	*Outcome*
Laporte *et al.* [43]	Case-control	87–88	Spain	Interview	Last week	Hospitalization for gastric or duodenal bleeding
Holvoet *et al.* [44]	Case-control	87–89	Belgium	Interview	Last week	Hospitalization for upper GI tract bleeding
Nobili *et al.* [38]	Case-control	87–88	Italy	Interview	Last week	Hospitalization for upper GI tract bleeding +
Keating [45]	Case-control	87–91	New Zealand	Records	Index day	Hospitalization for upper GI tract bleeding or perforation
Henry *et al.* [46]	Case-control	85–89	Australia	Interview	Last week	Hospitalization for upper GI tract bleeding or perforation
Savage *et al.* [47]	Case-control	86–90	New Zealand	Interview	Last week	Hospitalization for gastric or duodenal bleeding or perforation
Weil *et al.* [48]	Case-control	87–91	UK	Interview	Last month	Hospitalization for gastric or duodenal bleeding
Hallas *et al.* [49]	Cohort	91–92	Denmark	Records	Prescription coverage	Hospitalization for gastric or duodenal bleeding
Kelly *et al.* [51]	Case-control	87–94	US	Interview	Last week	Hospitalization for gastric or duodenal bleeding
Matikainen *et al.* [52]	Case-control	92–93	Finland	Interview	Last week	Hospitalization for upper GI tract bleeding
Pérez Gutthann *et al.* [54]	Nested Case-control	82–86	Canada	Records	Prescription last month	Hospitalization for gastric or duodenal bleeding or perforation
McMahon *et al.* [52]	Cohort	89–92	UK	Records	Prescription coverage	Hospitalization for upper GI tract bleeding or perforation
Wilcox *et al.* [53]	Case-control	91–93	US	Interview	Last week	Hospitalization for upper GI tract bleeding
García Rodríguez *et al.* [55]	Nested Case-control	91–95	Italy	Records	Prescription coverage	Hospitalization for gastric or duodenal bleeding or perforation
Lanas *et al.* [56]	Case-control	95–98	Spain	Interview	Last week	Hospitalization for upper GI tract bleeding
Sorensen *et al.* [57]	Cohort	91–95	Denmark	Records	Prescription coverage	Hospitalization for upper GI tract bleeding
De Abajo *et al.* [58]	Nested Case-control	93–98	UK	Records	Last month	Hospitalization for gastric or duodenal bleeding or perforation

five studies. Aspirin use was the main exposure of interest in four studies, was one among other anti-inflammatory drugs in 10, and was only considered as a potential confounder for other main associations in three studies.

Study design was associated with differences in RRs. Cohort studies and nested case-control studies ($n=6$) had a significantly lower summary estimate (RR = 2.2, 95% CI: 2.1, 2.4) than non-nested case-control studies (RR = 3.1, 95% CI: 2.8, 3.3). All nested case-control and cohort studies used computerized records as the source of exposure and outcome information, *vs* only one non-nested case-control study [45]. Exposure was defined as prescriptions that would cover the month before the index date or the index date itself in the six cohort studies or nested case-control studies. Once design was accounted, the other methodological characteristics mentioned in the paragraph above did not significantly affect the summary estimate of aspirin.

Heterogeneity of results within study design was mainly due to two non-nested case-control studies with high RR estimates (Figure 1) [38, 43]. Yet, even excluding these 'outliers', non-nested case-control studies had still a significantly higher average RR (RR = 2.6, 95% CI: 2.4, 2.9).

In addition, since aspirin has been widely used for cardioprotection (i.e. at lower doses) only in recent years, we estimated summary RRs for studies conducted only before and studies conducted at least in part after 1991. The pooled RR was 2.9 (95% CI: 2.6, 3.3) for earlier studies and 2.4 (95% CI: 2.2, 2.6) for later ones.

Regarding quality-related characteristics, all the studies had adequate definitions of exposure and outcome, five had slightly different inclusion criteria for cases and controls, and one had dissimilar ascertainment of compared groups. Thirteen studies verified the outcome with endoscopies, and the 6 studies using computerized records verified the information by chart review. All but two studies attempted to control for potential confounders. The most frequent confounders considered were age ($n=15$), sex ($n=15$), prior ulcer history ($n=9$), and concomitant medication ($n=9$). Among the 10 matched case-control studies, five utilized statistical analysis for matched data, three considered the matching factors in the multivariate model and two did not consider the matching factors during the analysis. Restricting the analysis to those publications with best quality did not substantially change the results.

Aspirin use factors

Five studies addressed the effect of different daily doses of aspirin in their analyses [46–48, 51, 58]; all of them found greater risks of UGIC for aspirin doses above 300 mg day^{-1} than for lower doses. However, the risk was still elevated for doses up to 300 mg day^{-1}. Studies reported a significantly increased risk of UGIC with daily doses below 300 mg, [47, 56] 150 mg [46, 57], and even as low as 75 mg [48, 58] (Table 3).

Only four studies reported data on aspirin formulation [48, 51, 57, 58]. The pooled RRs were 2.4 (95% CI: 1.9, 2.9) for coated and 2.6 (95% CI: 2.3, 2.9) for plain preparations. Two studies found buffered aspirin not to be associated with a lower UGIC risk than regular aspirin; the pooled RRs were 4.1 (95% CI: 3.2, 5.1) for plain and 5.3 (95% CI: 3.0, 9.2) for buffered aspirin in those two studies (Table 4).

When frequency of exposure was investigated, the RR was higher for patients using aspirin regularly (RR = 3.2; 95% CI: 2.6, 3.9) than for patients using aspirin occasionally (RR = 2.1; 95% CI: 1.7, 2.6) [48, 51]. The risk of UGIC associated with aspirin was higher during the first month of use (RR = 4.4; 95% CI: 3.2, 6.1) than in the subsequent months of treatment (RR = 2.6; 95% CI: 2.1, 3.1) [46, 48, 58].

Other factors

The relative risk associated with aspirin use was not significantly different in women than in men [43, 44, 46, 57]; nor for patients below or above 60 years of age [38, 43, 44, 46, 57].

Table 3 Original relative risks (RR) and 95% confidence interval (CI) of UGIC comparing aspirin users with nonusers according to aspirin dose, 1990–2001 studies.

Articles	*Cutoff points*	*RR*	*95% CI*
Henry *et al.* [46]			
	≤150 mg day^{-1}	1.4	1.0, 2.1
	>150 mg day^{-1}	2.7	2.0, 3.5
Savage *et al.* [47]			
	≤300 mg day^{-1}	1.3	0.8, 1.9
	>300 mg day^{-1}	3.1	3.1, 5.1
Weil *et al.* [48]			
	75 mg day^{-1}	2.3	1.2, 4.4
	150 mg day^{-1}	3.2	1.7, 6.5
	300 mg day^{-1}	3.9	2.5, 6.3
Kelly *et al.* [51]			
	≤325 mg day^{-1}	2.1	1.5, 2.9
	>325 mg day^{-1}	4.3	3.1, 6.0
Lanas *et al.* [56]	≤300 mg day^{-1}	2.4	1.8, 3.3
Sorensen *et al.* [57]			
	100 mg day^{-1}	2.6	1.8, 3.5
	150 mg day^{-1}	2.6	2.2, 3.0
De Abajo *et al.* [58]			
	75 mg day^{-1}	1.9	1.6, 2.4
	150 mg day^{-1}	2.1	1.6, 2.7
	300 mg day^{-1}	1.9	1.3, 2.7
	>600 mg day^{-1}	4.0	1.4, 11.5

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